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Improving Outcome in Gastrointestinal and Hepatopancreaticobiliary Surgical Oncology by Preoperative Risk Assessment and Optimization of Perioperative Care

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Abstract

This chapter discusses the most important challenges in the perioperative phase of the oncology patient undergoing surgery of the gastrointestinal tract. Because of the aging population, the surgeon is ever more confronted with frail patients at risk for an adverse surgical outcome. The chapter therefore reviews factors contributing to an impaired postoperative outcome such as sarcopenia, frailty, cachexia, and malnutrition and gives an insight into their pathophysiology. Next, it provides an overview of validated preoperative classification systems to identify the patients at risk for surgical complications. Furthermore, it discusses the most essential recommendations of standardized care for patients undergoing hepatopancreaticobiliary, gastric, and colorectal surgery. Special attention is paid to the use of clinical pathways in the perioperative phase that are aimed at a multimodal approach of reducing surgical morbidity by lowering the perioperative physiological and psychological stress. Recent literature is discussed regarding care in the intensive care unit, and the final paragraph focuses on improving postoperative outcome by means of prehabilitation or exercise as well as dietary interventions and optimized nutrition.

Keywords: surgical oncology, risk assessment, frailty, sarcopenia, cachexia, clinical pathways, prehabilitation, dietary interventions

1. Introduction in surgical oncology of the abdomen

1.1. General introduction

Cancers of the gastrointestinal (GI) and hepatopancreaticobiliary (HPB) tract entail some of the most prevalent, as well as some of the most lethal, cancers worldwide [1]. Surgery for cancer of the digestive tract involves extensive and complex procedures and is associated with high complication rates [2]. In the past decades, however, the clinical outcome of patients undergoing surgery for gastrointestinal malignancies has improved significantly. Besides the changes in surgical technique, such as the introduction of minimally invasive surgery and the implementation of novel medical devices, the anesthetic and perioperative care have also evolved [3]. Patients operated with laparoscopic techniques showed a reduction in various inflammatory responses and improved immune function when compared to patients undergoing open surgery in several randomized clinical trials. These studies, however, did not take into account the change in perioperative care that was brought about by the faster recovery following laparoscopic surgery. More recent randomized controlled trials standardized care for both arms and found better outcomes for patients treated with laparoscopy and clinical care pathways, in most [4, 5], but not in all cases [6].

Many important factors have been described that influence the surgical outcome of the surgical oncology patient population. These factors are present in a wide range of surgical patients, but particularly high rates have been described in the elderly population. Aging is accompanied by high prevalence of comorbidities and a decreased functional reserve, all of which can contribute to an increased risk for complications such as delirium, pressure ulcers, infection, functional decline, and other surgery-specific complications. While the increased quality of care is advantageous for the general oncological population, improvement in outcome for elderly patients has remained relatively limited [7, 8]. This is a worrisome fact, as the aging Western population leads to an increase of elderly people diagnosed with cancer and, consequently, more elderly people in need of surgical care. Many of the currently available treatment guidelines for surgical oncology patients are based on clinical data from a patient population with a relative low number of old and more frail patients. Therefore, in order to further improve outcomes also for our most vulnerable patients, identifying those at highest risk of poor outcome is of paramount importance.

The need for tools that provide insight in our patients' health status prior to undergoing surgery has become overt. It has been shown that functional compromise, defined by several conditions such as fatigue, sarcopenia, cachexia, malnutrition, vulnerability, and frailty, has a major impact on the risk of the development of complications and on postoperative outcome

in general. These conditions show strong overlap in several clinical features, which make strict separation of these syndromes rather difficult.

Several authors have described questionnaires and tests that allow surgeons to identify the patients at high risk. With these tools, patients that are prone to developing complications can be selected for a broad range of intervention types that are aimed at optimizing the condition of the surgical patient and consequently to improve postoperative outcome. To date, a wide variety of validated risk assessment tools have been described. Some of those have already successfully been introduced into clinical practice, such as the ASA (American Society of Anesthesiologist) classification, the Surgical Outcome Risk Tool (SORT) [9], and the Surgical Risk Calculator from the American College of Surgeons [10]. Many other, more specific scoring systems or tests have been designed to assess frailty (Comprehensive Geriatric Assessment [11], Fried Frailty Phenotype [12], timed “up and go” test [13], Groningen Frailty Index [14]), or nutritional state (Short Nutritional Assessment Questionnaire (SNAQ) [15], Malnutrition Universal Screening Tool (MUST)) [12, 16]. These assessment tools are designed to identify the patients at high risk for perioperative complications and adverse outcomes. Moreover, these may help the physician in the selection of patients that may benefit from “prehabilitation” and nutritional and other interventions.

During the course of the chapter, the most important challenges for the care of the gastrointestinal surgical oncology patient will be discussed. Special attention will be paid to identifying and treating the patient at highest risk of adverse outcome. A short overview of the different tumors of the gastrointestinal tract will be provided based on tumor location, as each of these types of cancer are defined by specific characteristics. Furthermore, the most important perioperative considerations are discussed, as well as the most common complications and their management.

1.2. Types of cancer

1.2.1. Esophageal cancer

Esophageal cancer is the eighth most prevalent cancer and the sixth most frequent cause of cancer-related death worldwide. Global incidence is threefold higher in men as compared to women. With a mortality:incidence ratio of 0.88 esophageal cancer has a poor prognosis, which resulted in 400,000 deaths in 2012 [1]. Over 95% of esophageal cancers consist of squamous cell (SCC) and adenocarcinomas. Incidence of SCC is especially high in Iran and Asia (the so-called esophageal cancer belt) [3]. In Western countries, incidence of adenocarcinomas has increased substantially over the past decades, of which the most frequently affected sites are the esophagogastric junction (ECJ) and the gastric cardia [17–20]. Alcohol consumption and smoking are the main risk factors in the etiology of esophageal cancer [21–24]. Others are Barrett’s esophagus, gastroesophageal reflux disease, poor diet and high body mass index [24]. Currently, radical surgical resection is considered the standard treatment for resectable esophageal carcinoma (T1-3N0-3M0) [25, 26]. Proximal and mid-esophageal tumors are approached transthoracically, distal tumors are resected through either transthoracic or transhiatal approach. Neoadjuvant chemoradiation has shown to improve local control and

survival and is commonly performed [27–30]. In case of unresectable carcinomas or contraindications for surgery, chemoradiation can be performed depending on the patient's condition [31–33].

1.2.2. Gastric cancer

Gastric cancer is the fifth most prevalent cancer and the third most common cause of cancer related death worldwide. About half of all cases occur in eastern Asia [1]. There are two types of gastric adenocarcinoma: the intestinal and the diffuse type. Both can be induced by *Helicobacter pylori* infection, the primary cause of gastric cancer [34]. Gastric ulcers, adenomatous polyps and intestinal metaplasia are known precursor lesions in the intestinal type gastric cancer, while no clear precursor lesions can be indicated for the diffuse type [35]. Smoking and alcohol consumption are important risk factors, as well as dietary factors such as high salt and low vegetable intake [36, 37].

In Western countries, gastric cancer is often diagnosed at an advanced stage [38, 39]. Proximal tumors are known to be more aggressive and to have a worse prognosis compared to distal gastric cancers [40]. Curative treatment is not possible in case of distant metastasis [41], leaving only 50% of patients eligible for curative surgery. Partial or total gastrectomy is performed depending on tumor location, clinical stage, and histological type. The extent of lymphadenectomy remains a topic of debate [42, 43]. Tumors of the esophagocardial junction (ECJ) and cardia are treated, like esophageal cancers, with neoadjuvant chemoradiation. To date, there is no clear consensus in literature regarding (neo-)adjuvant therapy for noncardia gastric cancers. It has been shown, however, that perioperative chemotherapy significantly improves survival [44, 45].

1.2.3. Cancer in the liver

Most of the malignant lesions that are diagnosed in the liver are metastases from primary tumors that are located in other organs. The majority of those metastases are of colonic or rectal origin, so-called colorectal liver metastasis (CRLM). The liver is the first organ in which colorectal tumors metastasize due to the venous drainage of the gastrointestinal tract via the portal vein. Radical surgical resection is the established curative treatment for CRLM.

Partial liver resections can be performed through anatomic or nonanatomic approach, depending on tumor localization and its relation to the portal vein, hepatic vein, and hepatic artery. Important considerations for performing liver surgery for CRLM are to ensure sufficient residual liver volume after resection and to plan a radical resection. Tumor size, the number of metastases, the patient's age, narrow resection margin, extrahepatic disease, synchronicity, and primary tumor stage can all be taken into consideration but are no absolute contraindications for performing a partial liver resection for CRLM. In case, a radical surgical resection cannot be performed, radiofrequent and microwave ablation techniques and stereotactic radiotherapy can be considered as alternative treatment.

In the case of CRLM, the majority of the patients receive (neo-)adjuvant chemotherapy because of the presence of metastatic disease. Chemotherapy can be used for down staging of the

tumors and to increase resectability. Because of its negative effects on the liver parenchyma, a larger residual liver volume must be ensured if chemotherapy was administered preoperatively.

Primary liver cancer occurs in the liver as well, usually as hepatocellular carcinoma (HCC). HCC has a mortality:incidence ratio of 0.95 liver cancer is the second most frequent cause of cancer death in the world, resulting in approximately 745,000 deaths in 2012 [1]. It is the sixth most prevalent cancer worldwide and incidence rates are about two- to threefold higher in men compared to women [1, 46]. Chronic liver disease (i.e., chronic hepatitis B or C infection, hereditary hemochromatosis, nonalcoholic fatty liver disease) and cirrhosis are associated with increased risk of hepatocellular carcinoma (HCC) [46–48]. Echographic surveillance in patients at increased risk can detect HCC at an earlier stage [49]. Depending on performance status, Child-Pugh classification and clinical stage, a partial liver resection or liver transplantation may be indicated [48]. Up to 80% of liver volume can be resected, provided the quality of the residual volume is high enough for regeneration and to avoid liver failure. In short, postoperative morbidity and mortality rates are only acceptable in patients with Child Pugh A and without portal hypertension. Therefore, due to liver dysfunction, most patients are ineligible for surgical treatment. Treatment options for unresectable HCC include radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), transcatheter chemo-embolization (TACE), stereotactic radiotherapy, and systemic chemotherapy [50–55].

1.2.4. Pancreatic cancer

Despite diagnostic and therapeutic advances, pancreatic cancer has a very poor prognosis. It is the twelfth most prevalent cancer worldwide yet the seventh most frequent cause of cancer-related death (M:I ratio 0.98) [1]. The majority of cases occur in western countries (possibly due to underdiagnosis in less developed regions) [1]. Smoking is a main risk factor associated with increased risk of pancreatic cancer [56, 57], as well as chronic pancreatitis [58, 59], high body mass index [60, 61], and having a first-degree relative with pancreatic cancer [62–64]. The majority of tumors are ductal adenocarcinomas and over 95% arises from the exocrine elements of the pancreas. Surgical resection is considered the only potentially curative treatment, however only about 15–20% of patients are eligible for a pancreaticoduodenectomy (Whipple) [65]. Prognosis is poor even in those patients; 5-year survival is about 10% in case of node-positive and about 25–30% in node-negative disease [66–68]. Tumor characteristics are the only significant prognostic factor influencing survival after surgery [69]. Adjuvant chemotherapy has proven to improve disease free survival [70–72]. Neo-adjuvant chemoradiation, as this may improve resectability of the tumor, decreases recurrence rates [73–76]. In a palliative setting, chemotherapy and biliodigestive bypass surgery can be useful [77–81].

1.2.5. Cancers of the biliary tract

Cancers of the gallbladder and of the bile duct are less common, however, highly fatal as they are often diagnosed at an advanced stage. Gallbladder carcinoma accounts for around 1.3% of cancer incidence worldwide and is one of the few malignancies that is more common in females than in males [1, 82, 83]. Statistics on cholangiocarcinoma are less accurate

as intrahepatic cholangiocarcinomas are often included in the primary liver cancers. Gallstone disease, gallbladder polyps, congenital biliary cysts, anomalous pancreaticobiliary junction, and chronic cholecystitis are predisposing factors for developing gallbladder cancer. Risk factors for cholangiocarcinoma include primary sclerosing cholangitis, choledochal cysts, chronic hepatolithiasis (recurrent pyogenic cholangitis), and chronic liver disease.

Resectability is dependent on the degree of infiltration into the proximal bile ducts and liver tissue, the absence of distant metastasis and involvement of the hepatic artery and/or portal vein and the expected residual liver tissue volume [84, 85]. To ensure radical (R0) resection of these aggressive tumors, extensive liver resection and resection of other neighboring organs is sometimes necessary [86–88]. The radicality of the resection is the most important prognostic factor [89, 90]. The adequate surgical approach is selected based on tumor location and extent of tumor ingrowth. A Whipple procedure (pancreaticoduodenectomy) may be indicated in case of a distal cholangiocarcinoma. In the preoperative setting, biliary drainage and/or embolization of the portal vein may be indicated [91–94]. The role of (neo-)adjuvant chemo- and radiotherapy remains controversial and is not part of standard treatment [88, 95–97].

1.2.6. Colorectal cancer

Colorectal cancer (CRC) is the second most prevalent cancer in women, and the third most prevalent in men worldwide. The majority of cases occur in the Western world, although in recent years an increase of CRC incidence has been observed in developing countries as well, which is likely to be a consequence of the adoption of Western lifestyle and diet. CRC resulted in 694,000 deaths in 2012, which makes it the fourth most frequent cause of cancer death [1]. In developed countries, the incidence and mortality have decreased over the past decades, which is largely attributable to the implementation of better screening tools and national screening programs [98–100].

Age, adenomatous polyps, genetic factors (FAP, HNPCC), inflammatory bowel disease, history of abdominal radiotherapy, and lifestyle are the main factors associated with increased risk of colorectal cancer [101–106]. The vast majority of colorectal cancers are adenocarcinomas. All tumors originate from adenomas or flat dysplasia. Tumors of the right colon are more polypoid shaped as opposed to the annular tumors in the left colon. The prognosis for both tumor locations is, however, similar [107]. Radical resection remains the cornerstone of curative treatment. The surgical approach of choice depends on tumor location and size (i.e., right/left hemicolectomy, low anterior resection, total mesorectal excision, or abdominoperitoneal resection). In case of locally advanced (T4) tumors, en-bloc multivisceral resection is advised [108, 109]. Local recurrence is more common in rectal cancer due to difficulty in obtaining adequate resection margins. In rectal cancer, neoadjuvant radiotherapy or chemoradiation may be indicated depending on disease stage. Neoadjuvant chemoradiation is also usually considered in case of locally advanced colon cancer [108]. Adjuvant chemotherapy has only proven to be beneficial for lymph node positive colon cancer.

2. Current challenges in gastrointestinal, hepatobiliary, and pancreatic surgical oncology

2.1. Frail elderly

With the aging of the population, patients undergoing surgery for gastrointestinal and hepatobiliary and pancreatic cancers are also becoming older: one of every three cancers is diagnosed in patients aged 65 years or older. A more worrying fact, however, is that the majority of cancer-related deaths occur in this group of patients [110]. Older patients are at increased risk for perioperative complications [111], which may lead to prolonged hospital stay, decreased quality of life and independency, increased disability and health-care costs, and increased mortality [112]. Nevertheless, carefully selected patients seem to benefit from surgery in the long-term [113]. Therefore, preoperative risk assessment, and multimodal perioperative care for elderly patients remain of paramount importance in the light of changing patient demographics [114]. Various risk classification systems, such as the American Society for Anesthesiologists (ASA) classification, Charlson Comorbidity Index, and the Eastern Cooperative Oncology Group (ECOG) performance status, have been developed to categorize patients' preoperative condition [115–117]. However, many of these classifications are inaccurate; they are subjective or focus on a single organ system [118]. The ASA classification for instance, shows large intraobserver variability [116, 119], and lacks specificity for cancer patients, who are known to have an altered metabolism that may affect ASA-score.

Factors contributing to an impaired postoperative outcome for vulnerable (elderly) patients are frequently referred to as “frailty.” Frailty has gained attention as a risk factor for adverse outcome after surgery over the past decades. Screening for and the assessment of frailty can aid risk assessment and therefore facilitate the decision making process for both patients and physicians. The concept of frailty was defined as a biologic syndrome, characterized by a decreased reserve and resistance to stressors [12, 109]. It incorporates a number of areas of functioning, including weight loss, muscle weakness (e.g., grip strength), slowness, low activity, and increased disability [12]. Increased 6-month mortality was observed in frail individuals in a study of patients who underwent major surgery (i.e., procedures that required standard ICU admission) [120]. Geriatric markers for frailty (e.g., cognitive function, poor nutritional status, falls, depressed mood, and anemia) were predictive for adverse outcome in this study [120]. Furthermore, increased complication rate and length of stay were observed in frail patients who underwent elective surgery [121]. Finally, frailty was shown to be associated with increased surgical complications, postoperative mortality, health care costs, and length of stay [118, 120, 122].

2.2. Sarcopenia and cachexia

A modifiable, hallmark sign of frailty is sarcopenia, a geriatric term for the involuntary loss of skeletal muscle mass and density [123–125]. The prevalence of sarcopenia increases with age; from 9% at 45 years to 64% at 85 years in healthy ambulatory individuals [126]. This condition is characterized by a loss of skeletal muscle mass and strength [127], leading to physical

impairment and disability in geriatric populations [128, 129]. Multiple studies have shown an association between the presence of sarcopenia and adverse outcome after surgery. For instance, following surgery for colorectal liver metastases, sarcopenia negatively affected short-term outcome with increased morbidity and mortality rates. In a study published in 2011 [130]. Sarcopenia also negatively influenced long-term outcome in patients who underwent surgery for pancreatic adenocarcinoma (i.e., 3-year survival), as well as for patients undergoing surgery for colorectal liver metastases (i.e., 5-year disease free and overall survival) [131, 132]. Similar studies found an unusually high prevalence of sarcopenia (57.7% of 180 patients) in Western gastric cancer patients [133]. However, this study did not find any association with adverse outcomes in patients with sarcopenia. Another recent study in Asian gastric cancer patients described a much lower prevalence of sarcopenia (12.5% of 255 patients). This study combined CT-scan measurements with hand-grip strength and get-up-and-go tests to define sarcopenia. In this study, sarcopenia was found to be an independent risk factor for postoperative complications [134]. Besides sarcopenia, older cancer patients may also suffer from cancer induced cachexia, a clinical condition leading to skeletal muscle loss with or without the loss of adipose tissue due to anorexia (resulting from e.g. metabolic changes) and malnutrition (resulting from e.g. (chemotherapy induced) nausea and loss of appetite) [135, 136]. It is estimated that cachexia is the cause of up to 30% of cancer related deaths [137, 138]. Sarcopenia and cachexia are therefore separate but overlapping entities, with different pathways that both lead to skeletal muscle wasting [139]. The assessment of sarcopenia will be elucidated further in the third paragraph.

2.3. Body composition and chemotherapy

Although surgery remains the cornerstone of curative cancer treatment in all gastrointestinal and hepatopancreatobiliary malignancies, a substantial part of patients is treated with chemotherapy [29, 140]. This could be either in a neoadjuvant setting to reduce the tumor load, as well as in an adjuvant or palliative setting in patients with locally advanced/metastasized disease or recurrence, respectively.

A recent report described that skeletal muscle loss during neoadjuvant chemotherapy is associated with poor short-term outcome in esophageal cancer patients [141]. Two other studies did not find an association with overall (long-term) survival [142, 143]. In a study among breast cancer patients who received neoadjuvant therapy, sarcopenic patients were more likely to have a complete pathologic response compared to nonsarcopenic patients [144]. Substantial loss of body weight, adipose tissue and skeletal muscle mass have been reported among pancreatic cancer patients who received neoadjuvant radiochemotherapy within phase I and II clinical trials. [145, 146]. Although the resection rate could not be predicted by body composition parameters (i.e., weight loss, overweight/obesity (pre-/posttreatment), sarcopenia with or without overweight/obesity), the extent of skeletal muscle and visceral adipose tissue loss was negatively associated with disease-free survival and overall- and progression-free survival, respectively [145]. Finally, an increasing number of studies show that low skeletal muscle mass is an independent determinant of chemotherapy toxicity in different patient populations treated with various chemotherapeutics [147–153]. Chemotherapy toxicity

frequently leads to dose limitation or abortion of therapy. Consequently, this may lead to less effective cancer treatment and impaired (disease-free) survival. Therefore, it is suggested that it would be better to base dose normalization on skeletal muscle mass rather than body surface area (BSA), as is commonly performed [147].

3. Identifying the patient with high perioperative risk

3.1. Preoperative assessment

Risk assessment in order to identify patients at risk for postoperative adverse events is a complex effort. It is made even more difficult by the great variety of primary diseases as well as comorbidities in surgical oncology patients.

Classically, preoperative risk assessment is based on a complex interaction of the clinician's view of the general status of the patient and The consideration of factors such as age, comorbidities and ASA classification. This can be a subjective process and its interpretation can vary greatly between clinicians. Even the assessment of the ASA classification seems to be a relatively subjective process [154]. Consultation of an experienced anesthesiologist is often advised for patients with a compromised physical status (e.g., ASA 3–4) or who are scheduled to undergo major surgical interventions that can cause physiological derangements.

3.2. Risk factors for adverse outcome

Gastrointestinal surgical oncology patients are often elderly patients. The elderly are at an increased risk for adverse events and mortality [155, 156]. A patient's ability to cope with surgical stressors is determined by a multitude of factors, of which physiological reserves are the most important. In recent years, improvements have been made to identify more objective risk factors for adverse outcome after surgery. These include comorbidity classifications, geriatric frailty assessment, sarcopenia, and malnutrition assessment.

3.3. Comorbidities

Almost all patients who undergo major gastrointestinal surgery have some degree of comorbidity. In order to classify these comorbidities and to determine a risk stratification for mortality, the Charlson Comorbidity Index (CCI) was introduced [115]. This index was also used for prediction of mortality risk after complex gastrointestinal surgery in a later study [157]. In Asian elderly patients (octo- and nonagenarians) undergoing surgery for gastric cancer, a CCI ≥ 5 was associated with a higher postoperative mortality rate [158]. In another study in elderly Italian patients who underwent curative surgery for gastric cancer, the presence of comorbidity and not age was the only independent risk factor for mortality [130].

3.4. Frailty

Assessment of frailty as depicted above can be diverse and often incorporates different measurement modalities. These include questionnaires on self-reported health and disability,

handgrip strength measurements, timed get-up-and-go tests and sometimes blood tests (hemoglobin, albumin). These measurements make frailty assessment difficult in an outpatient setting. Therefore, fast and easy to perform screening questionnaires have been developed over the recent years. Examples include PRISMA-7, Fried's Frailty criteria, Hopkins Frailty score and Groningen Frailty Indicator (GFI) [159]. Questionnaires such as the GFI encompass multiple aspects of frailty, i.e., mobility, physical fitness, vision, hearing, nourishment (i.e., unintended weight loss), morbidity (i.e., polypharmacy), and psychosocial status [14]. Despite the comprehensive nature of these questionnaires, the percentage of patients who are identified as frail vary strongly between different risk assessment tools (11.6–36.4%) [159]. However, these questionnaires have proved to be very useful to identify patients who are at risk for the development of postoperative adverse events. In gastric cancer patients, a GFI ≥ 3 was associated with postoperative mortality and morbidity (severe complications) [160]. Frail patients had an in-hospital mortality of 23.3% compared to 5.2% for nonfrail patients. Scores higher than 7 on the Edmonton Frail scale were associated with increased complications after non-cardiac surgery (OR 5.02, 95% CI 1.55–16.25) [121]. In another study, Fried's Frailty criteria were associated with increased complications after major, oncological and urological surgeries [118]. Geriatric assessment using several questionnaires was used in a study and showed that frailty is an independent risk factor for impaired 1-year and 5-year survival after colorectal cancer surgery [161].

In conclusion, frailty screening and assessment with referral to a geriatric specialist should be included in preoperative work-up and shared decision making in elderly patients scheduled to undergo gastrointestinal surgery for cancer.

3.5. Sarcopenia

A decline in muscle mass, or sarcopenia, is a phenomenon within the process of human aging but is also part of the cachexia syndrome [127, 162]. Sarcopenia is a complex syndrome and multiple factors have been identified that contribute to its development [163]. Inadequate nutrition (low protein intake and impaired metabolism) and inactivity are important contributing elements, as well as age-related and possibly endocrine factors [127].

The assessment of sarcopenia is performed by measuring muscle surface areas on abdominal CT-scans. At a designated level (e.g., transverse processes of lumbar spine L3), total psoas cross-sectional area or total muscle surface area are measured and corrected for patient height, resulting in an L3-index (see **Figure 2**). These measurements can be performed in a semiautomated fashion by the use of image analysis software. Sex and body mass index (BMI) specific cutoffs are available to define sarcopenia. For instance: for men $43 \text{ cm}^2/\text{m}^2$ (BMI $< 25.0 \text{ kg}/\text{m}^2$) and $53 \text{ cm}^2/\text{m}^2$ (BMI $\geq 25.0 \text{ kg}/\text{m}^2$), in women L3-index lower than $41 \text{ cm}^2/\text{m}^2$ [164].

Sarcopenia, as measured by low muscle mass CT-scans, is used in a multitude of studies and has been shown to be associated with adverse outcome. However, in 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a low muscle mass in combination with either low muscle strength or low physical activity [127]. The EWGSOP defines low muscle mass as only symptom as presarcopenia.

3.6. Malnutrition

An imbalance in energy expenditure and nutritional intake is the fundamental physiological derangement that causes cancer-induced weight loss. Tumor-related factors that contribute to weight loss include early satiety, obstruction complaints, but also tumor induced metabolic changes [162]. Especially, upper GI cancer patients are at risk for malnutrition, for example, in 31-43% of gastric cancer patients there can be a weight loss of >10% in the last 6 months. [165]. Malnutrition is a well-known risk factor for adverse outcomes after upper GI surgery, including interventions for esophageal, gastric cancer, liver and pancreatic cancer [162, 166, 167].

SNAQ		MUST	
Short Nutritional Assessment Questionnaire		Malnutrition Universal Screening Tool	
- Did you lose weight unintentionally?		Have you/the patient lost weight recently without trying?	
More than 6 kg in the last 6 month	•••	No	0
More than 3kg in the last month	••	Unsure	2
- Did you experience a decreased appetite over the last months?	•	Yes, How much (kg)?	
- Did you use supplemental drinks or tube feeding over the last month?	•	1-5	1
		6-10	2
		11-15	3
		> 15	4
		Unsure	2
• No intervention		Have you/the patient been eating poorly because of a decreased appetite?	
•• Moderately malnourished; nutritional intervention		No	0
••• Severely malnourished; nutritional intervention and treatment dietician		Yes	1
		Do you feel you look frail or under your most comfortable weight?	
		No	0
		Yes	1

Figure 1. Short Nutritional Assessment Questionnaire (SNAQ) and Malnutrition Universal Screening Tool (MUST). Partly adapted from Kruijzena et al. [15] and Rahman et al. [16].

Screening for malnutrition is therefore an important aspect of the preoperative risk assessment of upper GI cancer patients. Several questionnaires have been developed to screen for malnutrition, which include: NRS-2002 (nutritional risk screening), MUST (Malnutrition Universal Screening Tool), SNAQ (Short Nutritional Assessment Questionnaire) [15, 160, 168] (**Figure 1**).

These tools provide an easy and low-cost method for nutritional risk stratification and provide an indication as to when preoperative nutritional interventions are indicated. Patients at risk for malnutrition should be referred to a dietician for nutritional analysis and supplementation if needed, in order to optimize preoperative status.

3.7. Patient selection

Upper GI cancer patients are scheduled to undergo major surgery if they are considered “fit for surgery.” Proper preoperative evaluation can identify avoidable perioperative risks. As upper GI cancer surgery is often performed in elderly patients, chronic comorbidities are frequently present.

Basic preoperative assessment, including clinical history taking and physical examination, should aim at identifying chronic comorbidities. Preoperative evaluation should uncover any chronic comorbidities, particularly cardiovascular and pulmonary disease [169]. Advice from other departments should be obtained, e.g., adjustment of pulmonary medications and

corticosteroid supplementation in patients with pulmonary disease. This helps minimizing avoidable perioperative cardiopulmonary complications.

Another important risk factor for adverse outcome is the presence of diabetes mellitus. This should therefore be optimally controlled pre- and perioperatively. If necessary, referral to a specialist is recommended.

Referral to a geriatric specialist can be very helpful in the preoperative setting, especially for frail elderly. Advice can be obtained in the perioperative stage on prevention of delirium, and of physical and cognitive decline.

Exercise tolerance is also an important aspect to judge physiological reserves. It is most often determined by the patient's cardiopulmonary limitations. Metabolic equivalents of a task (MET) can be helpful with assessing exercise tolerance. Patients who are able to perform four MET's or greater are regarded to have a low risk for perioperative morbidity [169]. Climbing a flight of stairs roughly equates to four MET's; when patients are able to do so, they are considered to be fit for elective surgery.

When patients are adequately evaluated, risks can be communicated between treating physicians, patients and family members. If the patient is deemed fit for surgery, these preoperative consultations help provide an optimal perioperative environment for patients and minimize the risk of preventable complications.

4. Standardized care by the use of clinical pathways

An increasing number of surgical procedures are performed each year for abdominal malignant diseases. The indications for surgery are expanding and the surgical techniques are becoming more sophisticated. However, surgical morbidity remains high, especially after major abdominal surgery such as gastric, esophageal, liver, pancreatic or colorectal surgery. There is an increasing need for protocolized care and new care pathways for surgery to reduce surgical impact and perioperative morbidity [170].

Since the last decade of the twentieth century, fast-track or enhanced recovery care protocols for surgical care gained popularity. These clinical pathways are aimed at reducing surgical morbidity by reducing the perioperative physiological and psychological stress and enhancing patients' recovery (see **Figure 2**) [171, 172]. The physiological changes a patient must endure during and after surgery are influenced by many different factors. Therefore, enhanced recovery pathways are aimed at a multimodal approach in which the surgeon, anesthesiologist, nurse, nutritionist, and physiotherapist all contribute in improving the patient's recovery [173–175].

As mentioned before, the surgical stress is influenced by many factors, such as the surgical procedure itself, intraoperative hypothermia, low glucose levels due to perioperative fasting, intraoperative anesthetics, pain, and being bedridden. These stressors are specific targets for enhanced recovery pathways. The key elements in enhanced recovery pathways are mini-

mized preoperative fasting, limited use of incisions, catheters, and drains, early resumption of oral diet, early mobilization after surgery and optimal pain control using patient controlled (epidural) analgesia [170, 173, 174, 176–178].

These elements relieve patients of previously described stressors that are the cause of postoperative morbidity and delayed recovery. The result of enhanced recovery pathways can be seen in a reduction of postoperative complications and subsequently a shortening of median hospital stay [179–181].

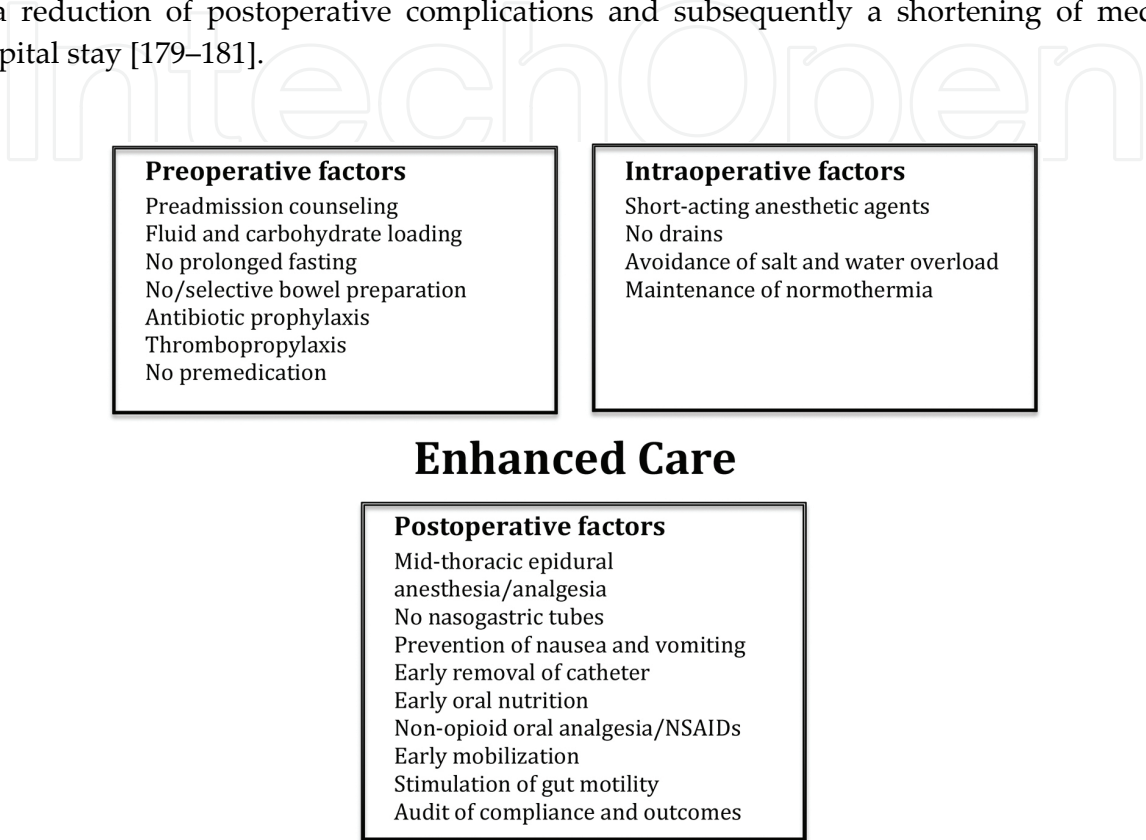


Figure 2. Important elements of enhanced care protocols for perioperative care.

4.1. Upper GI surgery

4.1.1. Standardized postoperative care

A number of general enhanced recovery pathways developed for colorectal cancer are also applicable to esophageogastric surgery patients. Aspects that will be discussed in this section are preoperative nutrition, timing of postoperative oral intake, use of nasogastric and decompression catheters, early mobilization, and urinary catheter use.

As stated before, malnutrition is associated with adverse outcome in esophageogastric surgery [182, 183]. Although evidence for preoperative feeding interventions is limited [184], it is still recommended to screen for and treat malnutrition in gastroesophageal cancer patients by optimization of nutritional intake with oral feeding supplements [178, 185]. Dietary interventions have not shown to be beneficial in patients who do not suffer from malnutrition [186].

Nasogastric decompression recommendations during the postoperative phase are different after gastric and esophageal surgery. Evidence against nasogastric decompression after gastrectomy is strong, as several meta-analyses show deleterious effects of routine nasogastric tube placement [187, 188]. Furthermore, its routine use does not reduce surgical morbidity. Additionally, patients without decompression have fewer pulmonary complications, earlier passage of flatus, earlier resumption of oral intake, and a shorter length of stay [188].

In patients undergoing esophagectomy, in contrast to gastrectomy patients, gastric conduit decompression is recommended. The aim of the nasogastric tube is to prevent gastric stasis, pain, vomiting, and aspiration. On the other hand, nasogastric tubes are associated with increased epistaxis, dislodgement of the catheter, and pulmonary infections [189]. One RCT that studied the effect of nasogastric tube decompression, however, found a reduction in pulmonary complications [190]. All in all, gastric conduit decompression via nasogastric tube is recommended [185].

Timing of resumption of oral diet is challenging after gastrectomy and esophagectomy with important differences between the two. After gastrectomy, there is evidence to support early resumption of liquid intake (the first day following surgery) and to further increase this according to tolerance, starting with light food on day two [178]. Conversely, there are no studies that report adverse outcome after early and patient controlled introduction of oral diet in gastrectomy patients [178].

Resumption of oral intake after esophagectomy is somewhat unclear and traditionally conservative. There are some studies that have investigated early oral intake after gastric and gastroesophageal resection [191, 192]. After total gastrectomy ($n = 77$) and esophagectomy ($n = 2$), earlier discharge was seen in the enteral feeding group [192]. However, no esophagectomy-specific studies have been published on this subject, which makes it difficult to give evidence-based recommendations.

After esophagogastric surgery, nutritional support is indicated if 60% of desired oral intake is not achieved by the end of the first week, as is suggested by a large review [162]. High-energy oral sip feeds is the preferred method, but enteral tube feeding can be used when this is not possible.

Strong evidence exists that bed rest is associated with several adverse outcomes. For example, even in healthy individuals, bed rest has been shown to decrease maximal oxygen uptake (VO_2 max) [193]. Despite this, very few specific postoperative protocols have been developed with good evidence-based support [194]. Nonetheless, early postoperative mobilization from day one, which can be supported by written day-to-day patient instructions, is regarded as good practice [178, 185]. Adequate analgesia is a requirement for effective early mobilization.

Urinary catheters are often used for patients monitoring, especially in the early postoperative stage. However, there are some notable disadvantages for the use of catheters, including restricted patient mobility and an increased risk of urinary tract infection. Furthermore, they have shown to be a predictor for longer length of stay [195]. Transurethral catheters can and should be removed on day one or two postoperatively if the presence of the catheter is not required for monitoring [178].

In conclusion, many aspects of enhanced recovery pathways can be implemented in upper GI surgery. However, there are some points specific to upper GI that require special attention. These include the use of nasogastric tubes, early mobilization, timing of resumption of oral diet, and use of urinary catheters. These points are generally not well studied but recommendations for daily practice can be made using the available evidence as outlined above.

4.2. Colorectal surgery

4.2.1. Colorectal surgery

Colorectal carcinoma (CRC) is the fourth most common cancer worldwide for both males and females. Surgery remains an important aspect of curative treatment of CRC, and also the patient in the palliative setting is frequently operated on due to the obstructive nature of the disease. Perioperative care for patients undergoing colorectal surgery has improved significantly over the past decades, mainly due to the introduction of enhanced recovery pathways and the implementation of less invasive surgical techniques. It has been shown that these programs have a positive influence on the duration of the hospital admission and overall complication rate [196].

The recommendations that are supported by grade A evidence will be further elucidated in this section. Furthermore, recommendations that require further high quality research will be mentioned here as well.

Preoperative preparation of the patient includes fasting protocols and mechanical bowel preparation. Recent guidelines have altered the traditional nil by mouth period (fasting from midnight) to a minimum period of two hours, based on a high-quality meta-analysis [197]. It has been shown that prolonged fasting before surgery does not increase the pH of gastric content nor does it influence the aspiration risk during and after surgery.

Mechanical bowel preparation (MBP) has been used in combination with oral antibiotic therapy since the 70's to decrease the bacterial load in the bowel lumen prior to surgery. However, from the many studies have been conducted since, no convincing evidence arose regarding the beneficial effects of MBP alone, which in part explains why MBP has been abandoned in many institutions. In fact, several articles described possible harmful effects associated with mechanically cleansing the bowel, such as prolonged postoperative ileus and spillage of bowel content into the abdominal cavity [198]. However, none of these studies included an arm where a combination of MBP and oral antibiotics was compared to MBP and oral antibiotics alone. Furthermore, several studies have shown a reduced length of stay and lower risk of surgical site infection when patients were subjected to both oral and mechanical bowel preparation [199, 200].

Another important change that has been observed in daily practice is the intravenous administration of antibiotics as opposed to oral administration, mostly because of practical reasons. A recently conducted Cochrane Review has focused on the timing, type and administration route of antibiotic prophylaxis and, but concluded that robust evidence on this is still lacking [201]. It seems that a combination of oral and intravenous prophylaxis is most effective in

decreasing the risk of surgical site infection, as are antibiotics that cover both aerobic and anaerobic bacteria [201]. For intravenous antibiotics, it is generally accepted that the optimal timing of administration is 30–60 min before surgery [202]. No recommendations can be made for timing of oral antibiotics based on the available literature.

An important way of reducing the surgical stress is the use of epidural analgesia. It reduces the use of opioids during the postoperative phase, which in turn provides rapid awakening, early intake and mobilization, and therefore improves gastrointestinal motility [203]. Besides the adverse effects on postoperative ileus, important side effects of opioids on the respiratory function and central nervous system have been described [204]. There is an important lack of level A evidence against the use of NSAIDs during the postoperative phase. However, retrospective data and animal studies have shown an increased risk for anastomotic leakage with the use of NSAIDs [205–207]. It is therefore recommended to refrain from the prescription of NSAIDs following colorectal surgery.

4.3. HPB surgery

In some centers worldwide that perform hepatopancreatobiliary surgery, similar enhanced recovery pathways have been implemented as to those that have been described in the previous sections for gastroesophageal and colorectal surgery. Naturally, there are similarities between the pathways for gastrointestinal surgery and HPB surgery such as early resumption of oral intake, early mobilization, the use of laxatives postoperatively and the use of epidural analgesia [176, 208, 209]. There are, however, a number of important specific considerations for enhanced care pathways in the field of liver and pancreatic surgery that will be addressed in this section.

4.3.1. Liver surgery

Laparoscopic surgery is being practiced increasingly more in the field of abdominal surgery in general and has become the gold standard for many procedures such as the cholecystectomy. Minimal invasive keyhole surgery decreases postoperative morbidity and facilitates faster recovery after surgery. Minimizing incisions is one of the elements of many enhanced care pathways for that reason. Due to surgical technical challenges, the laparoscopic approach for liver surgery was introduced later than for gastrointestinal surgery. In the early period of laparoscopic liver surgery, only minor liver resections were performed, such as the left lateral sectionectomy [210]. Today, the number of laparoscopic liver surgery procedures is growing both for minor and major liver resections, yielding promising results [211, 212].

Traditionally, the placement of prophylactic intra-abdominal drains after liver surgery is a strategy that has been used for the early detection of postresectional hemorrhage and bile leakage. Intra-abdominal drains, however, have negative effects as well; they can cause ascending intra-abdominal infections and can be uncomfortable for the patient, thereby delaying postoperative recovery. In this day and age, with improved abilities to perform CT- or ultrasound-guided drainage of intra-abdominal fluid collections, abdominal drains have

become obsolete for uncomplicated partial liver resection when regarding the number of postoperative complications and reinterventions [213]. In some cases, the use of a prophylactic drain can be advocated, for example, when surgery with vascular or biliary reconstruction is performed or when, in the case of central liver resection, the risk of a postoperative biloma or hemorrhage increases [214, 215].

4.3.2. *Pancreatic surgery*

Pancreatic adenocarcinomas are notorious for causing severe weight loss in patients, and, as mentioned before, cachexia is an important challenge in this patient group. Therefore, an optimal preoperative nutritional status is a key element in the enhanced recovery pathways for pancreatic surgery. Fortunately, the majority of the patients that undergo a pancreatic resection are not malnourished and have minor to intermediate weight loss. This group does not need additional nutritional support. However, patients that do suffer from severe weight loss and are in a state of malnourishment are in need of receiving additional nutrition. This can be administered either by oral supplements or by enteral tube feeding if necessary [176, 216].

Cholestasis is one of the side effects of pancreatic carcinoma. This occurs when the common bile duct is obstructed by the tumor mass. Preoperative biliary drainage of the common bile duct should be considered in severe jaundiced patients. Preoperative biliary drainage can be performed by the placement of a stent in the common bile duct via endoscopic retrograde cholangiopancreatography (ERCP). When the common bile duct is inaccessible via ERCP due to impassable obstruction in the bile duct or duodenum, biliary drainage can be performed via percutaneous transhepatic cholangiography (PTHC). A serum bilirubin concentration $>250 \mu\text{mol/l}$ is associated with an increased risk of postoperative morbidity. Patients with a higher serum concentration of bilirubin should therefore receive preoperative biliary drainage [176, 217].

In most enhanced recovery protocols, the routine use of prophylactic abdominal drains after surgery is discouraged because of drain-related morbidity. There has been a recent debate on the routine use of prophylactic abdominal drains after pancreaticoduodenectomy (PD). After a PD, an abdominal drain is normally placed for early detection of anastomotic leakage or hemorrhage. Leakages of the pancreaticojejunostomy or the hepaticojejunostomy can have detrimental effects and are potentially lethal. However, drain-related complications have also been reported, and earlier studies with small patient groups showed promising results regarding postoperative complications in patients that were treated without a prophylactic abdominal drain [218]. In addition, early drain removal was shown to be beneficial for postoperative morbidity [219]. In a recent RCT, the abandonment of prophylactic drain use had a detrimental effect on postoperative mortality. Therefore, prophylactic drain use is still advised for safe postoperative care after PD in all patients [220, 221]. In the coming years, new evidence will have to show if the use of prophylactic abdominal drains can be abandoned in low-risk patients undergoing a PD.

4.4. ICU care

4.4.1. Handover

The transfer from the operating theatre to the intensive care unit is the first step in standardized postoperative care, and should therefore be considered a crucial one. Agarwal et al. report a substantial improvement in quality of the handover when using a standardized and structured method of communication in pediatric patients who underwent cardiac surgery. They compared the knowledge of medical providers regarding patient information following the handover by means of a questionnaire. The knowledge of the clinical team members after the structured handover was 92% compared to 69% in case of the verbal handover. Furthermore, the outcome differences between these two groups were assessed. In the verbal handover group, 5.4% were in need of cardiopulmonary resuscitation compared to 2.6% in case of the structured handover ($p = 0.043$). The same was true for the need of mediastinal re-exploration: 9% versus 5.5% respectively ($p = 0.043$). Metabolic acidosis occurred in 6.7% of cases of verbal handover versus 2.6% structured handover ($p = 0.004$) and successful early extubation could be conducted in 43.2% and 50% respectively ($p = 0.04$). It could therefore be concluded that a structured handover should be a part of the standardized postoperative care.

4.4.2. Extubation

Early extubation is known to be a predictive factor for early discharge. Cheng et al. already stated that early extubation led to a decrease of 25% of the total costs of CABG surgery. This cost reduction is a result of early discharge of the ICU and, consequently, from the hospital itself. Consequences for the patients are not described in this article but can be imagined. In cases of intubation, patients are often sedated and immobile. Immobilization induces a significant decrease in muscle mass and strength. As stated before, the loss of muscle mass strongly hampers recovery in oncological surgery.

4.4.3. Mobilization

Mobilization is a crucial part of enhanced recovery programs that has been explained earlier in this chapter. In case of ICU admittance, the patient usually receives cardiovascular support by means of vasopressin or respiratory support by mechanic ventilation and oxygenation. Obviously, these conditions make mobilization rather difficult. However, Brahmhatt et al. conducted an intervention-based study in which the intervention group ($n = 49$) was subjected to daily interruptions of sedation. Patients in the intervention group received physical and occupational therapy during the earliest days of critical illness. Outcome parameters were functional status at hospital discharge, duration of delirium and ventilator-free days during the first 28 days. In 29 patients (59%) of the intervention group independent functional status was reached compared to 19 patients (35%) of the control group ($n = 55$) ($p = 0.02$). Furthermore, a shorter period of delirium (median 2 days) was observed in the intervention group compared to 4 days in the control group ($p = 0.02$), as well as a significant increase in ventilator free days: 23.5 versus 21.1 days respectively ($p = 0.05$).

4.4.4. *Complication management*

The intensive care unit uses several instruments to increase insight into risk management. The most used and internationally recognized are the Simplified Acute Physiologic Score (SAPS), Sequential Organ Failure Assessment (SOFA), ASA-score, and Acute Physiology and Chronic Health Evaluation (APACHE score).

4.4.5. *SAPS score*

The Simplified Acute Physiologic Score, otherwise known as SAPS, can be used to predict hospital mortality. Patients with a higher SAPS score have a higher mortality. The latest version of the SAPS score instrument is SAPS II. SAPS III has also recently been validated. Recent studies show a good discrimination by SAPS III, but a poor calibration.

4.4.6. *SOFA score*

The SOFA score consists of six different scores, which are organ specific. These score the respiratory, nervous, renal, and cardiovascular system, liver and coagulation. Each item can be scored between one and four, which results in a score between seven and 28.

American Society of Anesthesiologist (ASA) Physical Status	
Category	Description
ASA 1	Healthy patient
ASA 2	Mild to moderate systemic disease caused by the surgical condition or by other pathological processes, and medically well controlled
ASA 3	Severe disease process which limits activity but is not incapacitating
ASA 4	Severe incapacitating disease process that is a constant threat to life
ASA 5	Moribund patient not expected to survive 24h with or without an operation

Figure 3. American Society of Anesthesiologist (ASA) categorization.

4.4.7. *ASA classification score*

Originally, the ASA physical status classification system was developed by the American Society of Anesthesiologists and consisted of five categories (see **Figure 3**). The system was designed to have a quick method to classify the physical fitness of patients. Later a sixth category was added.

4.4.8. *APACHE score*

The APACHE score was originally designed for patients in the intensive care unit. The designers were trying to develop a quantification method for the severity of disease of ICU-admitted patients.

The score is calculated by the use of different parameters: PaO₂, temperature, mean arterial pressure, arterial pH, heart rate, respiratory rate, Glasgow Coma Scale and blood analysis for sodium, potassium, creatinine, hematocrit, and white blood cell count. All of these measurements should be conducted in the first 24 hours of admission; the score should not be changed

during the course of admission. The latest version is the APACHE IV, which has been constructed using a new logistical regression equation, a different set of variables and statistical modeling to improve accuracy.

5. Improving postoperative outcome

5.1. Cardiopulmonary exercise testing

With expanding indications for surgery and a population that grows increasingly older, patient selection for extensive surgery becomes more important. To assess if patients are fit for major abdominal surgery, surgeons and anesthesiologists need objective tools. Cardiopulmonary exercise testing (CPET) can be used as an objective instrument to assess the cardiopulmonary fitness of a patient in an outpatient setting.

The test originated from exercise physiology, and was later adopted by other clinical departments for the determination of physical condition. Since recent years, different surgical departments use CPET to objectively assess high-risk patients before taking the patients to the operation theatre.

Cardiopulmonary exercise testing is an objective way to assess a patient's maximal cardiorespiratory fitness. CPET is performed on a cycling ergometer or on a treadmill. During the test, ventilation gas exchange parameters are measured by breath analysis and cardiac parameters are monitored by electrocardiogram. Ventilation gas analysis is used to determine oxygen and carbon dioxide exchange. Different protocols can be used for CPET, but cycling ergometry with an incremental or 'ramped' workload is most common [222].

By gradually increasing the workload for the patient, the oxygen demand in the muscles also increases. When the oxygen demand exceeds oxygen delivery, the anaerobic threshold (AT) is passed. The AT, together with the maximal or peak oxygen uptake (VO_{2peak}), is valuable parameters which reflect the maximal cardiopulmonary capacity of a patient [222].

Several CPET-derived variables have been associated with morbidity, mortality and length of stay after major intra-abdominal surgery, in particular the AT and VO_{2peak} . Hence, CPET can be used to identify patients with decreased cardiopulmonary reserve, which are those patients who have an increased risk for morbidity and mortality after major intra-abdominal surgery [223–225].

Subsequently, patients with an increased perioperative risk based upon low CPET scores can be offered preoperative exercise therapy or so-called prehabilitation prior to surgery to improve their fitness and thereby reducing perioperative risk.

5.2. Prehabilitation/exercise interventions

Prehabilitation and exercise interventions can be applied in frail elderly to reduce the risks of perioperative morbidity and mortality. The main intention of exercise is to counter the weight

loss and therefore improve muscle strength and function. This will consequently lead to improved daily functioning and better quality of life in these patients.

Even though resistance exercise is known to increase muscle strength in older patients, it seems to have little effect on the actual muscle mass itself. However, several reviews and meta-analyses found an improved physical functioning and overall quality of life in cancer patients from physical exercise [226, 227]. Furthermore, it has been shown that low or decreased physical functioning in the preoperative phase is associated with postoperative complications [228, 229].

In addition to the role of exercise, nutritional intake has an important influence on physical functioning as well. Elderly often have a poor intake, which hampers muscle development and strengthening. It has been shown that the intake of amino acids combined with physical exercise elicits the greatest anabolic response [230], and that essential amino acids in particular stimulate muscle protein synthesis [231]. Beta-hydroxy-beta-methylbutyrate (HMB) has shown to be a promising effective nutritional supplement in the increase of protein turnover [232]. When in older men and women HMB supplementation was combined with a resistance training program, an increase in lean body mass and decrease in body fat was observed, when compared to the placebo group. [233]. When older men and women were administered additional nutrition supplements with HMB, their functionality, strength, and lean body mass improved [234], as did their protein turnover [235]. Other studies have found a positive effect of whey protein on protein turnover rates when consumed within 1 hour after their exercise regimen [236].

Recently, the PACES study (Physical exercise during Adjuvant Chemotherapy Effectiveness Study), experienced beneficial effects from exercise on functionality. In this study, 230 patients with breast cancer were included and got either a home-based physical activity program (Onco-Move), a moderate to high-intensity supervised training combined with resistance and aerobic exercise (OnTrack) or usual care program. Patients with either the Onco-Move or OnTrack program showed less decline in their cardiorespiratory fitness and physical functioning. They also showed less nausea, vomiting and pain during their therapy compared to the usual care program. Both intervention groups returned to work sooner and worked more hours per week compared to the control group [237].

As noted before, multiple dimensions can be assessed when evaluating frailty. In addition to physical parameters, emotional factors and cognition should be assessed as well [238]. Indeed, psychotherapy has showed to significantly reduce fatigue in patients who were treated for cancer [239]. Furthermore, interventions with a more general approach, aiming at psychological distress, mood and physical symptoms, are effective in reducing fatigue [240].

5.3. Dietary interventions/optimized nutrition

Malnutrition is very common amongst the hospitalized population as a whole, and the prevalence increases even further for patients undergoing surgery for upper gastrointestinal or colorectal malignancies [241, 242]. It has been stated that around 50% of all patients undergoing surgery for cancer suffer from malnutrition. It is associated with adverse out-

comes, including increased morbidity and mortality and decreased quality of life. Furthermore, it has been shown to be a prognostic indicator for disease specific survival in various types of cancers [243]. Interestingly, and despite the important impact malnutrition has on health care costs, the assessment of nutritional status has not yet been implemented in daily practice [244].

Several factors have been identified that predispose patients to malnutrition, including anorexia, cachexia and the early satiety sensation frequently experienced by individuals with cancer. Furthermore, metabolic alterations induced by the presence of the tumor or tumor factors can compromise nutritional status. An increased inflammatory status, which is often observed in patients suffering from a malignancy, can trigger a cascade of molecular events, including increased lipolysis and muscle proteolysis, a syndrome referred to as cancer cachexia [245]. Cachexia has been especially well described for patients with solid tumors of the pancreas and upper gastrointestinal tract and less often in patients with lower gastrointestinal cancer.

Clinicians have been aware of the importance of nutritional status for surgical outcome for over 80 years. Surprisingly, this has not yet led to the development of a generally accepted screening system for malnourished patients or patients at risk for malnourishment. Several screening tools have been proposed and validated for this purpose: the nutritional risk index (NRI), prognostic nutritional index (PNI), subjective global assessment (SGA), malnutrition universal screening tool (MUST) and short nutritional screening questionnaire (SNAQ) to name some. These tools, together with certain anthropometric measurements, such as body mass index (BMI) and serum markers of nutrition (e.g. albumin) can aid in the risk assessment and the development of a treatment plan. Significant weight loss (>5% of weight loss during the 6 months prior to surgery) was found to be as a reliable marker for malnutrition as SGA, MUST and NRS, whilst a low BMI was not [243, 246].

5.3.1. The obesity-paradox

A high BMI is associated with better outcome in cancer patients [247], which is often referred to as the obesity-paradox. However, recent studies investigated the hypothesis that adipose tissue may only have a protective effect in case of abundant muscle tissue, which is often the case in obesity. In order to do so, muscle mass, fat mass and BMI were measured in patients undergoing surgery for a malignancy. Indeed, a high BMI (>25) was associated with a longer overall survival. However, the shortest survival was observed in patients with a relatively high BMI but with a low muscle mass, i.e. in patients with sarcopenic obesity [248].

6. Conclusion

Surgery for cancer of the alimentary tract involves extensive and complex procedures. These surgical procedures have improved in the last decades; new techniques and treatment options have broadened the field of surgical oncology for abdominal cancers. Despite this improve-

ment, the postoperative outcome, in terms of postoperative morbidity, remains a significant issue for the patient and the physician.

One of the biggest challenges, in regard to postoperative outcome, is the aging population that undergoes surgery for cancer. Functional compromise, defined by several conditions such as fatigue, sarcopenia, cachexia, malnutrition, the presence of comorbidities and frailty, is especially common in the elderly patient, making them more susceptible to surgical stressors. Several screening tools have been developed to assess the presence of these conditions in order to identify avoidable perioperative risks.

There is an increasing need for protocolled care and new care pathways to reduce perioperative morbidity. The introduction of fast-track and enhanced recovery programs has led to a faster patient recovery and a reduction of complications after abdominal surgery. These care programs are aimed at reducing the surgical stressors. General principles of such programs are: minimized preoperative fasting, limited use of incisions, catheters and drains, early resumption of diet and early mobilization after surgery and optimal pain control. In addition, every type of surgery has its specific recommendations for protocolled care.

A multimodal approach is recommended when planning surgery for a compromised patient, including control of chronic diseases, referral to a geriatric specialist and optimizing nutritional status and exercise tolerance. Cardiopulmonary exercise testing can be used before surgery to determine the patient's cardiorespiratory fitness. Subsequently, exercise interventions before treatment can be used in cancer patients with a poor cardiorespiratory fitness to improve the treatment results. Regarding the nutritional status, this can be compromised due to cancer-related anorexia and cachexia. Preoperative assessment of the nutritional status should be considered, as malnourishment can have a negative effect on the postoperative outcome.

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References

- [1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer (Journal international du cancer)*. 2015 Mar 1;136(5):E359–86. PubMed PMID: 25220842. Epub 2014/09/16.
- [2] Jakobson T, Karjagin J, Vipp L, Padar M, Parik AH, Starkopf L, et al. Postoperative complications and mortality after major gastrointestinal surgery. *Medicina*. 2014;50(2):111–7. PubMed PMID: 25172605. Epub 2014/06/24.
- [3] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA: A Cancer Journal for Clinicians*. 2011 Mar–Apr;61(2):69–90. PubMed PMID: 21296855. Epub 2011/02/08.
- [4] Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). *Annals of Surgery*. 2011 Dec;254(6):868–75. PubMed PMID: 21597360.
- [5] Roulin D, Donadini A, Gander S, Griesser AC, Blanc C, Hubner M, et al. Cost-effectiveness of the implementation of an enhanced recovery protocol for colorectal surgery. *The British Journal of Surgery*. 2013 Jul;100(8):1108–14. PubMed PMID: 23754650.
- [6] Basse L, Jakobsen DH, Bardram L, Billesbolle P, Lund C, Mogensen T, et al. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. *Annals of Surgery*. 2005 Mar;241(3):416–23. PubMed PMID: 15729063. Pubmed Central PMCID: 1356979.
- [7] van Vugt JL, Reisinger KW, Derikx JP, Boerma D, Stoot JH. Improving the outcomes in oncological colorectal surgery. *World Journal of Gastroenterology: WJG*. 2014 Sep 21;20(35):12445–57. PubMed PMID: 25253944. Pubmed Central PMCID: PMC4168077. Epub 2014/09/26. eng.
- [8] Berrino F, Verdecchia A, Lutz JM, Lombardo C, Micheli A, Capocaccia R, et al. Comparative cancer survival information in Europe. *European Journal of Cancer*. 2009 Apr;45(6):901–8. PubMed PMID: 19217771. Epub 2009/02/17.
- [9] Protopapa KL, Simpson JC, Smith NC, Moonesinghe SR. Development and validation of the Surgical Outcome Risk Tool (SORT). *The British Journal of Surgery*. 2014 Dec;101(13):1774–83. PubMed PMID: 25388883. Pubmed Central PMCID: 4240514.
- [10] Cohen ME, Bilimoria KY, Ko CY, Hall BL. Development of an American College of Surgeons National Surgery Quality Improvement Program: morbidity and mortality risk calculator for colorectal surgery. *Journal of the American College of Surgeons*. 2009 Jun;208(6):1009–16. PubMed PMID: 19476884.
- [11] Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric

assessment in elderly patients with cancer: a systematic review. *The Lancet Oncology*. 2012 Oct;13(10):e437–44. PubMed PMID: 23026829.

- [12] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences*. 2001 Mar;56(3):M146–56. PubMed PMID: 11253156.
- [13] Soubeyran P, Fonck M, Blanc-Bisson C, Blanc JF, Ceccaldi J, Mertens C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2012 May 20;30(15):1829–34. PubMed PMID: 22508806.
- [14] Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JP. Old or frail: what tells us more? *The Journals of Gerontology Series A, Biological Sciences and Medical Sciences*. 2004 Sep;59(9):M962–5. PubMed PMID: 15472162.
- [15] Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). *Clinical Nutrition*. 2005 Feb;24(1):75–82. PubMed PMID: 15681104.
- [16] Rahman A, Wu T, Bricknell R, Muqtadir Z, Armstrong D. Malnutrition matters in Canadian hospitalized patients: malnutrition risk in hospitalized patients in a tertiary care center using the malnutrition universal screening tool. *Nutrition in Clinical Practice: Official Publication of the American Society for Parenteral and Enteral Nutrition*. 2015 Oct;30(5):709–13. PubMed PMID: 26253124.
- [17] Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2010 Jun;19(6):1468–70. PubMed PMID: 20501776. Epub 2010/05/27.
- [18] Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. *Seminars in Radiation Oncology*. 2013 Jan;23(1):3–9. PubMed PMID: 23207041. Pubmed Central PMCID: 3535292. Epub 2012/12/05.
- [19] Edgren G, Adami HO, Weiderpass E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. *Gut*. 2013 Oct;62(10):1406–14. PubMed PMID: 22917659. Epub 2012/08/25.
- [20] Bollschweiler E, Wolfgarten E, Gutschow C, Holscher AH. Demographic variations in the rising incidence of esophageal adenocarcinoma in white males. *Cancer*. 2001 Aug 1;92(3):549–55. PubMed PMID: 11505399. Epub 2001/08/16.
- [21] Zhang ZF, Kurtz RC, Sun M, Karpeh M, Jr., Yu GP, Gargon N, et al. Adenocarcinomas of the esophagus and gastric cardia: medical conditions, tobacco, alcohol, and socioeconomic factors. *Cancer Epidemiology, Biomarkers & Prevention: A Publication*

- of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 1996 Oct;5(10):761–8. PubMed PMID: 8896886. Epub 1996/10/01.
- [22] Zambon P, Talamini R, La Vecchia C, Dal Maso L, Negri E, Tognazzo S, et al. Smoking, type of alcoholic beverage and squamous-cell oesophageal cancer in northern Italy. *International Journal of Cancer (Journal International du cancer)*. 2000 Apr 1;86(1):144–9. PubMed PMID: 10728609. Epub 2000/03/23.
- [23] Launoy G, Milan C, Faivre J, Pienkowski P, Gignoux M. Tobacco type and risk of squamous cell cancer of the oesophagus in males: a French multicentre case-control study. *International Journal of Epidemiology*. 2000 Feb;29(1):36–42. PubMed PMID: 10750601. Epub 2000/04/06.
- [24] Engel LS, Chow WH, Vaughan TL, Gammon MD, Risch HA, Stanford JL, et al. Population attributable risks of esophageal and gastric cancers. *Journal of the National Cancer Institute*. 2003 Sep 17;95(18):1404–13. PubMed PMID: 13130116. Epub 2003/09/18.
- [25] Stahl M, Stuschke M, Lehmann N, Meyer HJ, Walz MK, Seeber S, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2005 Apr 1;23(10):2310–7. PubMed PMID: 15800321. Epub 2005/04/01.
- [26] Bedenne L, Michel P, Bouche O, Milan C, Mariette C, Conroy T, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCO 9102. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2007 Apr 1;25(10):1160–8. PubMed PMID: 17401004. Epub 2007/04/03.
- [27] Jin HL, Zhu H, Ling TS, Zhang HJ, Shi RH. Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: a meta-analysis. *World Journal of Gastroenterology*. 2009 Dec 21;15(47):5983–91. PubMed PMID: 20014464. Pubmed Central PMCID: 2795187. Epub 2009/12/17.
- [28] Lv J, Cao XF, Zhu B, Ji L, Tao L, Wang DD. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. *World Journal of Gastroenterology*. 2010 Apr 7;16(13):1649–54. PubMed PMID: 20355244. Pubmed Central PMCID: 2848374. Epub 2010/04/01.
- [29] van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *The New England Journal of Medicine*. 2012 May 31;366(22):2074–84. PubMed PMID: 22646630. Epub 2012/06/01.
- [30] Fiorica F, Di Bona D, Schepis F, Licata A, Shahied L, Venturi A, et al. Preoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis.

Gut. 2004 Jul;53(7):925–30. PubMed PMID: 15194636. Pubmed Central PMCID: 1774092. Epub 2004/06/15.

- [31] Kumar S, Dimri K, Khurana R, Rastogi N, Das KJ, Lal P. A randomised trial of radiotherapy compared with cisplatin chemo-radiotherapy in patients with unresectable squamous cell cancer of the esophagus. *Radiotherapy and Oncology: Journal of the European Society for Therapeutic Radiology and Oncology*. 2007 May;83(2):139–47. PubMed PMID: 17445928. Epub 2007/04/21.
- [32] Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Jr., Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. *JAMA*. 1999 May 5;281(17):1623–7. PubMed PMID: 10235156. Epub 1999/05/11.
- [33] Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus. *The Cochrane Database of Systematic Reviews*. 2001 (2):CD002092. PubMed PMID: 11406033. Epub 2001/06/19.
- [34] Solcia E, Fiocca R, Luinetti O, Villani L, Padovan L, Calistri D, et al. Intestinal and diffuse gastric cancers arise in a different background of *Helicobacter pylori* gastritis through different gene involvement. *The American Journal of Surgical Pathology*. 1996;20 Suppl 1:S8–22. PubMed PMID: 8694148. Epub 1996/01/01.
- [35] Correa P. A human model of gastric carcinogenesis. *Cancer Research*. 1988 Jul 1;48(13):3554–60. PubMed PMID: 3288329. Epub 1988/07/01.
- [36] Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, et al. A meta-analysis on alcohol drinking and gastric cancer risk. *Annals of Oncology: Official Journal of the European Society for Medical Oncology/ESMO*. 2012 Jan;23(1):28–36. PubMed PMID: 21536659. Epub 2011/05/04.
- [37] Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R, et al. Smoking and gastric cancer: systematic review and meta-analysis of cohort studies. *Cancer Causes & Control: CCC*. 2008 Sep;19(7):689–701. PubMed PMID: 18293090. Epub 2008/02/23.
- [38] Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma: review and considerations for future directions. *Annals of Surgery*. 2005 Jan;241(1):27–39. PubMed PMID: 15621988. Pubmed Central PMCID: 1356843. Epub 2004/12/29.
- [39] Haverkamp L, Brenkman HJ, Seesing MF, Gisbertz SS, van Berge Henegouwen MI, Luyer MD, et al. Laparoscopic versus open gastrectomy for gastric cancer, a multicenter prospectively randomized controlled trial (LOGICA-trial). *BMC Cancer*. 2015;15:556. PubMed PMID: 26219670. Pubmed Central PMCID: 4518687. Epub 2015/07/30.
- [40] Wanebo HJ, Kennedy BJ, Chmiel J, Steele G, Jr., Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. *Annals of Surgery*.

- 1993 Nov;218(5):583–92. PubMed PMID: 8239772. Pubmed Central PMCID: 1243028. Epub 1993/11/01.
- [41] Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2004 Jun 15;22(12):2395–403. PubMed PMID: 15197201. Epub 2004/06/16.
 - [42] Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, et al. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2004 Jun 1;22(11):2069–77. PubMed PMID: 15082726. Epub 2004/04/15.
 - [43] McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. *The Cochrane Database of Systematic Reviews*. 2004 (4):CD001964. PubMed PMID: 15495024. Epub 2004/10/21.
 - [44] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *The New England Journal of Medicine*. 2006 Jul 6;355(1):11–20. PubMed PMID: 16822992. Epub 2006/07/11.
 - [45] Ronellenfitsch U, Schwarzbach M, Hofheinz R, Kienle P, Kieser M, Slanger TE, et al. Perioperative chemo(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower esophagus. *The Cochrane Database of Systematic Reviews*. 2013;5:CD008107. PubMed PMID: 23728671. Epub 2013/06/04.
 - [46] European Association for the Study of the L, European Organisation For R, Treatment of C. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Journal of Hepatology*. 2012 Apr;56(4):908–43. PubMed PMID: 22424438. Epub 2012/03/20.
 - [47] Yang JD, Harmsen WS, Slettedahl SW, Chaiteerakij R, Enders FT, Therneau TM, et al. Factors that affect risk for hepatocellular carcinoma and effects of surveillance. *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association*. 2011 Jul;9(7):617–23 e1. PubMed PMID: 21459158. Epub 2011/04/05.
 - [48] Bruix J, Sherman M, American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011 Mar;53(3):1020–2. PubMed PMID: 21374666. Pubmed Central PMCID: 3084991. Epub 2011/03/05.
 - [49] Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with

cirrhosis. *Alimentary Pharmacology & Therapeutics*. 2009 Jul;30(1):37–47. PubMed PMID: 19392863. Epub 2009/04/28.

- [50] Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. *Hepatology*. 2009 Feb;49(2):453–9. PubMed PMID: 19065676. Epub 2008/12/10.
- [51] Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. *The British Journal of Surgery*. 2011 Sep;98(9):1210–24. PubMed PMID: 21766289. Epub 2011/07/19.
- [52] Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma: a meta-analysis. *Journal of Hepatology*. 2010 Mar;52(3):380–8. PubMed PMID: 20149473. Epub 2010/02/13.
- [53] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology*. 2003 Feb;37(2):429–42. PubMed PMID: 12540794. Epub 2003/01/24.
- [54] Camma C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology*. 2002 Jul;224(1):47–54. PubMed PMID: 12091661. Epub 2002/07/02.
- [55] Zhang T, Ding X, Wei D, Cheng P, Su X, Liu H, et al. Sorafenib improves the survival of patients with advanced hepatocellular carcinoma: a meta-analysis of randomized trials. *Anti-cancer Drugs*. 2010 Mar;21(3):326–32. PubMed PMID: 20016366. Epub 2009/12/18.
- [56] Lynch SM, Vrieling A, Lubin JH, Kraft P, Mendelsohn JB, Hartge P, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *American Journal of Epidemiology*. 2009 Aug 15;170(4):403–13. PubMed PMID: 19561064. Pubmed Central PMCID: 2733861. Epub 2009/06/30.
- [57] Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Annals of Oncology: Official Journal of the European Society for Medical Oncology/ESMO*. 2012 Jul;23(7):1880–8. PubMed PMID: 22104574. Pubmed Central PMCID: 3387822. Epub 2011/11/23.
- [58] Bang UC, Benfield T, Hyldstrup L, Bendtsen F, Beck Jensen JE. Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study. *Gastroenterology*. 2014 Apr;146(4):989–94. PubMed PMID: 24389306. Epub 2014/01/07.
- [59] Duell EJ, Lucenteforte E, Olson SH, Bracci PM, Li D, Risch HA, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-

- Control Consortium (PanC4). *Annals of Oncology: Official Journal of the European Society for Medical Oncology/ESMO*. 2012 Nov;23(11):2964–70. PubMed PMID: 22767586. Pubmed Central PMCID: 3477881. Epub 2012/07/07.
- [60] Arslan AA, Helzlsouer KJ, Kooperberg C, Shu XO, Steplowski E, Bueno-de-Mesquita HB, et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Archives of Internal Medicine*. 2010 May 10;170(9):791–802. PubMed PMID: 20458087. Pubmed Central PMCID: 2920035. Epub 2010/05/12.
- [61] Aune D, Greenwood DC, Chan DS, Vieira R, Vieira AR, Navarro Rosenblatt DA, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. *Annals of Oncology: Official Journal of the European Society for Medical Oncology/ESMO*. 2012 Apr; 23(4):843–52. PubMed PMID: 21890910. Epub 2011/09/06.
- [62] Jacobs EJ, Chanock SJ, Fuchs CS, Lacroix A, McWilliams RR, Steplowski E, et al. Family history of cancer and risk of pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *International Journal of Cancer (Journal International du Cancer)*. 2010 Sep 1;127(6):1421–8. PubMed PMID: 20049842. Pubmed Central PMCID: 2926939. Epub 2010/01/06.
- [63] Brune KA, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, et al. Importance of age of onset in pancreatic cancer kindreds. *Journal of the National Cancer Institute*. 2010 Jan 20;102(2):119–26. PubMed PMID: 20068195. Pubmed Central PMCID: 2808346. Epub 2010/01/14.
- [64] Schenk M, Schwartz AG, O'Neal E, Kinnard M, Greenson JK, Fryzek JP, et al. Familial risk of pancreatic cancer. *Journal of the National Cancer Institute*. 2001 Apr 18;93(8): 640–4. PubMed PMID: 11309441. Epub 2001/04/20.
- [65] Mancuso A, Calabro F, Sternberg CN. Current therapies and advances in the treatment of pancreatic cancer. *Critical reviews in oncology/hematology*. 2006 Jun;58(3):231–41. PubMed PMID: 16725343. Epub 2006/05/27.
- [66] Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Annals of Surgery*. 2006 Jul;244(1):10–5. PubMed PMID: 16794383. Pubmed Central PMCID: 1570590. Epub 2006/06/24.
- [67] Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. *American Journal of Surgery*. 1993 Jan;165(1):68–72; discussion -3. PubMed PMID: 8380315. Epub 1993/01/01.
- [68] Kang MJ, Jang JY, Chang YR, Kwon W, Jung W, Kim SW. Revisiting the concept of lymph node metastases of pancreatic head cancer: number of metastatic lymph nodes and lymph node ratio according to N stage. *Annals of Surgical Oncology*. 2014 May;21(5): 1545–51. PubMed PMID: 24419758. Epub 2014/01/15.

- [69] Garcea G, Dennison AR, Pattenden CJ, Neal CP, Sutton CD, Berry DP. Survival following curative resection for pancreatic ductal adenocarcinoma. A systematic review of the literature. *JOP: Journal of the Pancreas*. 2008;9(2):99–132. PubMed PMID: 18326920. Epub 2008/03/11.
- [70] Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. *British Journal of Cancer*. 2009 Sep 15;101(6):908–15. PubMed PMID: 19690548. Pubmed Central PMCID: 2743365. Epub 2009/08/20.
- [71] Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA*. 2007 Jan 17;297(3):267–77. PubMed PMID: 17227978. Epub 2007/01/18.
- [72] Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *The New England Journal of Medicine*. 2004 Mar 18;350(12):1200–10. PubMed PMID: 15028824. Epub 2004/03/19.
- [73] Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2008 Jul 20;26(21):3496–502. PubMed PMID: 18640930. Epub 2008/07/22.
- [74] Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Medicine*. 2010 Apr;7(4):e1000267. PubMed PMID: 20422030. Pubmed Central PMCID: 2857873. Epub 2010/04/28.
- [75] Quiros RM, Brown KM, Hoffman JP. Neoadjuvant therapy in pancreatic cancer. *Cancer Investigation*. 2007 Jun;25(4):267–73. PubMed PMID: 17612937. Epub 2007/07/07.
- [76] Tinkl D, Grabenbauer GG, Golcher H, Meyer T, Papadopoulos T, Hohenberger W, et al. Downstaging of pancreatic carcinoma after neoadjuvant chemoradiation. *Strahlentherapie und Onkologie: Organ der Deutschen Röntgengesellschaft [et al]*. 2009 Sep;185(9):557–66. PubMed PMID: 19756421. Epub 2009/09/17.
- [77] Nieveen van Dijkum EJ, Romijn MG, Terwee CB, de Wit LT, van der Meulen JH, Lameris HS, et al. Laparoscopic staging and subsequent palliation in patients with peripancreatic carcinoma. *Annals of Surgery*. 2003 Jan;237(1):66–73. PubMed PMID: 12496532. Pubmed Central PMCID: 1513968. Epub 2002/12/24.
- [78] Sultana A, Tudur Smith C, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer:

- results of secondary end points analyses. *British Journal of Cancer*. 2008 Jul 8;99(1):6–13. PubMed PMID: 18577990. Pubmed Central PMCID: 2453014. Epub 2008/06/26.
- [79] Van Heek NT, De Castro SM, van Eijck CH, van Geenen RC, Hesselink EJ, Breslau PJ, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. *Annals of Surgery*. 2003 Dec;238(6):894–902; discussion -5. PubMed PMID: 14631226. Pubmed Central PMCID: 1356171. Epub 2003/11/25.
- [80] Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. *The Cochrane Database of Systematic Reviews*. 2006 (3):CD002093. PubMed PMID: 16855985. Epub 2006/07/21.
- [81] Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2009 Nov 20;27(33):5513–8. PubMed PMID: 19858379. Epub 2009/10/28.
- [82] Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, et al. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). *Journal of Surgical Oncology*. 2008 Dec 1;98(7):485–9. PubMed PMID: 18802958. Epub 2008/09/20.
- [83] Konstantinidis IT, Deshpande V, Genevay M, Berger D, Fernandez-del Castillo C, Tanabe KK, et al. Trends in presentation and survival for gallbladder cancer during a period of more than 4 decades: a single-institution experience. *Archives of Surgery*. 2009 May;144(5):441–7; discussion 7. PubMed PMID: 19451486. Epub 2009/05/20.
- [84] van Gulik TM, Gouma DJ. Changing perspectives in the assessment of resectability of hilar cholangiocarcinoma. *Annals of Surgical Oncology*. 2007 Jul;14(7):1969–71. PubMed PMID: 17453297. Pubmed Central PMCID: 1914233. Epub 2007/04/25.
- [85] van Gulik TM, Kloek JJ, Ruys AT, Busch OR, van Tienhoven GJ, Lameris JS, et al. Multidisciplinary management of hilar cholangiocarcinoma (Klatskin tumor): extended resection is associated with improved survival. *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2011 Jan;37(1):65–71. PubMed PMID: 21115233. Epub 2010/12/01.
- [86] Hueman MT, Vollmer CM, Jr., Pawlik TM. Evolving treatment strategies for gallbladder cancer. *Annals of Surgical Oncology*. 2009 Aug;16(8):2101–15. PubMed PMID: 19495882. Epub 2009/06/06.
- [87] Lai CH, Lau WY. Gallbladder cancer— a comprehensive review. *The Surgeon: Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland*. 2008 Apr;6(2):101–10. PubMed PMID: 18488776. Epub 2008/05/21.

- [88] Gourgiotis S, Kocher HM, Solaini L, Yarollahi A, Tsiambas E, Salemis NS. Gallbladder cancer. *American Journal of Surgery*. 2008 Aug;196(2):252–64. PubMed PMID: 18466866. Epub 2008/05/10.
- [89] Baton O, Azoulay D, Adam DV, Castaing D. Major hepatectomy for hilar cholangiocarcinoma type 3 and 4: prognostic factors and longterm outcomes. *Journal of the American College of Surgeons*. 2007 Feb;204(2):250–60. PubMed PMID: 17254929. Epub 2007/01/27.
- [90] Kloek JJ, Ten Kate FJ, Busch OR, Gouma DJ, van Gulik TM. Surgery for extrahepatic cholangiocarcinoma: predictors of survival. *HPB: The Official Journal of the International Hepato Pancreato Biliary Association*. 2008;10(3):190–5. PubMed PMID: 18773053. Pubmed Central PMCID: 2504374. Epub 2008/09/06.
- [91] Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). *HPB: the official journal of the International Hepato Pancreato Biliary Association*. 2008;10(2):130–3. PubMed PMID: 18773090. Pubmed Central PMCID: 2504393. Epub 2008/09/06.
- [92] van der Gaag NA, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract*. 2009 Apr;13(4):814–20. PubMed PMID: 18726134. Epub 2008/08/30.
- [93] Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nagino M. Portal vein embolization before extended hepatectomy for biliary cancer: current technique and review of 494 consecutive embolizations. *Digestive Surgery*. 2012;29(1):23–9. PubMed PMID: 22441616. Epub 2012/03/24.
- [94] Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Annals of Surgery*. 2006 Mar;243(3):364–72. PubMed PMID: 16495702. Pubmed Central PMCID: 1448943. Epub 2006/02/24.
- [95] Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2012 Jun 1;30(16):1934–40. PubMed PMID: 22529261. Epub 2012/04/25.
- [96] Anderson C, Kim R. Adjuvant therapy for resected extrahepatic cholangiocarcinoma: a review of the literature and future directions. *Cancer Treatment Reviews*. 2009 Jun;35(4):322–7. PubMed PMID: 19147294. Epub 2009/01/17.
- [97] Skipworth JR, Olde Damink SW, Imber C, Bridgewater J, Pereira SP, Malago M. Review article: surgical, neo-adjuvant and adjuvant management strategies in biliary tract cancer. *Alimentary Pharmacology & Therapeutics*. 2011 Nov;34(9):1063–78. PubMed PMID: 21933219. Pubmed Central PMCID: 3235953. Epub 2011/09/22.

- [98] Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *The New England Journal of Medicine*. 2012 Feb 23;366(8):687–96. PubMed PMID: 22356322. Pubmed Central PMCID: 3322371. Epub 2012/02/24.
- [99] Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, Henry KA, et al. Annual report to the nation on the status of cancer, 1975–2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *Journal of the National Cancer Institute*. 2015 Jun;107(6):djv048. PubMed PMID: 25825511. Pubmed Central PMCID: 4603551. Epub 2015/04/01.
- [100] Atkin W, Dadswell E, Wooldrage K, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet*. 2013 Apr 6;381(9873):1194–202. PubMed PMID: 23414650. Epub 2013/02/19.
- [101] Chan AT, Giovannucci EL. Primary prevention of colorectal cancer. *Gastroenterology*. 2010 Jun;138(6):2029–43 e10. PubMed PMID: 20420944. Pubmed Central PMCID: 2947820. Epub 2010/04/28.
- [102] Rutter MD. Surveillance programmes for neoplasia in colitis. *Journal of Gastroenterology*. 2011 Jan;46 Suppl 1:1–5. PubMed PMID: 20798970. Epub 2010/08/28.
- [103] Henderson TO, Oeffinger KC, Whitton J, Leisenring W, Neglia J, Meadows A, et al. Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. *Annals of Internal Medicine*. 2012 Jun 5;156(11):757–66, W-260. PubMed PMID: 22665813. Pubmed Central PMCID: 3554254. Epub 2012/06/06.
- [104] Karahalios A, English DR, Simpson JA. Weight change and risk of colorectal cancer: a systematic review and meta-analysis. *American Journal of Epidemiology*. 2015 Jun 1;181(11):832–45. PubMed PMID: 25888582. Epub 2015/04/19.
- [105] Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. *PLoS One*. 2011;6(6):e20456. PubMed PMID: 21674008. Pubmed Central PMCID: 3108955. Epub 2011/06/16.
- [106] Botteri E, Iodice S, Bagnardi V, Raimondi S, Lowenfels AB, Maisonneuve P. Smoking and colorectal cancer: a meta-analysis. *JAMA*. 2008 Dec 17;300(23):2765–78. PubMed PMID: 19088354. Epub 2008/12/18.
- [107] Weiss JM, Pfau PR, O'Connor ES, King J, LoConte N, Kennedy G, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results—medicare data. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2011 Nov 20;29(33):4401–9. PubMed PMID: 21969498. Pubmed Central PMCID: 3221523. Epub 2011/10/05.

- [108] Cukier M, Smith AJ, Milot L, Chu W, Chung H, Fenech D, et al. Neoadjuvant chemoradiotherapy and multivisceral resection for primary locally advanced adherent colon cancer: a single institution experience. *European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2012 Aug;38(8):677–82. PubMed PMID: 22632848. Epub 2012/05/29.
- [109] Govindarajan A, Fraser N, Cranford V, Wirtzfeld D, Gallinger S, Law CH, et al. Predictors of multivisceral resection in patients with locally advanced colorectal cancer. *Annals of Surgical Oncology*. 2008 Jul;15(7):1923–30. PubMed PMID: 18473145. Pubmed Central PMCID: 2770244. Epub 2008/05/14.
- [110] Audisio RA, Ramesh H, Longo WE, Zbar AP, Pope D. Preoperative assessment of surgical risk in oncogeriatric patients. *Oncologist*. 2005 Apr;10(4):262–8. PubMed PMID: 15821246.
- [111] Polanczyk CA, Marcantonio E, Goldman L, Rohde LE, Orav J, Mangione CM, et al. Impact of age on perioperative complications and length of stay in patients undergoing noncardiac surgery. *Annals of Internal Medicine*. 2001 Apr 17;134(8):637–43. PubMed PMID: 11304103.
- [112] Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. *Journal of the American Geriatrics Society*. 2005 Mar;53(3):424–9. PubMed PMID: 15743284.
- [113] Colorectal Cancer Collaborative Group. Surgery for colorectal cancer in elderly patients: a systematic review. *Lancet*. 2000 Sep 16;356(9234):968–74. PubMed PMID: 11041397.
- [114] Blommers E, Klimek M, Hartholt KA, van der Cammen TJ, Klein J, Noordzij PG. Perioperative care of the older patient. *Zeitschrift für Gerontologie und Geriatrie*. 2011 Jun;44(3):187–91. PubMed PMID: 21607796.
- [115] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases*. 1987;40(5):373–83. PubMed PMID: 3558716. Pubmed Central PMCID: 3558716.
- [116] Daabiss M. American Society of Anaesthesiologists physical status classification. *Indian Journal of Anaesthesia*. 2011 Mar;55(2):111–5. PubMed PMID: 21712864.
- [117] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *American Journal of Clinical Oncology*. 1982 Dec;5(6):649–55. PubMed PMID: 7165009.
- [118] Makary MA, Segev DL, Pronovost PJ, Syin D, Bandeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. *Journal of the American College of Surgeons*. 2010 Jun;210(6):901–8. PubMed PMID: 20510798.

- [119] Mak PH, Campbell RC, Irwin MG, American Society of A. The ASA Physical Status Classification: inter-observer consistency. American Society of Anesthesiologists. Anaesthesia and Intensive Care. 2002 Oct;30(5):633–40. PubMed PMID: 12413266.
- [120] Robinson TN, Eiseman B, Wallace JL, Church SD, McFann KK, Pfister SM, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Annals of Surgery. 2009 Sep;250(3):449–55. PubMed PMID: 19730176. Pubmed Central PMCID: 19730176.
- [121] Dasgupta M, Rolfson DB, Stolee P, Borrie MJ, Speechley M. Frailty is associated with postoperative complications in older adults with medical problems. Archives of Gerontology and Geriatrics. 2009 Jan–Feb;48(1):78–83. PubMed PMID: 18068828. Pubmed Central PMCID: 18068828.
- [122] Saxton A, Velanovich V. Preoperative frailty and quality of life as predictors of post-operative complications. Annals of Surgery. 2011 Jun;253(6):1223–9. PubMed PMID: 21412145.
- [123] Roubenoff R. Sarcopenia: a major modifiable cause of frailty in the elderly. The Journal of Nutrition, Health and Aging. 2000;4(3):140–2. PubMed PMID: 10936900.
- [124] Cooper C, Dere W, Evans W, Kanis JA, Rizzoli R, Sayer AA, et al. Frailty and sarcopenia: definitions and outcome parameters. Osteoporosis International. 2012 Jul;23(7):1839–48. PubMed PMID: 22290243.
- [125] Marzetti E, Leeuwenburgh C. Skeletal muscle apoptosis, sarcopenia and frailty at old age. Experimental Gerontology. 2006 Dec;41(12):1234–8. PubMed PMID: 17052879.
- [126] Cherin P, Voronska E, Fraoucene N, de Jaeger C. Prevalence of sarcopenia among healthy ambulatory subjects: the sarcopenia begins from 45 years. Aging clinical and experimental research. 2014 Apr;26(2):137–46. PubMed PMID: 24129803.
- [127] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. Age and Ageing. 2010 Jul;39(4):412–23. PubMed PMID: 20392703. Pubmed Central PMCID: PMC2886201.
- [128] Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. American Journal of Epidemiology. 1998 Apr 15;147(8):755–63. PubMed PMID: 9554417.
- [129] Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. Journal of the American Geriatrics Society. 2002 May;50(5):889–96. PubMed PMID: 12028177.
- [130] Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB : the official journal of the International Hepato

- Pancreato Biliary Association. 2011 Jul;13(7):439–46. PubMed PMID: 21689226. Pubmed Central PMCID: 3133709.
- [131] Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. *Journal of Gastrointestinal Surgery*. 2012 Aug;16(8):1478–86. PubMed PMID: 22692586. Pubmed Central PMCID: 3578313. Epub 2012/06/14. eng.
- [132] van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *British Journal of Surgery*. 2012 Apr;99(4):550–7. PubMed PMID: 22246799. Epub 2012/01/17. eng.
- [133] Tegels JJ, van Vugt JL, Reisinger KW, Hulsewe KW, Hoofwijk AG, Derikx JP, et al. Sarcopenia is highly prevalent in patients undergoing surgery for gastric cancer but not associated with worse outcomes. *Journal of Surgical Oncology*. 2015 Sep;112(4):403–7. PubMed PMID: 26331988.
- [134] Wang SL, Zhuang CL, Huang DD, Pang WY, Lou N, Chen FF, et al. Sarcopenia adversely impacts postoperative clinical outcomes following gastrectomy in patients with gastric cancer: a prospective study. *Annals of Surgical Oncology*. 2015 Dec 14. PubMed PMID: 26668085.
- [135] Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. *European Journal of Cancer*. 2008 May;44(8):1124–32. PubMed PMID: 18375115.
- [136] Tisdale MJ. Mechanisms of cancer cachexia. *Physiological Reviews*. 2009 Apr;89(2):381–410. PubMed PMID: 19342610.
- [137] Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. *Clinical Nutrition*. 2008 Dec;27(6):793–9. PubMed PMID: 18718696.
- [138] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *The Lancet Oncology*. 2011 May;12(5):489–95. PubMed PMID: 21296615.
- [139] Rolland Y, Abellan van Kan G, Gillette-Guyonnet S, Vellas B. Cachexia versus sarcopenia. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2011 Jan;14(1):15–21. PubMed PMID: 21076295.
- [140] Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *New England Journal of Medicine*. 2010 Apr 8;362(14):1273–81. PubMed PMID: 20375404.
- [141] Reisinger KW, Bosmans JW, Uittenbogaart M, Alsoumali A, Poeze M, Sosef MN, et al. Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy predicts postoperative mortality in esophageal cancer surgery. *Annals of Surgical Oncology*. 2015 Apr 17. PubMed PMID: 25893413.

- [142] Awad S, Tan BH, Cui H, Bhalla A, Fearon KC, Parsons SL, et al. Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. *Clinical Nutrition*. 2012 Feb;31(1):74–7. PubMed PMID: 21875767.
- [143] Yip C, Goh V, Davies A, Gossage J, Mitchell-Hay R, Hynes O, et al. Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. *European Radiology*. 2014 May;24(5):998–1005. PubMed PMID: 24535076.
- [144] Del Fabbro E, Parsons H, Warneke CL, Pulivarthi K, Litton JK, Dev R, et al. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. *Oncologist*. 2012;17(10):1240–5. PubMed PMID: 22903527.
- [145] Cooper AB, Slack R, Fogelman D, Holmes HM, Petzel M, Parker N, et al. Characterization of anthropometric changes that occur during neoadjuvant therapy for potentially resectable pancreatic cancer. *Annals of Surgical Oncology*. 2015 Jul;22(7):2416–23. PubMed PMID: 25519927.
- [146] Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. *Journal of Pain and Symptom Management*. 2012 Aug;44(2):181–91. PubMed PMID: 22695045.
- [147] Ali R, Baracos VE, Sawyer MB, Bianchi L, Roberts S, Assenat E, et al. Lean body mass as an independent determinant of dose-limiting toxicity and neuropathy in patients with colon cancer treated with FOLFOX regimens. *Cancer Medicine*. 2016 Jan 27. PubMed PMID: 26814378.
- [148] Antoun S, Borget I, Lanoy E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. *Current Opinion in Supportive and Palliative Care*. 2013 Dec;7(4):383–9. PubMed PMID: 24189893.
- [149] Cousin S, Hollebecque A, Koscielny S, Mir O, Varga A, Baracos VE, et al. Low skeletal muscle is associated with toxicity in patients included in phase I trials. *Investigational New Drugs*. 2014 Apr;32(2):382–7. PubMed PMID: 24343673.
- [150] Cushen SJ, Power DG, Teo MY, Maceneaney P, Maher MM, McDermott R, et al. Body composition by computed tomography as a predictor of toxicity in patients with renal cell carcinoma treated with sunitinib. *American Journal of Clinical Oncology*. 2014 Apr 21. PubMed PMID: 24685884.
- [151] Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clinical Cancer Research*. 2007 Jun 1;13(11):3264–8. PubMed PMID: 17545532.

- [152] Prado CM, Lima IS, Baracos VE, Bies RR, McCargar LJ, Reiman T, et al. An exploratory study of body composition as a determinant of epirubicin pharmacokinetics and toxicity. *Cancer Chemotherapy and Pharmacology*. 2011 Jan;67(1):93–101. PubMed PMID: 20204364.
- [153] Tan BH, Brammer K, Randhawa N, Welch NT, Parsons SL, James EJ, et al. Sarcopenia is associated with toxicity in patients undergoing neo-adjuvant chemotherapy for oesophago-gastric cancer. *European Journal of Surgical Oncology*. 2015 Mar;41(3):333–8. PubMed PMID: 25498359.
- [154] Fitz-Henry J. The ASA classification and peri-operative risk. *Annals of the Royal College of Surgeons of England*. 2011 Apr;93(3):185–7. PubMed PMID: 21477427. Pubmed Central PMCID: 3348554.
- [155] Fujiwara Y, Tsujie M, Hara J, Kato H, Kitani K, Isono S, et al. Comparison of gastric cancer surgery between patients aged >80 years and <79 years: complications and multivariate analysis of prognostic factors. *Hepato-gastroenterology*. 2014 Sep;61(134):1785–93. PubMed PMID: 25513165. Pubmed Central PMCID: 25436380.
- [156] Takeshita H, Ichikawa D, Komatsu S, Kubota T, Okamoto K, Shiozaki A, et al. Surgical outcomes of gastrectomy for elderly patients with gastric cancer. *World Journal of Surgery*. 2013 Dec;37(12):2891–8. PubMed PMID: 24081528.
- [157] Grendar J, Shaheen AA, Myers RP, Parker R, Vollmer CM, Jr., Ball CG, et al. Predicting in-hospital mortality in patients undergoing complex gastrointestinal surgery: determining the optimal risk adjustment method. *Archives of Surgery*. 2012 Feb;147(2):126–35. PubMed PMID: 22006854. Epub 2011/10/19. eng.
- [158] Hsu JT, Liu MS, Wang F, Chang CJ, Hwang TL, Jan YY, et al. Standard radical gastrectomy in octogenarians and nonagenarians with gastric cancer: are short-term surgical results and long-term survival substantial? *Journal of Gastrointestinal Surgery*. 2012 Apr;16(4):728–37. PubMed PMID: 22350724. Pubmed Central PMCID: 22350724.
- [159] Hoogendijk EO, van der Horst HE, Deeg DJ, Frijters DH, Prins BA, Jansen AP, et al. The identification of frail older adults in primary care: comparing the accuracy of five simple instruments. *Age and Ageing*. 2013 Mar;42(2):262–5. PubMed PMID: 23108163. Epub 2012/10/31. eng.
- [160] Tegels JJ, de Maat MF, Hulsewe KW, Hoofwijk AG, Stoot JH. Value of geriatric frailty and nutritional status assessment in predicting postoperative mortality in gastric cancer surgery. *Journal of Gastrointestinal Surgery*. 2014 Mar;18(3):439–45; discussion 45–6. PubMed PMID: 24420730.
- [161] Ommundsen N, Wyller TB, Nesbakken A, Jordhoy MS, Bakka A, Skovlund E, et al. Frailty is an independent predictor of survival in older patients with colorectal cancer. *Oncologist*. 2014 Dec;19(12):1268–75. PubMed PMID: 25355846. Pubmed Central PMCID: PMC4257747.

- [162] Mariette C, De Botton ML, Piessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? *Annals of Surgical Oncology*. 2012 Jul;19(7):2128–34. PubMed PMID: 22322948.
- [163] Morley JE. Sarcopenia in the elderly. *Family Practice*. 2012 Apr;29 Suppl 1:i44–i8. PubMed PMID: 22399555.
- [164] Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2013 Apr 20;31(12):1539–47. PubMed PMID: 23530101.
- [165] Ryu SW, Kim IH. Comparison of different nutritional assessments in detecting malnutrition among gastric cancer patients. *World Journal of Gastroenterology: WJG*. 2010 Jul 14;16(26):3310–7. PubMed PMID: 20614488. Pubmed Central PMCID: PMC2900724.
- [166] Bo Y, Yao M, Zhang L, Bekalo W, Lu W, Lu Q. Preoperative Nutritional Risk Index to predict postoperative survival time in primary liver cancer patients. *Asia Pacific Journal of Clinical Nutrition*. 2015;24(4):591–7. PubMed PMID: 26693742.
- [167] Probst P, Haller S, Dorr-Harim C, Bruckner T, Ulrich A, Hackert T, et al. Nutritional risk in major abdominal surgery: protocol of a prospective observational trial to evaluate the prognostic value of different nutritional scores in pancreatic surgery. *JMIR Research Protocols*. 2015;4(4):e132. PubMed PMID: 26573991. Pubmed Central PMCID: PMC4704883.
- [168] Kondrup J, Allison SP, Elia M, Vellas B, Plauth M, Educational, et al. ESPEN guidelines for nutrition screening 2002. *Clinical Nutrition*. 2003 Aug;22(4):415–21. PubMed PMID: 12880610.
- [169] Webster S, Fletcher SJ. Fit for surgery? Preoperative assessment. *Surgery – Oxford International Edition*. 29(3):112–4.
- [170] Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clinical Nutrition*. 2005 Jun;24(3):466–77. PubMed PMID: 15896435.
- [171] Kehlet H, Wilmore DW. Fast-track surgery. *The British Journal of Surgery*. 2005 Jan; 92(1):3–4. PubMed PMID: 15635603.
- [172] Wilmore DW. From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Annals of Surgery*. 2002 Nov;236(5):643–8. PubMed PMID: 12409671. Pubmed Central PMCID: 1422623.
- [173] Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After

Surgery (ERAS((R))) Society recommendations. *World Journal of Surgery*. 2013 Feb; 37(2):259–84. PubMed PMID: 23052794.

- [174] Feldheiser A, Aziz O, Baldini G, Cox BP, Fearon KC, Feldman LS, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiologica Scandinavica*. 2016 Mar;60(3): 289–334. PubMed PMID: 26514824.
- [175] Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *American Journal of Surgery*. 2002 Jun;183(6):630–41. PubMed PMID: 12095591.
- [176] Lassen K, Coolsen MM, Slim K, Carli F, de Aguilar-Nascimento JE, Schafer M, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. *Clinical Nutrition*. 2012 Dec;31(6): 817–30. PubMed PMID: 23079762.
- [177] Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. *World Journal of Surgery*. 2013 Feb;37(2):285–305. PubMed PMID: 23052796.
- [178] Mortensen K, Nilsson M, Slim K, Schafer M, Mariette C, Braga M, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. *British Journal of Surgery*. 2014 Sep;101(10):1209–29. PubMed PMID: 25047143.
- [179] Wu SJ, Xiong XZ, Lu J, Cheng Y, Lin YX, Zhou RX, et al. Fast-track programs for liver surgery: a meta-analysis. *Journal of Gastrointestinal Surgery*. 2015 Jul 10. PubMed PMID: 26160321. Epub 2015/07/15. Eng.
- [180] Hall TC, Dennison AR, Bilku DK, Metcalfe MS, Garcea G. Enhanced recovery programmes in hepatobiliary and pancreatic surgery: a systematic review. *Annals of the Royal College of Surgeons of England*. 2012 Jul;94(5):318–26. PubMed PMID: 22943226. Pubmed Central PMCID: PMC3954372. Epub 2012/09/05. eng.
- [181] Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. *The Cochrane Database of Systematic Reviews*. 2011 (2):CD007635. PubMed PMID: 21328298.
- [182] Grotenhuis BA, Wijnhoven BP, Grune F, van Bommel J, Tilanus HW, van Lanschot JJ. Preoperative risk assessment and prevention of complications in patients with esophageal cancer. *Journal of Surgical Oncology*. 2010 Mar 1;101(3):270–8. PubMed PMID: 20082349.
- [183] van Stijn MF, Korkic-Halilovic I, Bakker MS, van der Ploeg T, van Leeuwen PA, Houdijk AP. Preoperative nutrition status and postoperative outcome in elderly general surgery patients: a systematic review. *JPEN Journal of Parenteral and Enteral Nutrition*. 2013 Jan;37(1):37–43. PubMed PMID: 22549764.

- [184] Sultan J, Griffin SM, Di Franco F, Kirby JA, Shenton BK, Seal CJ, et al. Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. *British Journal of Surgery*. 2012 Mar;99(3):346–55. PubMed PMID: 22237467. Pubmed Central PMCID: PMC3625735.
- [185] Findlay JM, Gillies RS, Millo J, Sgromo B, Marshall RE, Maynard ND. Enhanced recovery for esophagectomy: a systematic review and evidence-based guidelines. *Annals of Surgery*. 2014 Mar;259(3):413–31. PubMed PMID: 24253135.
- [186] Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F, et al. ESPEN Guidelines on parenteral nutrition: surgery. *Clinical Nutrition*. 2009 Aug;28(4):378–86. PubMed PMID: 19464088.
- [187] Yang Z, Zheng Q, Wang Z. Meta-analysis of the need for nasogastric or nasojejunal decompression after gastrectomy for gastric cancer. *British Journal of Surgery*. 2008 Jul; 95(7):809–16. PubMed PMID: 18551533.
- [188] Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Systematic Reviews*. 2007 (3):CD004929. PubMed PMID: 17636780.
- [189] Sato T, Takayama T, So K, Murayama I. Is retention of a nasogastric tube after esophagectomy a risk factor for postoperative respiratory tract infection? *Journal of Infection and Chemotherapy*. 2007 Apr;13(2):109–13. PubMed PMID: 17458679.
- [190] Shackcloth MJ, McCarron E, Kendall J, Russell GN, Pennefather SH, Tran J, et al. Randomized clinical trial to determine the effect of nasogastric drainage on tracheal acid aspiration following oesophagectomy. *British Journal of Surgery*. 2006 May;93(5): 547–52. PubMed PMID: 16521172.
- [191] Suehiro T, Matsumata T, Shikada Y, Sugimachi K. Accelerated rehabilitation with early postoperative oral feeding following gastrectomy. *Hepato-gastroenterology*. 2004 Nov–Dec;51(60):1852–5. PubMed PMID: 15532842.
- [192] Lassen K, Kjaeve J, Fetveit T, Trano G, Sigurdsson HK, Horn A, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Annals of Surgery*. 2008 May;247(5):721–9. PubMed PMID: 18438106.
- [193] Convertino VA. Cardiovascular consequences of bed rest: effect on maximal oxygen uptake. *Medicine & Science in Sports & Exercise*. 1997 Feb;29(2):191–6. PubMed PMID: 9044222.
- [194] Castelino T, Fiore JF, Jr., Niculiseanu P, Landry T, Augustin B, Feldman LS. The effect of early mobilization protocols on postoperative outcomes following abdominal and thoracic surgery: a systematic review. *Surgery*. 2016 Jan 21. PubMed PMID: 26804821.

- [195] Aarts MA, Okrainec A, Glicksman A, Pearsall E, Victor JC, McLeod RS. Adoption of enhanced recovery after surgery (ERAS) strategies for colorectal surgery at academic teaching hospitals and impact on total length of hospital stay. *Surgical Endoscopy*. 2012 Feb;26(2):442–50. PubMed PMID: 22011937.
- [196] Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbolle P, Hendel HW, et al. Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *The British Journal of Surgery*. 2002 Apr;89(4):446–53. PubMed PMID: 11952586.
- [197] Soreide E, Ljungqvist O. Modern preoperative fasting guidelines: a summary of the present recommendations and remaining questions. *Best Practice & Research Clinical Anaesthesiology*. 2006 Sep;20(3):483–91. PubMed PMID: 17080698.
- [198] Mahajna A, Krausz M, Rosin D, Shabtai M, Hershko D, Ayalon A, et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. *Diseases of the Colon and Rectum*. 2005 Aug;48(8):1626–31. PubMed PMID: 15981063.
- [199] Englesbe MJ, Brooks L, Kubus J, Luchtefeld M, Lynch J, Senagore A, et al. A statewide assessment of surgical site infection following colectomy: the role of oral antibiotics. *Annals of Surgery*. 2010 Sep;252(3):514–9; discussion 9–20. PubMed PMID: 20739852. Pubmed Central PMCID: 2997819.
- [200] Anthony T, Murray BW, Sum-Ping JT, Lenkovsky F, Vornik VD, Parker BJ, et al. Evaluating an evidence-based bundle for preventing surgical site infection: a randomized trial. *Archives of Surgery*. 2011 Mar;146(3):263–9. PubMed PMID: 21079110.
- [201] Nelson RL, Gladman E, Barbateskovic M. Antimicrobial prophylaxis for colorectal surgery. *The Cochrane Database of Systematic Reviews*. 2014;5:CD001181. PubMed PMID: 24817514.
- [202] Steinberg JP, Braun BI, Hellinger WC, Kusek L, Bozikis MR, Bush AJ, et al. Timing of antimicrobial prophylaxis and the risk of surgical site infections: results from the Trial to Reduce Antimicrobial Prophylaxis Errors. *Annals of Surgery*. 2009 Jul;250(1):10–16. PubMed PMID: 19561486.
- [203] Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *The Cochrane Database of Systematic Reviews*. 2000 (4):CD001893. PubMed PMID: 11034732.
- [204] Marret E, Remy C, Bonnet F, Postoperative Pain Forum G. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *The British Journal of Surgery*. 2007 Jun;94(6):665–73. PubMed PMID: 17514701.
- [205] Klein M. Postoperative non-steroidal anti-inflammatory drugs and colorectal anastomotic leakage. NSAIDs and anastomotic leakage. *Dan Med J*. 2012 Mar;59(3):B4420. PubMed PMID: 22381097. Epub 2012/03/03. eng.

- [206] Gorissen KJ, Benning D, Berghmans T, Snoeijs MG, Sosef MN, Hulsewe KW, et al. Risk of anastomotic leakage with non-steroidal anti-inflammatory drugs in colorectal surgery. *The British Journal of Surgery*. 2012 May;99(5):721–7. PubMed PMID: 22318712. Epub 2012/02/10. eng.
- [207] Klein M, Krarup PM, Burcharth J, Agren MS, Gogenur I, Jorgensen LN, et al. Effect of diclofenac on cyclooxygenase-2 levels and early breaking strength of experimental colonic anastomoses and skin incisions. *European Surgical Research (Europäische chirurgische Forschung Recherches chirurgicales europeennes)*. 2011;46(1):26–31. PubMed PMID: 21135559. Epub 2010/12/08. eng.
- [208] Hughes MJ, McNally S, Wigmore SJ. Enhanced recovery following liver surgery: a systematic review and meta-analysis. *HPB (Oxford)*. 2014 Aug;16(8):699–706. PubMed PMID: 24661306. Pubmed Central PMCID: PMC4113251. Epub 2014/03/26. eng.
- [209] Savikko J, Ilmakunnas M, Makisalo H, Nordin A, Isoniemi H. Enhanced recovery protocol after liver resection. *British Journal of Surgery*. 2015 Nov;102(12):1526–32. PubMed PMID: 26331595.
- [210] van Dam RM, Wong-Lun-Hing EM, van Breukelen GJ, Stoot JH, van der Vorst JR, Bemelmans MH, et al. Open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery ERAS(R) programme (ORANGE II-trial): study protocol for a randomised controlled trial. *Trials*. 2012;13:54. PubMed PMID: 22559239. Pubmed Central PMCID: 3409025.
- [211] Mirnezami R, Mirnezami AH, Chandrakumaran K, Abu Hilal M, Pearce NW, Primrose JN, et al. Short- and long-term outcomes after laparoscopic and open hepatic resection: systematic review and meta-analysis. *HPB (Oxford)*. 2011 May;13(5):295–308. PubMed PMID: 21492329. Pubmed Central PMCID: PMC3093641.
- [212] Schiffman SC, Kim KH, Tsung A, Marsh JW, Geller DA. Laparoscopic versus open liver resection for metastatic colorectal cancer: a metaanalysis of 610 patients. *Surgery*. 2015 Feb;157(2):211–22. PubMed PMID: 25282529.
- [213] Gurusamy KS, Samraj K, Davidson BR. Routine abdominal drainage for uncomplicated liver resection. *Cochrane Database Systematic Reviews*. 2007(3):CD006232. PubMed PMID: 17636837. Epub 2007/07/20. eng.
- [214] Breitenstein S, DeOliveira ML, Raptis DA, Slankamenac K, Kambakamba P, Nerl J, et al. Novel and simple preoperative score predicting complications after liver resection in noncirrhotic patients. *Annals of Surgery*. 2010 Nov;252(5):726–34. PubMed PMID: 21037427.
- [215] Zimmitti G, Roses RE, Andreou A, Shindoh J, Curley SA, Aloia TA, et al. Greater complexity of liver surgery is not associated with an increased incidence of liver-related complications except for bile leak: an experience with 2,628 consecutive resections. *Journal of Gastrointestinal Surgery* 2013 Jan;17(1):57–64; discussion p -5. PubMed PMID: 22956403. Pubmed Central PMCID: 3855461.

- [216] Goonetilleke KS, Siriwardena AK. Systematic review of peri-operative nutritional supplementation in patients undergoing pancreaticoduodenectomy. *JOP*. 2006;7(1):5–13. PubMed PMID: 16407613.
- [217] van der Gaag NA, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *New England Journal of Medicine*. 2010 Jan 14;362(2):129–37. PubMed PMID: 20071702.
- [218] Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Coit DG, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. *Annals of Surgery*. 2001 Oct;234(4):487–93; discussion 93–4. PubMed PMID: 11573042. Pubmed Central PMCID: 1422072.
- [219] Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Annals of Surgery*. 2010 Aug;252(2):207–14. PubMed PMID: 20622661.
- [220] Van Buren G, 2nd, Bloomston M, Hughes SJ, Winter J, Behrman SW, Zyromski NJ, et al. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. *Annals of Surgery*. 2014 Apr;259(4):605–12. PubMed PMID: 24374513.
- [221] Wang YC, Szatmary P, Zhu JQ, Xiong JJ, Huang W, Gomatos I, et al. Prophylactic intra-peritoneal drain placement following pancreaticoduodenectomy: a systematic review and meta-analysis. *World Journal of Gastroenterology*. 2015 Feb 28;21(8):2510–21. PubMed PMID: 25741162. Pubmed Central PMCID: PMC4342931.
- [222] American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. *American Journal of Respiratory and Critical Care Medicine*. 2003 Jan 15;167(2):211–77. PubMed PMID: 12524257.
- [223] Moran J, Wilson F, Guinan E, McCormick P, Hussey J, Moriarty J. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. *British Journal of Anaesthesia*. 2016 Feb;116(2):177–91. PubMed PMID: 26787788.
- [224] Dunne DF, Jones RP, Lythgoe DT, Pilkington FJ, Palmer DH, Malik HZ, et al. Cardiopulmonary exercise testing before liver surgery. *Journal of Surgical Oncology*. 2014 Sep;110(4):439–44. PubMed PMID: 24894657. Epub 2014/06/05. eng.
- [225] Ausania F, Snowden CP, Prentis JM, Holmes LR, Jaques BC, White SA, et al. Effects of low cardiopulmonary reserve on pancreatic leak following pancreaticoduodenectomy. *British Journal of Surgery*. 2012 Sep;99(9):1290–4. PubMed PMID: 22828960. Epub 2012/07/26. eng.
- [226] Remels AH, Gosker HR, Schrauwen P, Langen RC, Schols AM. Peroxisome proliferator-activated receptors: a therapeutic target in COPD? *The European Respiratory Journal*. 2008 Mar;31(3):502–8. PubMed PMID: 18310397.

- [227] Sandri M, Lin J, Handschin C, Yang W, Arany ZP, Lecker SH, et al. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. *Proceedings of the National Academy of Sciences of the United States of America*. 2006 Oct 31;103(44):16260–5. PubMed PMID: 17053067. Pubmed Central PMCID: 1637570.
- [228] Mayo NE, Feldman L, Scott S, Zavorsky G, Kim do J, Charlebois P, et al. Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. *Surgery*. 2011 Sep;150(3):505–14. PubMed PMID: 21878237.
- [229] Dale W, Hemmerich J, Kamm A, Posner MC, Matthews JB, Rothman R, et al. Geriatric assessment improves prediction of surgical outcomes in older adults undergoing pancreaticoduodenectomy: a prospective cohort study. *Annals of Surgery*. 2014 May; 259(5):960–5. PubMed PMID: 24096757.
- [230] Breen L, Phillips SM. Skeletal muscle protein metabolism in the elderly: interventions to counteract the 'anabolic resistance' of ageing. *Nutrition & Metabolism*. 2011;8:68. PubMed PMID: 21975196. Pubmed Central PMCID: 3201893.
- [231] Volpi E, Kobayashi H, Sheffield-Moore M, Mittendorfer B, Wolfe RR. Essential amino acids are primarily responsible for the amino acid stimulation of muscle protein anabolism in healthy elderly adults. *The American Journal of Clinical Nutrition*. 2003 Aug;78(2):250–8. PubMed PMID: 12885705. Pubmed Central PMCID: 3192452.
- [232] Kornasio R, Riederer I, Butler-Browne G, Mouly V, Uni Z, Halevy O. Beta-hydroxy-beta-methylbutyrate (HMB) stimulates myogenic cell proliferation, differentiation and survival via the MAPK/ERK and PI3K/Akt pathways. *Biochimica et Biophysica Acta*. 2009 May;1793(5):755–63. PubMed PMID: 19211028.
- [233] Vukovich MD, Stubbs NB, Bohlken RM. Body composition in 70-year-old adults responds to dietary beta-hydroxy-beta-methylbutyrate similarly to that of young adults. *The Journal of Nutrition*. 2001 Jul;131(7):2049–52. PubMed PMID: 11435528.
- [234] Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of beta-hydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. *Nutrition*. 2004 May; 20(5):445–51. PubMed PMID: 15105032.
- [235] Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-beta-methylbutyrate (HMB), L-arginine, and L-lysine. *JPEN Journal of Parenteral and Enteral Nutrition*. 2009 Jan–Feb;33(1):71–82. PubMed PMID: 19164608.
- [236] Li C, Carli F, Lee L, Charlebois P, Stein B, Liberman AS, et al. Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. *Surgical Endoscopy*. 2013 Apr;27(4):1072–82. PubMed PMID: 23052535.

- [237] van Waart H, Stuiver MM, van Harten WH, Geleijn E, Kieffer JM, Buffart LM, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES Randomized Clinical Trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2015 Jun 10;33(17):1918–27. PubMed PMID: 25918291.
- [238] Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research*. 1995 Apr;39(3):315–25. PubMed PMID: 7636775.
- [239] Gielissen MF, Verhagen S, Witjes F, Bleijenberg G. Effects of cognitive behavior therapy in severely fatigued disease-free cancer patients compared with patients waiting for cognitive behavior therapy: a randomized controlled trial. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2006 Oct 20;24(30):4882–7. PubMed PMID: 17050873.
- [240] Goedendorp MM, Gielissen MF, Verhagen CA, Bleijenberg G. Psychosocial interventions for reducing fatigue during cancer treatment in adults. *The Cochrane Database of Systematic Reviews*. 2009;(1):CD006953. PubMed PMID: 19160308.
- [241] Nitenberg G, Raynard B. Nutritional support of the cancer patient: issues and dilemmas. *Critical Reviews in Oncology/Hematology*. 2000 Jun;34(3):137–68. PubMed PMID: 10838261.
- [242] Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. *Journal of Human Nutrition and Dietetics: The Official Journal of the British Dietetic Association*. 2010 Aug;23(4):393–401. PubMed PMID: 20337847.
- [243] Afaneh C, Gerszberg D, Slattery E, Seres DS, Chabot JA, Kluger MD. Pancreatic cancer surgery and nutrition management: a review of the current literature. *Hepatobiliary Surgery and Nutrition*. 2015 Feb;4(1):59–71. PubMed PMID: 25713805. Pubmed Central PMCID: 4318958.
- [244] Schindler K, Pernicka E, Laviano A, Howard P, Schutz T, Bauer P, et al. How nutritional risk is assessed and managed in European hospitals: a survey of 21,007 patients findings from the 2007–2008 cross-sectional nutritionDay survey. *Clinical Nutrition*. 2010 Oct; 29(5):552–9. PubMed PMID: 20434820.
- [245] Skipworth RJ, Fearon KC. The scientific rationale for optimizing nutritional support in cancer. *European Journal of Gastroenterology & Hepatology*. 2007 May;19(5):371–7. PubMed PMID: 17413286.
- [246] Loh KW, Vriens MR, Gerritsen A, Borel Rinkes IH, van Hillegersberg R, Schippers C, et al. Unintentional weight loss is the most important indicator of malnutrition among surgical cancer patients. *The Netherlands Journal of Medicine*. 2012 Oct;70(8):365–9. PubMed PMID: 23065984.

- [247] Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2015 Jan 1;33(1):90–9. PubMed PMID: 25422490.
- [248] Gonzalez MC, Pastore CA, Orlandi SP, Heymsfield SB. Obesity paradox in cancer: new insights provided by body composition. *The American Journal of Clinical Nutrition*. 2014 May;99(5):999–1005. PubMed PMID: 24572565.