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REVIEW ARTICLE

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ERAS: Improving outcome in the cachectic HPB patient

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The enhanced recovery after surgery (ERAS) program has reduced postoperative morbidity and duration of hospital stay but not mortality in patients undergoing hepatopancreatobiliary (HPB) surgery. Many HPB patients suffer from cancer cachexia, a syndrome of severe weight and muscle loss. This may affect outcomes of HPB surgery even within an ERAS program. A tailored ERAS approach may be essential in further improving outcome in this vulnerable patient category.

KEYWORDS
body composition, cancer cachexia, enhanced recovery after surgery, hepatopancreatobiliary surgery, outcome

1 | INTRODUCTION

In the past, surgery of the liver and pancreas was associated with high morbidity and mortality. Hepatopancreatobiliary (HPB) surgery was therefore not commonly performed. Nowadays, HPB surgery has become accepted as primary treatment for cancer of the liver, pancreas, and biliary tract and the number of HPB procedures performed worldwide still increases every year.[1–3] Not all hepatic and pancreatic surgery is high-complex surgery, but HPB procedures can be technically challenging, long, and invasive. HPB surgery is still accompanied by a high rate of postoperative morbidity and a high mortality for some procedures although postoperative morbidity and mortality for all HPB procedures have improved drastically.[2,4,5] Some major developments have greatly improved outcomes after HPB surgery. Improved intra-operative techniques and better anesthesia have allowed surgeons to operate with less blood loss under better patient surveillance. With the procedures becoming safer over the years, the indications for large hepatic and pancreatic resections have been extended. In the past, there used to be age restrictions with respect to HPB surgery as morbidity and mortality were much higher in the older patient. Today, elderly patients with extensive disease can undergo a major hepatectomy safely.[6] In some countries such as the Netherlands and United Kingdom, HPB surgery has been centralized to a limited number of specialized centers. This drive to centralization was based on data showing that complication rates were similar in high-volume hospitals compared to low-volume hospitals but mortality was far lower in high volume units.[7] By setting a minimum number of procedures that must be performed in a center yearly, the quality of the surgery and perioperative care has improved considerably over the years.[8]

Despite all progress within the technical field, HPB surgery still presents some challenges at the patient side. Most patients undergoing HPB surgery have oncologic pathology, and often suffer from cancer cachexia: a syndrome of severe weight loss and muscle wasting.[9] More than half of all oncologic HPB patients are affected by cancer cachexia with overall mortality rates up to 80%.[10,11] In addition, the tumors are usually located in the gastro-intestinal tract, causing mechanical obstructions further contributing to weight loss and malnutrition. Adequate preoperative identification and perioperative management of this vulnerable patient category is a key step to further improve outcome in HPB surgery. The enhanced recovery after surgery (ERAS) program has been developed successfully to optimize perioperative care and postoperative recovery initially in patients with colorectal cancer and later also HPB surgery,[12] and could serve as framework for improving perioperative care of the vulnerable HPB patient.

2 | ENHANCED RECOVERY AFTER SURGERY (ERAS)

Fast-track programs have been introduced in the 1990s primarily for the improvement of patient outcome after colonic surgery. In 1997, a multimodal approach to fasten postoperative recovery was introduced by the Danish surgeon Henrik Kehlet. This approach was called "multimodal rehabilitation."[13] It was emphasized that multimodal interventions in preoperative, intraoperative, and postoperative care may lead to earlier recovery after surgical procedures by maintaining pre-operative organ function, and reducing the stress response following surgery. This would then lead to earlier recovery and a reduction in length of hospital stay and costs.[13] In 2005, the ERAS group formulated specific recommendations for perioperative care in colonic surgery: the ERAS program.12 These were later translated to other fields of surgery, including HPB.[14,15]

Interventions of the ERAS program are standardized, multimodal, and protocolized. The strength of ERAS is that all individual evidence-based interventions are administered to the patient in one standard care plan. The main components of ERAS consist of intensive preoperative counseling, the absence of bowel preparation and premedication, no preoperative fasting, the intake of carbohydrate-loaded liquids until 2–h before surgery, tailored anesthesiology encompassing thoracic epidural anesthesia and short-acting anesthetics, perioperative high inspired oxygen concentrations, avoidance of perioperative fluid overload, small incisions, non-opioid pain management, avoidance of drains, tubes and catheters, standard laxatives and prokinetics, and early enhanced postoperative feeding and mobilization.[12,14,15]

After successful implementation in colonic surgery,[16] ERAS programs have been developed and implemented in other fields including hepatic and pancreatic surgery. Overall, the enhanced recovery principles for HPB surgery remain the same as for colonic surgery. There are however distinctive differences within the perioperative care pathway of hepatic and pancreatic surgery. For pancreatic surgery, for instance, improving nutritional status by perioperative feeding, controlling exocrine and endocrine function, and also biliary drainage are specific disease-related targets. In liver surgery, these issues are frequently less important, but maintaining a low central venous pressure and fluid management during surgery are important procedure related targets. As mentioned before, oncologic HPB patients are a vulnerable group who need a more tailored approach. The ERAS group therefore developed and published specific guidelines and recommendations for pancreas and liver surgery separately.[14,15]

3 | ERAS OUTCOMES IN HPB

Consistent outcome reporting is extremely important in medical research, especially in multimodal interventions such as ERAS. In both pancreatic and hepatic surgeries, consensus definitions have been established for major surgery specific complications by the International Study Group of Liver Surgery and International Study Group of Pancreatic Surgery.[17–20] In addition, composite endpoints have been established for both pancreatic and liver surgery consisting of the most important major complications.[21,22] Such composite endpoints facilitate standardized reporting and also to reduce the sample size needed in studies to prove the benefit of an intervention. A next step would be the development of a pancreas and liver surgery specific core outcome set. This is the minimum set of outcomes that should be studied and reported in any trial for a certain disease, thereby facilitating consistent outcome reporting and data pooling among different studies.[23] At the moment, most studies in ERAS focus on duration of hospital stay, readmissions, and postoperative complications. An ERAS specific core outcome set should be developed to assist in homogeneous outcome reporting when conducting ERAS studies. Preferably patients should be involved in addition to medical professionals to establish the most important outcomes in ERAS.

Traditionally, the median length of stay after pancreatic resections is relatively long. A recent meta-analysis pooled the data of 2719 patients in Western countries and found a significant reduction in length of stay of approximately 4 days after PD. In the same meta-analysis, postoperative morbidity was reduced in ERAS (46%) versus conventional care (57%).[24] Still, the overall complication rates after pancreatic surgery remain high. In a subanalysis, postoperative pancreatic fistula rates (POPF) were not significantly reduced but the rate of delayed gastric emptying (DGE) was shown to be lower in the ERAS group (11%) versus conventional care (18%). Readmissions and mortality rates were not different between ERAS and conventional care.[24]

Hepatic surgery has become increasingly safer over the years and mortality has declined to under 5% for major liver resections.[4] The postoperative complication rates however remain high for even the most experienced centers.[4,25,26] A recent meta-analysis showed a reduction in length of stay of 2 days for ERAS in a pooled data group of 2504 patients.[27] Postoperative morbidity after hepatic surgery was reduced in ERAS (28%) versus conventional care (38%). Readmission and mortality rates after hepatic surgery were not significantly different between ERAS and conventional care.[27]

At present, the implementation of ERAS has been beneficial for reducing length of stay in HPB patients, but a reduction of postoperative complication rates and mortality has not yet been completely achieved. Mortality in HPB surgery may be more related to host factors than surgery and duration of stay. In this context, as mentioned earlier, it should be realized that morbidity rates may be similar in high- and low-volume centers, but mortality rates are far lower in high volume centers.[7] This relates to the failure to rescue concept, implying that once a complication occurs there is a risk of consecutive complications,[28] alternately leading to fatal outcomes. This is particularly true in the elderly and vulnerable patient such as those with cancer cachexia. To truly improve long-term outcome and adapt ERAS to the HPB patient, a full understanding of the problems and needs of the cachectic HPB patients is required.

4 | CANCER CACHEXIA

Of the myriad of preoperative risk factors identified in HPB surgery, cancer cachexia is perhaps the most important burden for cancer patients.[29] It is characterized by severe weight and muscle loss, and affects more than 80% of pancreatic cancer patients and more than 50% of colorectal cancer patients.[9,10] Although the international consensus definition of cancer cachexia only includes weight loss, low muscle mass (sarcopenia), and low body mass index, the syndrome of cancer cachexia can include many more pathophysiological drivers such as inflammation, altered protein metabolism, skeletal muscle loss, adipose tissue loss, anorexia, malabsorption, and neuro-hormonal changes.[9,30] Cancer cachexia is associated with a mortality rate of up to 80%,[11] though it should not be seen as a terminal illness. Symptoms of cachexia can already occur preclinically with subtle metabolic changes (eg, mild systemic inflammation or anorexia) which is considered precachexia.[9] Precachexia can develop into cachexia with clinically evident weight loss with or without muscle and/or adipose tissue loss. Only patients with refractory cachexia can be considered as terminal with a permanently altered metabolism, unresponsiveness to anti-cancer therapy, and a life expectancy of less than 3 months.[9] The majority of surgical HPB patients present with cachexia or precachexia, but the symptoms and clinical presentation can vary widely.[31,32] In this context, it is important to consider how one should assess and address cachexia, in order to improve perioperative outcomes within an ERAS program.

Weight loss is the most universally used symptom of cancer cachexia and therefore the main criterion in the international consensus definition of cancer cachexia.[9] Eighty-five percent of patients with pancreatic cancer and around 60% of patients with colorectal liver metastases present with weight loss at the time of diagnosis.[10,33] Although having weight loss has been reported to have an effect on overall survival in univariate analysis in both pancreas and colorectal cancer patients,[10] it is not a risk factor in multivariate analysis.[34] This is probably because the etiology of weight loss can vary considerably among patients, from reduced food intake to increased catabolism.[9] In addition, weight loss does not specify what part of the body is lost; this can be either skeletal muscle, adipose tissue, or both. On top of that, edema and tumor load can cause an increase in weight, potentially masking weight loss. While weight loss can be useful to suspect cachexia, a more thorough nutritional assessment is necessary to identify the drivers of weight loss (and possibly cachexia) in each patient.

Assessing body composition and changes in body composition over time can give valuable information on the patient's cachectic state. Recent progress in computed tomography analysis allows for relatively easy body composition assessment using a single preoperative CT-image.[35] By measuring the total area of skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue at the level of the third lumbar vertebra and adjusting it for patient height, precise estimations of total body mass and composition can be made. This approach has been used in a number of studies in surgical HPB patients. In pancreatic (cancer) surgery, low skeletal muscle mass (ie, sarcopenia) has been associated with shorter survival in some studies.[36–38] However, other studies did not find an association between low skeletal muscle mass and survival specifically in pancreatic cancer patients,[31,37,39] indicating that other factors might have a more important impact on overall survival. Low skeletal muscle mass is also associated with increased postoperative complications,[39] specifically the development of pancreatic fistula.[40] In liver surgery, low muscle mass also has been associated with poor overall survival and increased postoperative complications in patients with colorectal liver metastases[41,42] and hepatocellular carcinoma.[43,44]

Large amounts of adipose tissue (specifically visceral adipose tissue) have a negative impact on postoperative outcome in HPB patients. In pancreatic cancer, high amounts of visceral adipose tissue are associated with higher incidence of major complications,[45] pancreatic fistula,[46,47] and surgical site infections.[31] Visceral adiposity was associated with shorter survival in patients with hepatocellular carcinoma[43] but not colorectal liver metastases.[41] Specific combinations of body composition can have an additional effect on outcome. Patients with pancreatic cancer and a low muscle mass combined with overweight/obesity (also known as sarcopenic obesity) had a shorter survival compared with patients with only a low muscle mass or overweight/obesity.[48]

Next to tissue area, CT-body composition measurements at the L3 level also provide additional information on tissue characteristics. The radiation attenuation or radiodensity of a specific tissue is calculated as the average Hounsfield units of the total tissue area at the L3-level. A low radiation attenuation can indicate increased tissue fat content; in the case of skeletal muscle this is called myosteatosis.[49] However, the true nature, distribution, and the effects of myosteatosis on muscle quality are still unknown. The phenomenon of myosteatosis has already been reported in many types of cancer. There is a strong relation between low muscle radiation attenuation and short survival in surgical patient with pancreatic[31,36] as well as periampullary cancer.[50] Also in patients with hepatocellular carcinoma low muscle radiation attenuation has been consistently associated with poor survival.[43,51,52] As a relatively new parameter, radiation attenuation shows potential and its relation to pathophysiology should be further explored as well as the effect of radiation attenuation of other tissues such as adipose tissue.

Importantly, studies on body composition only assess a single CT-scan for each patient. This generates a snapshot of the patient's body composition while changes in body composition over time—certainly in the light of cachexia—could provide more valuable information. A few studies assessing multiple CT-scans over time in other cancers during chemotherapy showed a strong relation between skeletal muscle loss and survival, whereas there was no or little effect of baseline skeletal muscle mass.[53,54] Utilizing all available preoperative CT-scans in HPB patients should therefore be encouraged in future studies to assess the effects of skeletal muscle loss and adipose tissue loss.

Importantly, cancer cachexia is often accompanied by inflammation. Patients show elevated levels of interleukin-1 (IL-1), IL-6, and TNF-alpha and show an ongoing acute phase response which is clinically apparent by elevated serum C-reactive protein and reduced albumin levels.[55] This inflammatory state contributes to activation of pro-catabolic pathways that lead to further muscle wasting and lipolysis.[56] Elevated CRP levels have been associated with increased resting energy expenditure and increased whole-body protein turnover.[57,58] Pancreatic cancer patients with elevated CRP-levels have a strongly reduced survival compared with patients without signs of an ongoing acute phase response.[34,59] Similar effects were found in surgical patients with colorectal liver metastases.[60,61] In one study, elevated preoperative CRP was associated with an increase in post-operative infectious complications.[62] Both CRP and albumin levels can be used to assess the acute phase response, of which CRP consistently is the strongest predictor for survival in HPB patients.[34,60,61] The most commonly used cut-off level for increased serum CRP was >10 mg/L, considerably lower than the cut-off used to detect infections.[63] Considering the availability and low costs of serum CRP measurements it could be readily implemented into standard preoperative work-up in surgical HPB patients for adequate risk assessment.

Malabsorption and maldigestion are major drivers of weight loss in patients with cancer, particularly in those with pancreatic cancer but sometimes also in those with liver cancer associated with liver cirrhosis or jaundice. Forty to sixty percent of patients with pancreatic cancer suffer from exocrine pancreatic insufficiency preoperatively, which is caused by blockage of the pancreatic duct and destruction of acinar cells.[64–68] Blockage of bile flow also contributes to malabsorption by affecting lipid emulsification, which can also occur in patients with tumors of the proximal bile duct or liver hilum. After pancreatic surgery for cancer, the percentage of exocrine insufficiency increases toward 74–100%.[67,69] Interestingly, exocrine insufficiency is associated with a low muscle mass,[70] indicating that it contributes to muscle wasting in pancreatic cancer cachexia. Pancreatic exocrine insufficiency should therefore be identified pre- and postoperatively and adequately managed as soon as possible. Pancreatic enzyme replacement therapy might offer adequate support,[71] however, the method of administration has been poorly studied in pancreatic cancer patients. While the commonly used enteric coated granules are effective in other diseases, the acidic environment in the duodenum and jejunum in pancreatic cancer[72] causes the granules to start releasing enzymes later in the intestine making them less effective.[73] A more effective approach might be co-administration of uncoated pancreatic enzymes with a proton-pump inhibitor to prevent enzyme degradation in the stomach. Randomized controlled trials in the preoperative setting are needed to properly address this important driver of cachexia.

Anorexia is a common problem in jaundiced HPB patients with bile duct obstruction, leading to poor nutritional intake which contributes to cachexia. Stenting of the bile duct usually relieves jaundice and anorexia symptoms.[74] However, in patients with pancreatic cancer anorexia can persist even after adequate relief of the bile duct obstruction. Probably, pro-inflammatory cytokines as a result of an acute phase response are responsible for anorexia related symptoms.[75]

5 | BEYOND ERAS; SELECTING THE PATIENT FIT FOR SURGERY

The ERAS program has proven to be successful for the patient with colorectal cancer and it can also be applied for patients undergoing hepatic and pancreatic surgery. A critical question remains if vulnerable patients should receive the same perioperative care plan as the standard patient. Patients are becoming increasingly older. Within an older population, comorbidities and age related sarcopenia are more prevalent. This may have a negative effect on the patient's fitness and postoperative outcome.[76] As the majority of HPB patients have oncologic pathology, management of cancer cachexia will be the greatest challenge in perioperative care. Preoperative screening to identify vulnerable patients is essential since every (cachectic) patient presents with specific problems and comorbidities. This way, patients who are at risk for complications can receive additional pre- and postoperative support and timely interventions in case of complications, potentially reducing complication related mortality (ie, reducing "failure to rescue"). See Figure 1 for recommendations for clinical practice. In the end, preoperative interventions (eg, exercise, nutritional support, and pharmacological support) should be developed for vulnerable patients to improve outcome: the "better in, better out" principle.

Recommendations for clinical practice

1. Surgeons should be aware that many HPB patients may be vulnerable by amongst others cancer cachexia, which is not always apparent at first sight.
2. Nutritional status, CT-based body composition, serum C-reactive protein, and fecal elastase should be assessed in HPB patients with cancer.
3. Vulnerable patients should receive additional preoperative supportive care (e.g. dietitian support).
4. Active postoperative monitoring of vulnerable patients and timely interventions in case of complications may reduce complication related morbidity and failure to rescue.

FIGURE 1 Recommendations for clinical practice

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