The impact of sarcopenia on the postoperative outcome in colorectal cancer surgery

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Abstract

Background and aim. Malnutrition-induced sarcopenia predicts poorer clinical outcomes for patients with cancer. Postoperative complications such as wound infection, anastomotic leak (AL), cardiorespiratory events are the most frequent and devastating postoperative complications in colorectal cancer surgery and are frequently associated with malnutrition.

Methods. We reviewed the recent available literature to assess the relationship between the patient nutritional status and sarcopenia in colorectal surgery. The PubMed database was searched for publications. The included studies were original articles, prospective and randomized trials, clinical, systematic reviews and meta-analyses. The information was structured in a narrative review form.

Results. A simple method to assess malnutrition is to define the presence of sarcopenia (skeletal muscle mass reduction and modified composition) by radiological image analysis. Quantifying the material composition and quality is a novel method in patient-specific therapy. This could be a new perspective in colorectal surgery to reduce postoperative mortality, improve surgical planning, and enhance clinical outcomes. A few recent studies have objectively investigated the presence of sarcopenia in colorectal cancer and its impact on morbidity and mortality, but sometimes the results are contradictory.

Conclusion. There is evolving research to find the most appropriate management method , surgeons must be aware of the existence of sarcopenia to identify this risk factor in the occurrence of postoperative complications in colorectal cancer surgery.

Keywords: colorectal cancer, sarcopenia, postoperative complications, anastomotic leak, mortality

Introduction

Colorectal cancer (CRC) represents the third most commonly detected cancer worldwide and is the second leading cause of death in the US. Most cases of CRC are detected in Western countries, with its incidence increasing year by year [1,2]. The prognosis is generally influenced and determined by clinical and pathological stages and the outcomes of surgical treatment. The patient-related factors and postoperative complications play a key role in the treatment management and determine the long-term overall survival and disease-free survival. Identification of the patient-related factors in the preoperative phase is very important in the improvement of surgical outcomes [3]. Postoperative complications can have critical implications including higher mortality and morbidity, disease recurrence, or impaired tolerance to adjuvant therapies. There is evidence that besides the preoperative modifiable risk factors such as smoking and alcohol consumption [4], the neoadjuvant therapy [5], older age [6], male sex [7], malnutrition-induced body composition [8] are common host-related factors. Identification of these modifiable risk factors with targeted prophylactic strategies is promising to improve

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treatment outcomes [9]. There is increasing evidence that body composition parameters like skeletal muscle mass, muscle radiodensity, visceral adipose tissue, and changes of these parameters will influence the prognosis for patients with colorectal cancer [3,10]. Though sarcopenia has a high prevalence in a variety of gastrointestinal cancers, including CRC, and is associated with increased risk of total postoperative complications, in surgical oncology practice it is not a target of the standard perioperative management [11].

Methods

This review aims to identify the relationship between sarcopenia and postoperative outcome and to describe the most frequent postoperative complications in colorectal cancer surgery by reviewing the most recent literature, in the form of a narrative review [12].

The available online literature was searched in PubMed – Medline database using the combination of the following medical terms: sarcopenia, frailty, myopenia, psoas muscle index, colon, rectal, colorectal, cancer, anastomotic leak, surgical site infection, complications. The time filter for the search was from 2015 to present. We excluded studies without proper preoperative CT based evaluation and incomplete postoperative complication follow-up. Differences between sarcopenic and non-sarcopenic patients with colorectal cancer are presented by original articles, randomized controlled trials, prospective and retrospective studies, systematic reviews and meta analyses by preoperative evaluation.

Malnutrition, sarcopenia

Malnutrition or subnutrition is described as a lack of intake or uptake of nutrition that leads to altered body composition. There are five criteria in definition, three in the phenotypic group (weight loss, low body mass index, reduced muscle mass) and two etiologic criteria (reduced food intake or assimilation, inflammation). From these five, at least one criterion must be present in the phenotypic group and one from the etiologic group for the diagnosis of malnutrition [13]. Malnutrition by reduced muscle mass is one of the key pathophysiological causes of sarcopenia. Frequently, malnutrition and sarcopenia are present simultaneously, and they appear clinically through a combination of decreased body weight and nutrient intake, along with a decrease in muscle mass and function. These two entities result in numerous and substantial negative outcomes [14]. Sarcopenia is present when there is a progressive and generalized loss of skeletal muscle mass, strength and function and is associated with risk of adverse outcomes, higher hospital costs, comorbidity, and mortality. Also, changes in body composition such as the alteration of fat and muscle mass balance are another important aspect of sarcopenia pathogenesis [15,16]. The diagnosis is confirmed when the muscle quantity and quality are low [17]. This is an age-associated deterioration of skeletal muscles and exacerbation of obesity which will lead to numerous consequences. The prevalence of obesity-associated sarcopenia especially in the elderly is increasing and this can highlight the risk for synergistic complications [18,19]. The process direction is highly debated, by the theory of obese sarcopenia is that the adipose tissue induces inflammation which will sustain a chronic low-grade inflammation of skeletal muscle and will lead to muscle dysfunction [20]. A rising trend in obesity-related cancer explained by the induction of systemic changes as the imbalance of insulin, insulin-like growth factor-1, leptin, adiponectin, steroid hormones, and cytokines has the potential to create an environment in tumor initiation and progression and will focus on this public health problem [21]. The close relationship between obesity and cancer is demonstrated, but it is inevitable not to mention that 50% of all cancer deaths on a worldwide basis are associated with malnutrition. These include esophageal, gastric, colorectal, pancreatic, hepatic, and lung cancers [22]. In the condition of malnutrition, cancer-associated sarcopenia can contribute to poor surgical outcomes and survival [23]. It has been clarified that besides the well-known body mass index (BMI) and body surface area (BSA) we need supplementary analyses to assess the body composition. In the case of cancer patients, the BMI or BSA is not strongly correlated with muscle mass [24].

In this context, identifying sarcopenia plays a key role in postoperative complications prevention and is responsible for decreased survival in gastrointestinal cancer patients, since it reflects muscle wasting and poor nutritional status [25].

There is evidence that the above-mentioned disorders such as obesity, cancer, and sarcopenia are linked too closely and frequently and we need to understand the mechanism to improve the clinical outcome.

Screening for sarcopenia

As in 2016 sarcopenia was introduced by the World Health Organization (WHO) in the list of International Classification Disease (ICD) list, it is accepted as the most important marker of frailty in older persons [26]. Recognition of sarcopenia as a disease has led to major research efforts into the best practices for its screening, diagnosis and management. Various methods can be used to assess muscle mass and strength [27]. Assessment of body composition typically refers to the quantification of body fat and muscle mass, and it is most assessed by medical imaging. Currently, DXA (dual-energy X-ray) and CT(computer tomography) /MRI (magnetic resonance imaging) are the most commonly used imaging modalities for sarcopenia assessment. For diagnosis of the disease quantitative approaches are required to assess body composition and muscle loss. The first line in the literature is predominantly DXA or computed tomography [28,29]. The application of CT has recently been popularized in patients

who had an indication for CT scan as part of their standard medical care. The use of CT measured body composition is increasing by the simple quantification of total lumbar muscle cross-sectional area because this region appears on the majority of CT scans and this area of the body includes a diverse representation of muscles (psoas, erector spinae, quadratus lumborum, transverse abdominis, external and internal obliques, and rectus abdominis). Lumbar muscle area is also well correlated with whole-body muscle mass [30]. A single-muscle approach to the diagnosis of clinically important depletion of skeletal muscle is a recent trend in the literature on CT-defined muscle quantification. The single muscle is most often the psoas and manually measured cross-sectional areas are most commonly used. It has been demonstrated that the iliopsoas volume was significantly related to height, BMI, age and that there was an acceleration in muscle volume decrease in men with age [31,32]. Focused on this novel diagnostic method the results of a study group from the USA highlight that the prevalence of sarcopenia especially in the elderly is higher than the prevalence of sarcopenia in patients without cancer and the BMI alone is a poor indicator of lean body mass [33].

The most accepted and widely used method in sarcopenia evaluation is based on a CT scan. The psoas muscle area at the level of the third lumbar vertebra (L3) on a single abdominal cross-sectional CT slice is obtained and then is normalized for patient height to calculate the L3 muscle index and expressed in cm^2/m^2. The most frequently used sex specific cut-off values for sarcopenia were 52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women, based on the study of Prado et al. Patients below these values usually were classified as having sarcopenia [34].

Results

Postoperative complications

Although colorectal cancer surgery is associated with a great number of complications, sometimes the early identification of these possible causes could affect the outcomes. The most frequent complications are shown in table I.

Anastomotic leakage (AL) remains a devastating problem for the patient associated with high morbidity and mortality and is a continuing challenge to the surgeon operating on high-risk areas of the gastrointestinal tract [35]. A recent meta-analysis including a total of 154,981 patients highlighted that AL had a negative impact on overall survival [36]. This fact makes the AL on patients undergoing colorectal resection "the most important quality indicator" [37]. Although surgical techniques have improved over time, the anastomotic leakage is still a reality in colorectal surgery with rates ranging from as low as 1% for low-risk anastomoses, such as enteroenteric or ileocolic, to 19% for high-risk coloanal anastomoses [38]. Even though many studies have identified risk factors for anastomotic leakage, to date it is difficult to predict the occurrence for each patient. There is a large number of studies based on the identification of these risk factors, some of them grouped the risk factors as locals and generals [39], technical and patient-related, but probably the most appropriate to group by modifiable (obesity, smoking, malnutrition, etc.) and not modifiable (gender, history of radiotherapy, etc.) risk factors [9].

Surgical site infection (SSI) is the second most prevalent hospital-based infection and affects surgical therapeutic outcomes. They are associated with an increased hospital stay, readmission and higher cost. The occurrence is frequently accumulated when the patient-related risk factors meet with the surgery-related risk factors [40]. Patient and disease factors are higher ASA class, obesity, tobacco use, cardiopulmonary diseases, diabetes, age and inflammatory bowel disease. Surgical risk factors include blood transfusion, open surgery, prolonged operative time, contamination [41].

Cardiac complications are common after non-cardiac surgery, all surgeons must be aware of the fact that pre-existing cardiovascular comorbidity is associated with high-grade postoperative complications following colorectal surgery [42,43].

Early identification and treatment of these complications are essential, but if the perioperative case management is more appropriate and patient-specific, we can rule out a large proportion of these complications.

Table I. Postoperative complications after CRC surgery.

Anastomotic leakage
Infections
Cardiopulmonary complications/Thrombosis
Adhesion and small bowel obstruction
Anastomotic bleeding
Port site metastases (minimally invasive surgery)
Ileus
Colonic ischemia

Sarcopenia related complications

There is growing evidence that body composition parameters, especially in patients undergoing CRC surgery, sarcopenia poses a big health challenge and risk and provide prognostic implications. In current literature, there is evidence and wide recognition that sarcopenia is associated with poor surgical outcomes and is an independent predictor of worse survival [44]. In several gastrointestinal and pelvic malignancies, including esophagus, stomach, liver, pancreas, bladder, and more, sarcopenia is known to adversely affect outcomes [45]. Table II presents the results of different study groups and the relationship between sarcopenia postoperative outcome in colorectal cancer surgery.

In a recent meta-analysis by Trejo-Avila et al including 18,891 patients, the results confirm the association between sarcopenia and a higher risk of postoperative complications [46]. The negative impact of sarcopenia is also demonstrated by studies on CRC-related surgeries, such as hepatic resection for colorectal liver metastasis, where an increased risk of postoperative morbidity and longer hospital stay are documented [47].

Table II. Postoperative outcomes in CRC surgery.

Study	No. cases	Sarcopenia		AL	P	MO	p	POC	p	SSI	P	LOS	p
Giani, 2020 [48]	122	No	95	8	0.865	2	0.016	36	0.002	17	0.024	-	-
		Yes	27	2		4		23		12			
Pereira, 2020 [49]	272	No	220	16	0.392	14	0.235	25	0.002	27	1.00	7	0.915
		Yes	52	6		6		13		6		7	
Reisinger, 2015 [50]	249	No	133	24	0.13	1	0.009	-	-	-	-	-	-
		Yes	116	13		13		-				-	
Herrod, 2019 [51]	169	No	118	2	0.026	-	0.23	18	0.007	-	-	-	-
		Yes	51	4				10		-		-	
Aro, 2020 [52]	348	No	140	5	0.35	2	0.19	16	0.20	-	-	9.60	0.24
		Yes	208	12		8		34		-		10.4	
Chen, 2020 [53]	360	No	227	9	-	-	-	62	0.029	18	-	19	0.444
		Yes	133	4		-		51		14		20	
Ouchi, 2016 [54]	60	No	40	1	-	-	-	2	1.00	1	-	13	0.80
		Yes	20	2		-		1		2		13	
Richards, 2020 [55]	350	No	235	10	-	1	0.04	21	<0.01	-	-	7	<0.01
		Yes	115	10		4		35				13	
Jochum, 2019 [56]	47	No	23	1	-	-	-	7	0.03	-	-	11.4	0.33
		Yes	24	3		-		15		-		9.4	
Choi, 2018 [57]	188	No	114	11	0,598	9	0.007	-	-	-	-	10.9	0.261
		Yes	74	5		16		-		-		11.6	
Nakanishi, 2018 [58]	494	No	196	8	0,20	-	-	11	0.01	16	0.08	16.3	0.01
		Yes	298	20		-		37		39		19.4	
Hanaoka, 2017 [59]	133	No	105	4	-	0	-	11	0.032	8	0.012	-	-
		Yes	28	2		1		5		8			
Malietzis, 2016 [60]	718	No	283	26	0,079	2	0.337	45	0.920	-	-	6	0.648
		Yes	435	24		8		67		-		7	

AL - anastomotic leakage, MO – mortality, POC – postoperative complications (Clavien-Dindo ≥3), SSI – surgical site infection, LOS – length of hospital stay.

Discussion

Anastomotic leakage - the most feared complication

The anastomotic leakage represents an important factor in the short postoperative period. Frequently the anastomosis leakage is considered as the failure of the surgeon or related to the suturing technique or devices, but for a functional anastomosis, two components are mandatory: the surgeon and the host with a balanced healing process. For the healing process, malnutrition is one of the most important modifiable factors.

Kwag et al. identified the nutritional risk to be an independent factor for postoperative morbidity and associated with a high risk of AL [61]. Sometimes the early recognition of abnormalities could be essential in patients who require colorectal surgery. For example, monitoring perioperatively the serum albumin can identify anastomotic leakage [62] or C-reactive protein (CRP) can predict anastomotic dehiscence [63]. Furthermore, inflammation has been shown to stimulate muscle wasting, ultimately inducing protein catabolism and suppressing muscle synthesis, creating a connection between sarcopenia and elevated serum CRP level [64]. The importance of the body composition or muscle mass quality assessment for a long time was neglected, but during the last decade gained attention by the progression of personalized medicine.

The association between anastomotic leakage in colorectal surgery and body composition is documented only by a few articles, all of them not earlier than 2015.

Regarding the studies reporting on anastomotic

leakage following surgical resection of CRC, different results have been reported. A retrospective observational study by Herrod et al. [51] appreciates the CT-based evaluation as a quick and easy method to assess sarcopenia and highlights the association with an increased anastomotic leak in patients with sarcopenia. Nakanishi et al. [58] in a retrospective single-center study included 494 patients who underwent surgical resection. Sarcopenia was defined based on the sex-specific skeletal muscle mass index measured by CT scan preoperatively. They found an association with male gender, low BMI, higher incidence of postoperative complications and mortality. The higher rate of anastomotic leak in patients with sarcopenia is suggestive for increased risk but is not significant. A meta-analysis performed by Sun et al. [3], indicated that patients with sarcopenia would have longer hospital stays, higher incidence of postoperative morbidity, mortality and increased infection rate, but the difference in anastomotic leakage is not significant.

Postoperative infections

Surgical site infections associated with colorectal surgery are 4 times more than any other abdominal surgery. Lieffers et al. [65] showed that sarcopenia was an independent predictor of postoperative infection and prolonged hospitalization in patients undergoing intervention for colon cancer. It seems that sarcopenia is an indicator of septic complications after CRC elective surgery. A prospective study by Huang et al. [66] on 142 patients, found that sarcopenic patients had a higher incidence of postoperative and septic complications. A well-documented study conducted by Hanaoka et al. [59] identified severe sarcopenia and open surgery as independent factors in the occurrence of infectious complications.

Cardiopulmonary complications

Besides the infectious component, the cardio-respiratory involvement is considered as an influenced complication by sarcopenia. Has been demonstrated that sarcopenia plays an important role in the comorbidity of cardiovascular disease [67]. Moreover, a study by Aro et al. [52] proved that if is followed by surgical intervention the difference in cardiopulmonary complications will be significant between sarcopenic and non-sarcopenic patients.

Length of hospital stay

Studies performed to assess the association between low skeletal muscle mass and hospitalization showed a positive association [68]. A recent study by Wang et al. recommended that sarcopenia needs to be evaluated as a perioperative risk to avoid negative outcomes as prolonged hospital stay and mortality following gastrointestinal oncological surgery [69]. Hospital stay, mortality and postoperative complications were significantly longer in patients with sarcopenia than in those without for all patients undergoing surgery for CRC and CRC metastases. Due to sarcopenia, the total hospital cost is also increased compared with patients with normal skeletal muscle mass [70].

Mortality

Sarcopenia is a prevalent syndrome and is associated with premature mortality among older adults [71]. It has been proven one by one in the past few years the importance of its negative influence on mortality in case of several diseases: liver cirrhosis [72], diabetes [73], chronic kidney disease [74] and cancer [75]. The negative impact on postoperative mortality in colorectal cancer is also demonstrated by our review.

Malietzis et al. [60] included 805 patients who were diagnosed and operated with colorectal cancer and found alarming evidence. In the thirty-day follow-up the mortality rate was significantly higher among patients with myopenic in those without myopenic obesity.

A meta-analysis by Hajibandeh et al. [76] investigated the effect of sarcopenia on postoperative mortality in patients undergoing emergency and elective abdominal procedures. They have concluded that sarcopenia is an independent predictor of postoperative mortality and the emergency condition has a poorer prognosis.

Conclusions

This review discusses the topics surrounding the relationship between sarcopenia and postoperative outcomes in colorectal cancer surgery.

While most of the studies point toward a higher prevalence of postoperative complications, a few studies show a significantly increased mortality rate among patients with sarcopenia. When anastomotic leak as a specific postoperative complication was assessed, there is no significant difference between sarcopenic and non-sarcopenic patients, but the occurrence sometimes is higher in the sarcopenic group.

There is evidence that sarcopenia is generally associated with postoperative complications, it has an important influence on surgery-related infections, cardiovascular complications, prolonged hospitalization and seems to be a good overall predictor in CRC surgery.

Additionally, adequate perioperative sarcopenia assessment can be beneficial in the early identification of the anastomotic leak to improve the postoperative outcome.

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