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Emerging Impact of Malnutrition on Surgical Patients: Literature Review and Potential Implications for Cystectomy in Bladder Cancer

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Abstract

Purpose—Malnutrition is emerging as a significant factor in patient outcomes. A contemporary review of malnutrition has not been performed for the urologist. We review the available literature and current standards of care for malnutrition screening, assessment and intervention, focusing on patients with bladder cancer treated with cystectomy.

Materials and Methods—Our multidisciplinary team searched PubMed® for available literature on malnutrition, focusing on definition and significance, importance to urologists, screening, assessment, diagnosis, immunological and economic impacts, and interventions.

Results—The prevalence of malnutrition in hospitalized patients is estimated to range from 15% to 60%, reaching upward of 71% in those with cancer. Malnutrition has been shown to increase inflammatory markers, further intensifying catabolism and weight loss. Bladder cancer is catabolic and patients undergoing cystectomy have increased resting energy expenditure postoperatively. Data are emerging on the impact of malnutrition in the cystectomy population. Recent studies have identified poor nutritional status based on low albumin or sarcopenia (loss of muscle) as having an adverse impact on length of hospitalization, complications and survival. The current standard of care malnutrition assessment tool, the 2012 consensus statement of the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition, has not been evaluated in the urological literature. Perioperative immunonutrition in patients undergoing colorectal surgery has been associated with significant decreases in postoperative complications, and recent pilot

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work has identified the potential for immunonutrition to positively impact the cystectomy population.

Conclusions—Malnutrition has a significant impact on surgical patients, including those with bladder cancer. There are emerging data in the urological literature regarding how best to identify and improve the nutritional status of patients undergoing cystectomy. Additional research is needed to identify malnutrition in these patients and interventions to improve surgical outcomes.

Keywords

malnutrition; urinary bladder neoplasms; cystectomy; patient outcome assessment

Malnutrition is a medical condition that specifically refers to undernutrition resulting from nutritional imbalance. The condition consists of an imbalance in which the intake of calories, protein or other nutrients is inadequate to meet requirements for tissue maintenance and repair. Malnutrition has been described to be due to a combination of factors, including inadequate nutritional intake, increased nutritional requirements, impaired absorption and altered nutrient transport or utilization. The clinical criteria for identification of malnutrition (undernutrition), as set forth by the consensus statement of the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition, include 6 key characteristics, which consist of unintentional weight loss, evidence of inadequate intake, muscle loss, subcutaneous fat loss, fluid accumulation and diminished functional status as measured by handgrip strength.¹ The presence of 2 or more of these characteristics is considered diagnostic of malnutrition.

Malnutrition is also related to cachexia and sarcopenia. Cachexia is rapid weight loss and muscle wasting due to an underlying illness such as cancer. Sarcopenia is gradual muscle wasting associated with aging but can also occur with cancer. Both conditions may be relevant in the bladder cancer population and in older patients beginning cancer treatment with features of sarcopenia who also have an underlying cancer diagnosis. The pathophysiology of MN and cachexia related weight loss in patients with cancer is thought to be related to a combination of undernutrition, inflammation and cancer induced catabolism.² This catabolic process creates a challenging treatment paradigm as cachexia is difficult to fully reverse by conventional nutritional support once it reaches later stages and leads to progressive functional impairment. An international consensus group recently suggested incorporating sarcopenia as a diagnostic criterion for cachexia.³ In addition, decreased muscle mass and handgrip strength are components of recommended MN assessment.¹

Although clinicians and urologists are inherently familiar with the term “malnutrition,” there is persistent evidence of widespread failure to identify MN in patients, a fact that has the potential to negatively impact patient outcomes. We compiled a multidisciplinary team to provide a background primer on MN for urologists, to review the relevant literature, and to present potential opportunities for improved MN care and intervention. While we focus on the implication for patients with bladder cancer undergoing RC, the topic is relevant for other high risk urological procedures as utilization of nutrition care by urologists has the potential to improve patient and hospital outcomes.

EMERGENCE AND SIGNIFICANCE OF MALNUTRITION

Based on a lack of perceived attention, Butterworth in 1994 referred to MN as the “skeleton in the hospital closet.”⁴ This assessment was based on inattention to the essential role of good nutrition and neglect of patient nutritional health during hospitalization. To improve the standards of nutritional care, the Joint Commission on Accreditation of Healthcare Organizations in 1996 mandated completion of nutritional screenings within 24 hours after inpatient admission.⁵ A survey conducted in 2012 to 2013 assessed implementation of the mandated screening in various hospital settings.⁶ Of the 1,777 respondents 50.8% reported screening within 24 hours, and only 27% of patients were diagnosed with MN via use of a nutrition assessment form, suggesting a lack of precision in diagnosis. Insufficient personnel and inadequate resources were described as barriers to appropriate nutrition assessment.

Increased attention has recently been turned toward improving the quality of care for MN. The Academy of Nutrition and Dietetics in 2013 began work on its Malnutrition Quality Improvement Initiative.⁷ In addition, the European School of Oncology has described a need for earlier identification of MN and cachexia in patients undergoing treatment for cancer.⁸ Recently the Agency for Healthcare Research and Quality released a statistical brief on the characteristics of hospital stays involving MN, reporting that 1.95 million hospital stays in 2013 involved MN, which was associated with an economic burden of \$42 billion.⁹

IMPORTANCE OF MALNUTRITION IDENTIFICATION FOR UROLOGISTS

In doing this review we hope to improve the understanding of the urological community regarding MN and to highlight the impact of nutrition on clinical outcomes. Identification of MN is especially pertinent for patients with bladder cancer who undergo RC since this operation has been associated with significant catabolic changes, including net fat oxidation and lean tissue loss.¹⁰ Mathur et al reported that at 2 weeks after RC patients had experienced a loss of body protein and at 6 months postoperatively they had regained only 63% of the lost protein.¹¹ Patients also had a significant decrease in body weight and decrease in grip strength at 2 weeks postoperatively, as well as an increase in resting energy expenditure of 11%. At 6 months postoperatively resting energy expenditure and grip strength had returned to normal but body weight was still decreased. This altered metabolism represents one of many challenges of treating patients with bladder cancer. To improve outcomes postoperatively, it is imperative to explore modifiable risk factors such as preoperative nutrition status.

Prevalence of Malnutrition in Radical Cystectomy and Other High Risk Populations

The prevalence of MN is estimated to range from 15% to 60% in hospitalized patients and to be as high as 71% in those with cancer.¹² Several retrospective and prospective studies have been conducted that evaluate the rate of MN in the inpatient population. In a review of 20 studies targeting at risk surgical patients, intensive care unit patients and the geriatric population the rate of MN was 20% to 50%, with a weighted average of 41.7%.¹³

To date, a limited number of studies have focused on assessing MN specifically in the RC population. Estimates range from 16% to 33% (see table). However, many of these studies

used low albumin as the definition for MN.¹⁴ It is noteworthy that a recent MN consensus statement did not mandate laboratory tests such as albumin and prealbumin to diagnose MN because data suggest that these parameters do not respond to feeding interventions during an acute inflammatory response.¹ In a focused study with strict reporting guidelines that used a definition of NRS score 3 or greater the rate of MN was 55%.¹⁵

Implementation of neoadjuvant chemotherapy as the standard of care for patients with muscle invasive bladder cancer represents an additional nutritional concern. In a study of patients with esophageal cancer the rate of MN increased 22% after neoadjuvant chemotherapy ($p = 0.046$).¹⁶ The benefits of neoadjuvant chemotherapy on cancer specific survival are well documented. However, recognizing and addressing the side effects can improve outcomes even further.

The wide range in MN rates among these studies highlights the problem of underdiagnosis and the heterogeneity of the RC population. Despite multiple large scale studies (see table), the exact prevalence of MN in the RC population is difficult to estimate as there is substantial variability in the method used for MN diagnosis.

Clinical Impact of Malnutrition in Cystectomy Patients

MN represents a potentially modifiable risk factor for patients undergoing RC. Multiple studies have demonstrated an association between low preoperative albumin (used as a surrogate for MN) and postoperative complications and mortality.^{17,18} In a review of 1,097 patients undergoing RC Garg et al reported that decreased preoperative albumin was associated with increased complications ($p = 0.011$) and 90-day mortality ($p = 0.008$).¹⁸ Decreased albumin is associated with increased length of stay in patients undergoing RC (OR 2.1, 95% CI 1.2 to 3.8).¹⁹

Patients undergoing RC with evidence of MN have been observed to have increased cancer specific and overall mortality.^{17,20,21} In a study of 538 patients nutritional deficiency, including prealbumin less than 3.5 gm/dl, BMI below 18.5 and preoperative weight loss greater than 5%, was significantly associated with an increase in 90-day mortality and increased overall mortality at 3 years ($p < 0.01$).²⁰ Psutka et al studied 205 patients with a median followup of 6.7 years and observed that sarcopenia was independently associated with increased cancer specific ($p < 0.007$) and all cause mortality ($p < 0.004$).²¹

It is well known that MN interferes with wound healing and increases potential susceptibility to infections.⁴ In a study of 709 hospitalized patients Correia and Waitzberg reported that malnourished patients were more likely to exhibit infectious complications compared to well nourished patients (19.4% vs 10.1%, $p < 0.01$).²² Improvement in nutritional status has been observed to decrease infections in critically ill patients. In a RCT that assessed the effects of parenteral nutrition in patients unable to take in adequate nutrition orally those receiving nutritional support had a decrease in mean number of nosocomial infections ($p = 0.02$).²³ To our knowledge, no study has assessed the association of MN and infection in patients undergoing RC.

Principles of Measuring Malnutrition: Screening, Assessment and Diagnosis

To establish a diagnosis of MN in the hospital setting, an intradisciplinary stepwise process is recommended by the Malnutrition Quality Improvement Initiative (see figure).²⁴ On admission to the hospital patients are typically screened for MN by nursing staff. Those who are deemed at risk are evaluated by a registered dietitian, and the results are given to the care provider, who establishes the diagnosis and provides documentation.

Methods of Malnutrition Screening

Effective nutrition screening identifies patients with early signs and symptoms of MN who may benefit from more thorough nutrition assessment and intervention. Data from a national survey by Patel et al reveal that although United States institutions are compliant with the Joint Commission on Accreditation of Healthcare Organizations mandate for nutrition screening within 24 hours of hospital admission, only 50% are using validated screening tools and ensuring nutrition assessment and interventions for positive screens.⁶ Ideally a validated tool would be used for screening and repeated throughout hospitalization to monitor potential changes. While many validated nutrition screening tools exist for use in surgical or oncology populations, 2 tools have the strongest evidence of validity and reliability, NRS 2002 and MUST.

NRS 2002 is composed of a nutritional score, a gradation for disease severity and an age adjustment for patients 70 years old or older.²⁵ The nutritional score includes parameters such as weight change, food intake and BMI. The total NRS score classifies patients as no, low, medium or high risk. Most notably for the cystectomy population NRS 2002 is the only MN screening tool validated for surgery patients and allows for a gradation of disease with specific scoring for abdominal surgery. In prospective evaluations 21% to 55% of cystectomy patients are considered at risk for MN, with a NRS score of 3 or higher.^{15,26–28}

MUST is composed of 2 patient reported outcomes, weight change and loss of appetite. These factors are assessed by yes and no questions, and amount of unintentional weight loss as quantified by the patient. However, Kyle et al showed that NRS 2002 has higher sensitivity and specificity than MUST.²⁹ Also, NRS 2002 and MUST require an accurate weight to determine BMI and weight loss but neither requires the examiner to have nutritional training.

Adequate nutrition screening and monitoring are particularly important for the bladder cancer population undergoing cystectomy. This population undergoes multiple treatments that could affect nutrition status during a lengthy period of therapy. Early on cystectomy patients may have symptoms that affect their nutrition status from neoadjuvant chemotherapy, which then are compounded as they proceed to radical cystectomy.¹¹ Given the catabolic nature of bladder cancer and the response to radical cystectomy, routine use of one of these validated tools preoperatively should be considered for identifying patients in need of nutritional intervention to better prepare them for surgery.

Methods of Malnutrition Assessment

Once patients are identified as being at risk for MN, they are referred to a dietitian for nutrition assessment. Results of the evaluation direct the appropriate intervention. Subjective global assessment was originally used as an assessment tool for poor surgical outcomes.³⁰ This instrument uses 5 components of medical history, including weight change, dietary intake, gastrointestinal symptoms, functional capacity and metabolic stress, as well as physical examination findings, fat loss, muscle wasting and alterations in fluid balance. Administration of SGA requires a trained examiner to perform a brief physical examination, patient interview and chart review, making the tool more appropriate for comprehensive nutrition assessment. SGA is a useful method to assess nutrition across many disease states and provides a diagnosis of well nourished, moderately malnourished or severely malnourished.³¹ However, SGA does not have the specificity to detect improvements in nutritional status within a short time frame as one would expect during hospitalization.³² Therefore, the PG form was adapted from the SGA and developed for patients with cancer.³³

PG-SGA has been the accepted MN assessment tool for the oncology population and has been used in many studies.³⁴ The PG portion of the tool may also be used as a nutrition screen. However, the professional component must be performed by an examiner knowledgeable regarding the nutrition physical examination. In addition to a diagnosis of well nourished, moderately malnourished or severely malnourished, the PG-SGA also provides a continuous score, with higher scores indicating the need for nutrition intervention. Strengths of the PG-SGA are that patients can fill out many of the medical history components to save the practitioner time, and the device includes questions about eating meant to identify a broader range of nutrition impact symptoms.³²

The consensus statement of the Academy of Nutrition and Dietetics and ASPEN standardizes identification and documentation of MN based on 6 key characteristics, consisting of unintentional weight loss, evidence of inadequate intake, muscle loss, subcutaneous fat loss, fluid accumulation and diminished functional status as measured by handgrip strength.¹ Identification of 2 or more of these characteristics is considered diagnostic of adult MN.

Diagnosis of Malnutrition

Diagnosis of malnutrition must be documented by a care provider, which is typically done following assessment by a registered dietitian. However, there continues to be a discrepancy between the rates of diagnosed and documented MN. For example the rate of MN was evaluated for 39 million hospital discharges between 1993 and 2010.⁷ In 2010 the rate of reported MN was only 3.2%. Real-world data represent an alarmingly low rate of reported MN diagnoses compared to the established prevalence of MN during prior focused research efforts. A recent report by the Agency for Health-care Research and Quality and ASPEN demonstrated that protein calorie MN was documented in 4.5% of all inpatient stays.⁹

In a survey targeting members of ASPEN multiple factors were highlighted as reasons for the difference between the high prevalence of MN per dietitian assessment and the low rate

of documentation of an MN diagnosis by providers.⁶ These factors included lack of awareness, inadequate multidisciplinary care, lack of knowledge and inadequate training.

POTENTIAL IMPACT OF MALNUTRITION ON IMMUNE FUNCTION

Development of disease related MN has been referred to as a vicious cycle in which chronic and acute illness contributes to anorexia and/or intestinal malabsorption, which in turn leads to starvation, stress related catabolic activity, cachexia and unregulated inflammation. This cyclic process ultimately leads to alterations in immune function, increased morbidity and decreased patient well-being.¹³ The immune system in patients is further hampered by age related reduction in adaptive immunity, anergic immune activation and functional decline.³⁵ Taken together these findings indicate that in MN there is a significant shift toward catabolic metabolism at the expense of immune function.

Human and mouse studies suggest that MN is associated with suppression of innate and adaptive immune responses. As summarized in a review by Schaible and Kaufmann, MN is associated with decreased T cell survival, diminished memory T cell maturation and dysfunctional polarization of the T cell response.³⁶ In addition, MN leads to reduced macrophage responses to antigen.³⁷ Significant work in cancer related inflammation has revealed a shift toward the development of immunosuppressive macrophages and dendritic cells via secretion of high levels of IL-6, IL-1B, IL-4 and IL-10, and direct tumor progression via high levels of IL-6.³⁸

A short course of preoperative enhanced nutrition with the goal of modulating the immune system, called immunonutrition, has been shown to decrease immunosuppression, increase lymphocyte count, and modify and enhance circulating systemic cytokines.^{39–41} In the studies published to date immunonutrition has consisted of diets supplemented with nutrients such as glutamine, arginine, omega-3 fatty acids and ribonucleic acid.

ECONOMIC IMPACT OF MALNUTRITION

There are few published studies highlighting the economic impact of MN in patients undergoing cystectomy. However, there is evidence in other high risk populations demonstrating an association between MN and increased hospital costs. In a post hoc analysis from a prospective study of 453 patients undergoing colorectal surgery in France a diagnosis of MN was associated with increased hospital costs.⁴² In that series there were no differences in complications or mortality, but length of hospitalization was 3.41 days longer in malnourished patients ($p = 0.017$) and hospital costs were increased. In a study of 709 patients randomly selected from 25 Brazilian hospitals a 60.5% increase in daily hospital costs was observed in patients with MN.²² When costs of medications and tests were accounted for and compared to those in patients with a respiratory infection, MN increased costs by 308.9% compared to costs in well nourished patients.

Hospital reimbursement is based on Medicare Severity-DRG according to the presence or absence of comorbidities and/or complications. With the known economic impact of MN accurate documentation should be emphasized to ensure adequate hospital reimbursement. In a study of 541 patients in which 19% of the cohort was malnourished Ockenga et al found

that the coding of MN according to the appropriate DRG category increased total hospital reimbursement by 8.3%.⁴³ They also found that the mean $\pm$ SD complexity/comorbidity level increased from 2.69 ± 1.4 to 3.47 ± 0.82 ($p < 0.0001$) when MN was added to the DRG. The heterogeneity of these results is more indicative of the patient populations studied. However, these findings emphasize that the diagnosis and documentation of MN have important impacts on health care costs and hospital reimbursement.

MALNUTRITION INTERVENTIONS

Few nutrition intervention studies in the cystectomy population have been published. Early series focused on perioperative nutrition preparation and recovery from surgery. Recently adopted enhanced postoperative recovery pathways in urology have emphasized early feeding.⁴⁴ This protocol captures the known benefits of enteral nutrition. Guidelines from the Society of Critical Care Medicine and ASPEN suggest that using the gut is the best way to maintain intestinal integrity and modulate the immune response.⁴⁵

A recent prospective nonrandomized study of cystectomy subjects revealed that following an early feeding protocol similar to a regular diet decreased the length of stay compared to use of postoperative total parenteral nutrition.⁴⁴ Similar to other surgical nutrition support literature, a study of TPN in RC showed a higher infection rate compared to when a regular diet was consumed (32% vs 11%, $p = 0.001$).²⁸ This study had the strength of a RCT but was stopped early due to the harm of TPN. Additionally traditional TPN was evaluated without use of other supplemental nutrition such as lipids.

A Cochrane review of early enteral feeding (within 24 hours) in the colorectal surgery population analyzed multiple postoperative outcomes including wound infections, intra-abdominal abscesses, complications, length of stay, mortality and other adverse events.⁴⁶ The authors concluded that although the results were not statistically significant, there was no benefit to withholding enteral nutrition. Their results are based on 14 randomized trials of small heterogeneous populations with uncertain methodology. Feeding the gut early after RC offers an effective method for practitioners to address MN and improve outcomes.

There is emerging emphasis on immunotherapy in urological malignancies. As understanding increases regarding dysfunction of the malnourished immune system and the mechanisms underlying immune rescue with administration of immunonutrition, more importance will be placed on pre-habilitation and possibly additional immune targeted therapeutic interventions. In addition to improved pathways postoperatively, attention has been turned toward nutritional status preoperatively. Based on a systematic review of 35 studies predominantly from the colorectal surgery literature, Drover et al reported that perioperative immunonutrition with arginine supplementation strongly reduced infections (OR 0.59, 95% CI 0.50 to 0.70, $p < 0.0001$) and decreased mean hospital stay (OR -2.38, 95% CI -3.39 to -1.36, $p < 0.0001$).⁴⁷ There was no association with patient mortality (OR 1.08 95% CI 0.65 to 1.80, $p = 0.76$). This series was a review of multiple RCTs with strong methodological quality, yet it included studies spanning 2 decades and many were of small sample size.

Only 2 immunonutrition interventions have been published in the cystectomy population. Bertrand et al conducted a 60-patient, multicenter, case-control pilot study.⁴⁸ Arginine, fish oil, vitamin A and nucleotides were taken orally preoperatively. The authors found a reduction in postoperative complications (40% in prospective cohort vs 77% in retrospective controls, $p = 0.008$) and infection rate (23% vs 60%, $p = 0.008$). A limitation of this study was the use of a control historical cohort, which may have impacted clinical intervention and standards of care.

An additional immunonutrition intervention was evaluated in a randomized controlled trial of 29 patients by Hamilton-Reeves et al.⁴⁹ The intervention compared calorie and nitrogen matched oral nutrition support before and after bladder surgery in 29 patients. The authors reported that absolute rates of postoperative complications of RC were decreased by 33% ($p = 0.060$) and infections were reduced by 39% ($p = 0.027$). They demonstrated that consuming immunonutrition perioperatively impacted the immune system by restraining the expansion of myeloid derived suppressor cells between groups through time ($p = 0.005$). This study was not powered to robustly detect differences in clinical outcomes or MN. An adequately powered randomized trial of immunonutrition would be of value in the cystectomy population.

In the RC population 1 study revealed that routine intervention with total parenteral nutrition during the first 5 days postoperatively was associated with higher rates of infections and increased costs compared to oral nutrition alone.²⁸ Immunonutrition has shown promise and further studies are needed. Several potential interventions have been proposed to mitigate the risk of MN and decrease gastrointestinal complications. Although not tested in RC, these approaches include carbohydrate loading and protein nutritional supplementation, which have resulted in improved outcomes in other surgical interventions.⁵⁰

FUTURE DIRECTIONS

There remains limited level I evidence in the urological community regarding the impact of malnutrition. The paradigm established in the colorectal community provides a model to further study this clinical problem. All aspects of malnutrition care are ready for investigation, including preoperative malnutrition assessment and diagnosis, nutritional counseling strategies, perioperative nutritional supplementation, frailty evaluation, and short (readmissions, complications) and long-term (bone health, micronutrient deficiencies) clinical outcomes research.

CONCLUSIONS

Malnutrition is a significant and often underrecognized problem in high risk surgical patients such as those undergoing cystectomy. In addition, mounting evidence suggests that MN may have a significant impact on immune function and clinical outcomes. Appropriately MN has moved to the forefront in clinical care as a potentially modifiable risk factor and is being recognized by the urological community as a critical issue. Because patients undergoing cystectomy represent a high risk population in urology, it is imperative that urologists identify MN, understand its clinical implications and focus on interventions.

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Abbreviations and Acronyms

ASPEN	American Society for Parenteral and Enteral Nutrition
BMI	body mass index
DRG	diagnosis related group
IL	interleukin
MN	malnutrition
MUST	Malnutrition Universal Screening Tool
NRS	Nutritional Risk Screening
PG	patient generated
RC	radical cystectomy
RCT	randomized controlled trial
SGA	subjective global assessment
TPN	total parenteral nutrition

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Figure.

Flowchart for diagnosing malnutrition in hospitalized patients. Nutritional interventions would follow appropriate MN screening, assessment and diagnosis. Adapted from MQii Toolkit.²⁴

Table

Prevalence of malnutrition in radical cystectomy populations

References	No. Pts	Surgery	Malnutrition Rate	Malnutrition Definition
Gregg et al ²⁰	538	RC	19.1%	Albumin less than 3.5 gm/dl, BMI 18.5 or less, or wt loss 5% or more
Lambert et al ¹⁷	187	RC	16.6%	Albumin less than 3.5 gm/dl
Hollenbeck et al ¹⁹	2,538	RC	21.5%	Albumin less than 3.5 gm/dl
Karl et al ²⁶	897	Urological (RC in 20%)	32.5%	NRS 2002 score 3 or higher
Karl et al ²⁷	320	Urological	21.3%	NRS 2002 score 3 or higher
Roth et al ²⁸	157	RC	21.7%	NRS 2002 score 3 or higher
Cerantola et al ¹⁵	110	Urological (RC in 18%)	55% in Pts undergoing RC	NRS 2002 score 3 or higher

Data adapted from Munbauhal et al.¹⁴