JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2025.68552
J Inonu Liver Transpl Inst 2025;3(Suppl. 1): S78-S97

Review

Perioperative Medicine in Oncologic Hepato-Pancreato-Biliary Surgery – An Evidence- Based Narrative Review of Perioperative Concepts

Jacqueline Braun,* **Anna Magdolen Rotert,*** **Andreas Hecker,** **Martin Schneider,** **Martin Reichert**

Division of Hepato-Pancreato-Biliary Surgery, Department of General, Visceral, Thoracic and Transplant Surgery, Giessen University Hospital, Justus-Liebig University Giessen, Rudolf-Buchheim-Strasse 7, 35390 Giessen, Germany

JB and AMR contributed equally and share first authorship.

Abstract

Optimizing perioperative care in oncologic hepato-pancreato-biliary (HPB) surgery is critical to improving surgical outcomes and long-term prognosis. This narrative review provides a comprehensive synthesis of current concepts in perioperative medicine, including risk stratification, prehabilitation, enhanced recovery after surgery (ERAS) pathways, neoadjuvant therapy, and the management of procedure-specific complications in pancreatic and hepato- biliary surgery.

In pancreatic cancer surgery, advances in neoadjuvant strategies for borderline resectable disease, individualized antibiotic prophylaxis, and structured ERAS pathways have significantly influenced clinical outcomes. Similarly, in hepato-biliary surgery, neoadjuvant concepts are evolving for hepatocellular and cholangiocarcinoma, while prehabilitation and risk-based ERAS implementation are gaining importance. Special attention is given to complications such as postoperative pancreatic fistula, bile leakage, portal vein thrombosis, small-for-size syndrome, and liver failure.

Drainage strategies are discussed in light of recent guideline-based recommendations, emphasizing the importance of avoiding prophylactic drainage in uncomplicated liver and pancreatic resections. Novel concepts such as staged hepatectomy with ALPPS, combined vein embolization, and minimally invasive liver surgery, including robotic approaches, expand the surgical toolbox but demand strict patient selection and high expertise.

Taken together, perioperative care in HPB oncology is transitioning toward a multimodal, individualized approach. Future directions include the integration of precision medicine in surgical oncology and perioperative care into standard pathways to further reduce complication-related failure-to-rescue and improve oncological outcomes.

Keywords: HPB surgery, Neoadjuvant therapy, Oncologic surgery, Perioperative medicine, Prehabilitation, Preoperative optimization

Please cite this article as "Braun J, Rotert AM, Hecker A, Schneider M, Reichert M. Perioperative Medicine in Oncologic Hepato-Pancreato-Biliary Surgery – An Evidence- Based Narrative Review of Perioperative Concepts. J Inonu Liver Transpl Inst 2025;3(Suppl. 1): S78-S97".

Oncologic hepato-pancreato-biliary (HPB) surgery comprises some of the most complex and high-risk procedures in surgical oncology. Patients undergoing liver, bile duct, pancreatic surgery or combined resections in the HPB system frequently present with advanced disease stages, impaired organ function, and systemic comorbidities. These characteristics, combined with the invasiveness of the surgical procedures themselves, render the periop-

Address for correspondence: Martin Reichert, MD. Division of Hepato-Pancreato-Biliary Surgery, Department of General, Visceral, Thoracic and Transplant Surgery, Giessen University Hospital, Justus-Liebig University Giessen, Rudolf-Buchheim-Strasse 7, 35390 Giessen, Germany
E-mail: martin.reichert@chiru.med.uni-giessen.de **Available Online Date:** 10.12.2025
Journal of Inonu Liver Transplantation Institute - Available online at www.jilti.org

erative period particularly vulnerable to severe and potentially life-threatening complications. Despite centralization and improvements in surgical techniques, anesthetic and intensive care medicine, morbidity after major HPB procedures remains high.

The field of perioperative medicine aims to optimize the entire surgical pathway – before, during, and after the operation – through evidence-based interventions designed to reduce complication rates and improve short- as well as long-term outcomes. In the HPB setting, where postoperative liver failure, pancreatic fistula, cholangitis, bile leaks, and hemorrhage may lead to life-threatening complications, a structured, multidisciplinary perioperative strategy implemented in experienced high-volume centers is essential to minimize major morbidity and reduce failure-to-rescue rates.[1–4] This includes precise patient selection, individualized risk stratification, and targeted prehabilitation as well as tailored intraoperative techniques and postoperative complication management. Thereby, perioperative medicine in HPB oncology should be understood as a dynamic, evidence-based framework that integrates surgical, anesthetic, oncologic, infectious disease, and interventional perspectives. Its goal is not only to improve recovery from major resection but also to facilitate access to curative therapies and improve long-term survival.

Over the past decade, the concept of perioperative medicine has evolved beyond anesthesiology and is increasingly recognized as a multidisciplinary responsibility. Particularly in HPB oncology, recent years have seen growing evidence supporting the use of structured preoperative conditioning ("prehabilitation"), neoadjuvant or induction and conversion therapies, selective use of drainage procedures, and patient-specific antimicrobial prophylaxis [4–6]. These interventions not only reduce surgical risk but may also improve oncologic outcomes by faster recovery and consecutively avoiding delays in adjuvant or additive oncologic treatment protocols, reducing recurrence, or enabling secondary resectability.

Preoperative optimization encompasses several domains: nutritional and functional conditioning; management of jaundice, cholangitis, and biliary drainage; tailored antibiotic prophylaxis; and, in select cases, augmentation of liver volume to avoid small-for-size syndrome and postoperative liver insufficiency. Each component requires careful balance between oncologic urgency and physiological stabilization. In patients with borderline resectable tumors, neoadjuvant chemotherapy or chemoradiotherapy is increasingly used to improve R0 resection rates and reduce systemic dissemination. At the same time, minimally invasive techniques, including robotic surgery, are being integrated into HPB practice with the goal of reducing surgical trauma and accelerating recovery.

A major challenge in the implementation of perioperative strategies lies in the heterogeneity of disease patterns and treatment algorithms across the hepato-biliary and pancreatic spectrum. This review narratively summarizes the current evidence and emerging concepts in perioperative medicine for oncologic HPB surgery. The review is organized by organ system and follows the patient pathway: from neoadjuvant therapy and preoperative optimization, through intraoperative considerations, to postoperative (complication) management (Table 1 illustrates common post-pancreatectomy and post-hepatectomy specific complications). In the hepato-biliary section, key focus areas include neoadjuvant approaches in hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCC), management of malignant biliary obstruction, drainage strategies, antibiotic treatment, and techniques to avoid small-for-size syndrome. In the pancreatic section, we address neoadjuvant therapy in borderline resectable pancreatic cancer, prehabilitation, the role of biliary drainage, antimicrobial prophylaxis, drain management, and post-pancreatectomy specific complications.

Evidence in Perioperative Medicine of Pancreatic Surgery

Neoadjuvant Concepts Against Pancreatic Carcinoma

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive malignancies in gastrointestinal oncology and contribute significantly to the population-based cancer burden. In 2022, the incidence in Germany alone was over 18,000 new cases.[5] The mortality in the same year was around 19,000, underlining the aggressive nature of PDAC.[5]

Most patients present at advanced stages, and the five-year survival rate remains dismal. Curative treatment requires complete surgical resection with tumor-free margins (R0 resection), meaning that the tumor-free surgical margin is at least at 1 mm.[6] Formal resections are intended to achieve this including partial pancreaticoduodenectomy, distal pancreatectomy or total pancreatectomy. However, whether these standard procedures should be expanded by more radical surgical concepts – such as the TRIANGLE operation or anterior/ posterior RAMPS (radical antegrade modular pancreatosplenectomy) in left-sided tumors (depicted in Fig. 1) – is currently under investigation in ongoing clinical trials. Nevertheless, surgical resection is usually followed by adjuvant chemotherapy.[7]

Standard therapy naturally depends on the location and lo-

Table 1. Specific complications in hepato-pancreato-biliary surgery

	Complication	Grade A	Grade B	Grade C
ISGPS	**Postoperative pancreatic fistula**			
	Increased amylase activity >3 times upper limit institutional normal serum value	Biochemical leak without clinical consequence	Clinically relevant change in management, drainage >3 weeks, intervention without surgery	Clinically relevant change in management of POPF with angiographic procedures for POPF- related bleeding, signs of POPF- related infection with organ failure, POPF-related reoperation, POPF-related death
	Delayed gastric emptying with			
	Nasogastric tube needed	4-7 d or reinsertion after POD 3	8-14 d or reinsertion after POD 7	>14 d or reinsertion after POD 14
	Post-pancreatectomy hemorrhage			
	Time of onset, location, severity and clinical impact of bleeding	Early (≤24 hours after the surgery), intra- or extraluminal, mild	Early, intra- or extraluminal, severe or Later (>24 hours after the surgery), intra- or extraluminal, mild	Late, intra- or extraluminal, severe
	Clinical condition	Well	Often well/intermediate, very rarely life-threatening	Severely impaired, life-threatening
	Diagnostic consequence	Observation, blood count, US and, if necessary, CT	Observation, blood count, US, CT, angiography, endoscopy	CT, angiography, endoscopy
	Therapeutic consequence	No	Transfusion of blood, intermediate care unit, therapeutic endoscopy, embolization, relaparotomy for early PPH	Localization of bleeding, angiography and embolization, endoscopy or relaparotomy, ICU
	Post-pancreatectomy acute pancreatitis			
	Elevated serum amylase levels	Elevated serum amylase levels for at least 48 hours without clinical impact or changes in management	Clinically relevant changes in patient management	Severe, life-threatening complications, organ failure for at least 48 hours, intensive care, reoperation, or death
ISGPS / ISGLS	**Biliary leakage**			
	Increased bilirubin concentration (>3 times upper than serum bilirubin) in intraabdominal fluid or drain fluid on/after POD 3	No changes in clinical management	Diagnostic or interventional procedures required	Reoperation for biliary peritonitis or failure
ISGLS	**Post-hepatectomy hemorrhage**			
	Postoperative reduction of haemoglobin level > 3 g/dl compared to baseline and/or necessity for PRBCs and/or necessity for invasive re- intervention (e.g. embolization, re-laparotomy)	Hb drop >3g/dl and/or ≤2 PRBCs, no intervention	Require for transfusion > 2 units of PRBCs	Require for radiological interventional treatment or relaparotomy
	Post-hepatectomy liver failure			
	Postoperative deterioration of liver function, e.g. increased INR, hyperbilirubinemia on or after POD 5 and/or neurological symptoms.	Abnormal liver function without changes in clinical management	Abnormal liver function with changes in clinical management but no invasive treatment	Invasive treatment required, incl. ICU or death

This table summarizes the clinical definitions, grading systems, and management strategies for major postoperative complications relevant to pancreatic and liver surgery. Complications are listed in procedural order from pancreatic fistula to liver failure. Definitions are based on consensus statements and relevant guideline criteria from the International Study group of Pancreatic Surgery (ISGPS) and International Study group of Liver Surgery (ISGLS).[131–137] Management approaches are stratified by severity and include interventional, medical, and surgical options. ICU = Intensive care unit, PRBC = Packed red blood cells, POD = Postoperative day.

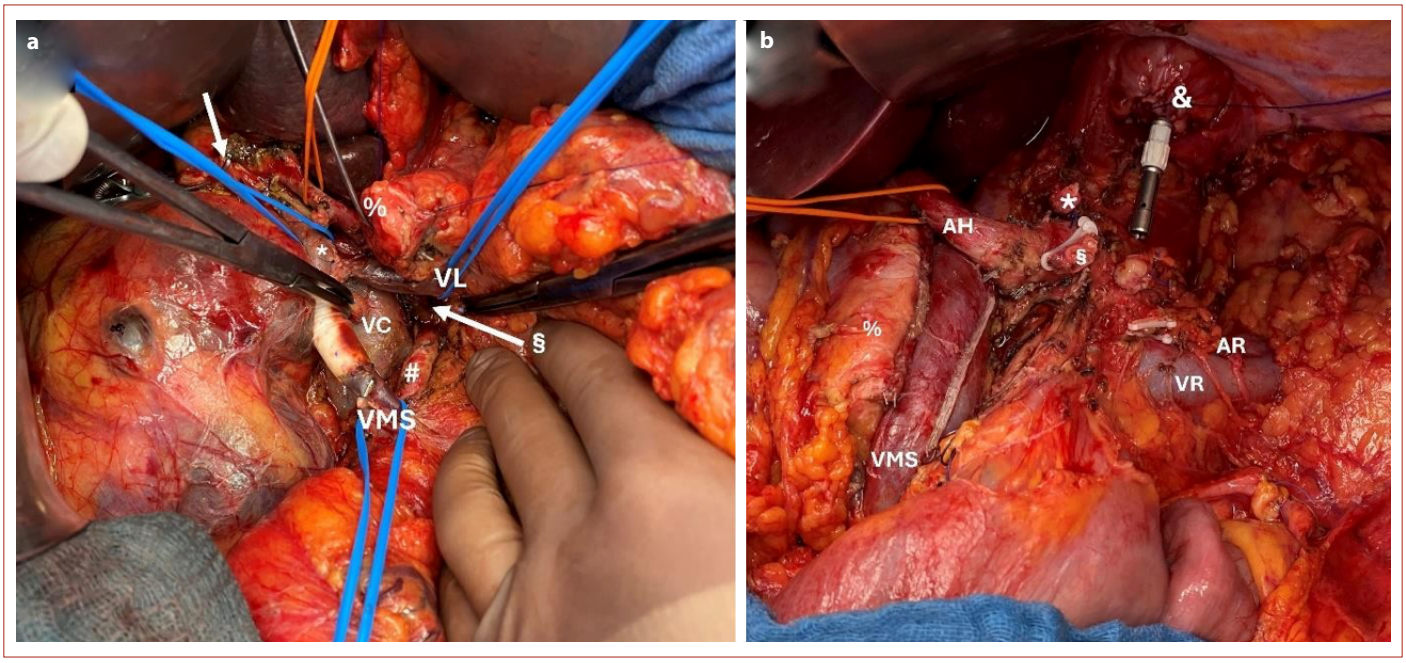

Figure 1. Intraoperative View of Advanced Pancreatic Resections: Triangle Dissection and Posterior RAMPS.

(a) Intraoperative situs following partial pancreatoduodenectomy (Whipple) with completed triangle dissection. The clip (⟶) closes the transected, dilated common bile duct (DHC). The probe (%) identifies a narrow pancreatic duct. The proper hepatic artery (AH) is looped with a red vessel loop. A venous interposition graft connects the superior mesenteric vein (VMS) and portal vein (*). The "triangle" between the superior mesenteric artery (#), celiac trunk (§⟶), and portal vein has been fully dissected. VC = vena cava; blue loops mark the portal vein (*), superior mesenteric vein (VMS), and reimplanted splenic vein (VL). **(b)** Intraoperative situs after extended left-sided pancreatic resection for pancreatic body cancer (posterior RAMPS: radical antegrade modular pancreatosplenectomy). Multivisceral resection including subtotal proximal gastrectomy (anvil of stapler inserted into esophageal stump [&]), left adrenalectomy, and left colonic flexure resection. The staple line (%) indicates the pancreatic transection margin. The splenic vein is stapled at the superior mesenteric vein (VMS). The splenic artery (§) and left gastric artery (*) are transected at the celiac trunk. Dissection includes the left adrenal gland and perirenal fat with identification of left renal vein (VR) and artery (AR). Due to tumor infiltration, the transverse mesocolon and left colonic flexure were resected en-bloc.

cal extend of the tumor, the presence of metastases, and the tumor's involvement in major blood vessels. In patients with resectable tumors, neoadjuvant therapy has not demonstrated a consistent survival benefit and is therefore not routinely recommended by guidelines.[7] A recent meta-analysis confirmed that overall survival of patients with resectable pancreatic cancer who received neoadjuvant therapy are similar to those of patients who underwent upfront surgery.[8,9] Accordingly, neither the "local" German guideline for exocrine pancreatic cancer nor the international NICE guideline recommend chemotherapy, radiotherapy, or chemoradiotherapy for patients with pancreatic cancer assessed as resectable.[7,10]

Criteria for different treatment modalities and resecatbility of PDAC have been clearly defined by multiple international societies, including the National Comprehensive Cancer Network (NCCN), the European Society For Medical Oncology (ESMO), and the International Association of Pancreatology (IAP)[11–13] (Fig. 2). These classifications integrate anatomical, oncological, biological, and functional parameters to guide individualized treatment decisions.

- Anatomical criteria are based on the extent of tumor contact with surrounding vessels – particularly the portomesenteric venous axis and the superior mesenteric artery – and are used to define tumors as resectable, borderline resectable, or locally advanced. Absence of vessel contact defines a resectable tumor, while limited abutment or encasement of venous structures (with reconstructability) or ≤180° contact with the superior mesenteric artery (SMA) may categorize a tumor as borderline resectable.

Unreconstructable venous occlusion or encasement of the SMA >180° indicates locally advanced, non-resectable disease.

- Oncological criteria include the presence or absence of distant metastases (e.g., hepatic, peritoneal, pulmonary), which preclude curative-intent surgery.
- Biological criteria, such as elevated CA 19-9 levels, may indicate occult metastatic disease or biologically aggressive tumor behavior and should be considered in the multidisciplinary assessment.

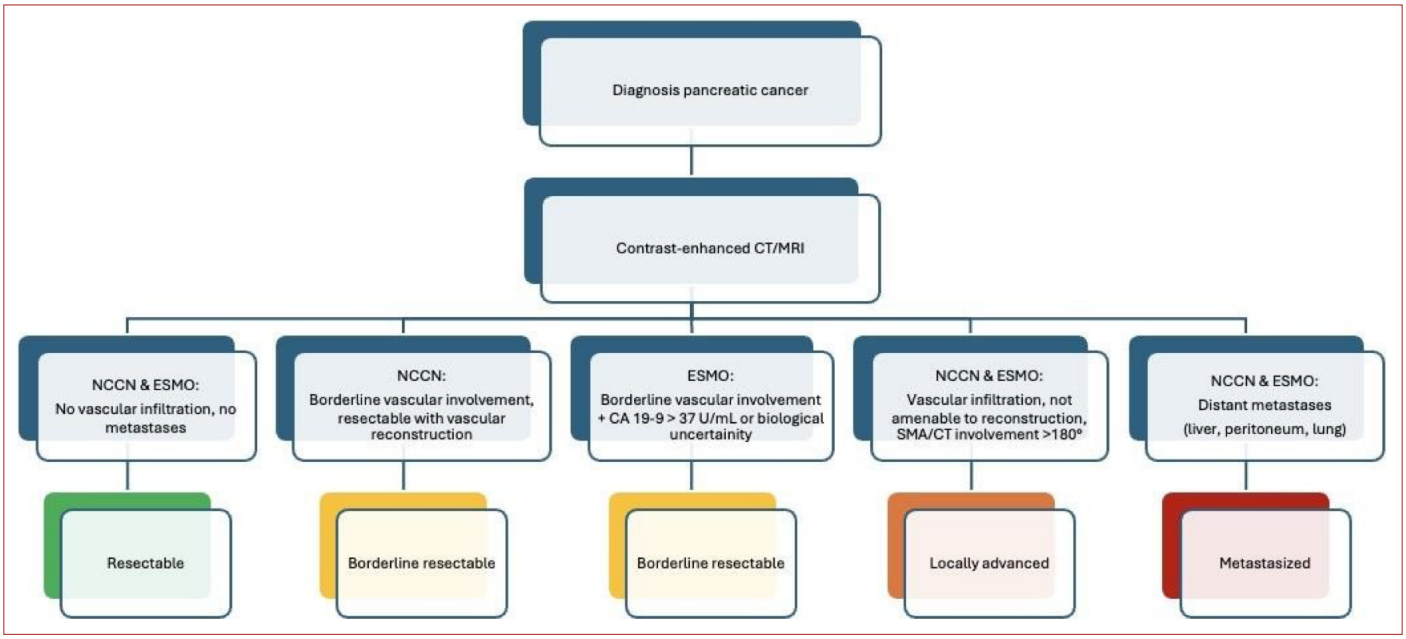

Figure 2. Resectability criteria for pancreatic cancer according to NCCN and ESMO guidelines.

This flowchart illustrates the resectability stratification of pancreatic cancer based on contrast- enhanced CT/MRI and guideline-specific criteria. Resectability is defined by the absence of vascular involvement or metastases. Borderline resectable tumors show limited vascular involvement, potentially resectable after vascular reconstruction (NCCN) or in the presence of biological uncertainty (ESMO). Locally advanced tumors involve major vessels beyond reconstructive options. Distant metastases define non-resectable, systemic disease. CT = Computed tomography, MRI = Magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, ESMO = European Society For Medical Oncology, CA 19-9 = Carbohydrate Antigen 19-9, SMA = Superior mesenteric artery.[11,13]

- Functional or conditional status, commonly assessed via the Eastern Cooperative Oncology Group (ECOG) performance score, is also critical. An ECOG score <2 is generally required for major surgery and is predictive of postoperative recovery and long-term outcome.

In patients without distant metastases, clinical resectability is primarily determined by anatomical criteria, with localized tumors without vascular involvement considered resectable. In contrast, tumors with borderline anatomical involvement – for example, limited contact with the superior mesenteric vein, portal vein, or superior mesenteric artery – are classified as borderline resectable, provided that biological (e.g., CA 19-9) and functional (e.g., ECOG performance status <2) parameters are favourable. For many years, neoadjuvant therapy was offered only to "inoperable" patients, with locally advanced, technically unresectable tumor status.[14] However, its role has significantly expanded. In borderline resectable PDAC, defined by abutment or short-segment encasement of critical vasculature without frank unresectability, neoadjuvant treatment aims to: downstage tumor-vessel involvement, thereby facilitating technically feasible resection, increase the likelihood of R0 resection, and address occult micrometastatic disease early in the treatment course. Emerging evidence from recent trials and meta-analyses suggests that this strategy leads to improved margin-negative resection rates, lower rates of early recurrence, and potentially improved overall survival compared to upfront surgery.[7,15]

One of the earliest randomized trials from Korea in 2018 demonstrated a significant improvement in median overall survival (21 vs. 12 months; p=0.028) and R0 resection rates (51.8% vs. 26.1%) with gemcitabine-based perioperative chemoradiotherapy in 27 borderline resectable PDAC patients versus only adjuvant gemcitabine in 23 patients.[16] Similarly, the large multicentric PREOPANC trial from 2019 confirmed superior outcomes in patients with resectable and borderline resectable pancreatic cancer receiving gemcitabine-based neoadjuvant chemoradiotherapy. The neoadjuvant therapy group demonstrated significantly better outcomes in terms of overall survival (17.1 months vs. 13.5 months; p=0.047), R0 resection rate (65% vs. 31%; p=0.001), disease-free survival (12.1 months vs. 7.9 months; p=0.01), and time to distant metastasis (17.1 months vs. 10.2 months; p=0.012). Furthermore, in the subgroup of patients who ultimately underwent resection after neoadjuvant therapy, overall survival was markedly improved (29.9 months vs. 16.8 months; p=0.001).[17] In more recent studies, the survival benefit is becoming increasingly evident in patients with borderline resectable PDAC. As recently summarized in a meta-analysis, the survival benefits

are most pronounced in this subgroup.[9] Consequently, these data have influenced treatment algorithms in multidisciplinary tumor boards and are reflected in updated NCCN and ESMO guidelines.[11,13]

Preoperative Optimization

Risk Stratification

Although a large meta-analysis involving 49,449 patients found that patients aged <80 years compared to those aged ≥80 years are at higher risk for 30-day postoperative mortality (OR=2,22; 95 % CI 1,48-3,31, p<0,001) and for postoperative complications (OR 1,51 95 % CI 1,25-1,83, p<0,001),[18] but, age alone should not be considered a contraindication for major pancreatic surgery. Nevertheless, the complication profile in elderly patients – including higher incidences of respiratory complications and cardiac events contributing to prolonged hospital stay[18] – highlights the importance of performing a thorough preoperative risk assessment that considers comorbidities and the patient's overall condition. Therefore, the ECOG performance status, which stratifies patients into groups <2 and ≥2, can provide direct prognostic information regarding overall survival.[19]

In a consequence, the IAP recommends in their 2017 International Consensus on Definition and Criteria of Borderline Resectable Pancreatic Ductal Adenocarcinoma that resection should be performed in patients with an ECOG performance status of 0, 1, or 2 – provided the tumor is resectable. Patients with an ECOG performance status of ≥3 should not undergo resection.[20]

Preoperative Optimization, Prehabilitation and ERAS

Multiple measures – avoiding substance abuse, maintaining balanced diet, improving nutritional status, and enhancing physical activity – have shown benefits with regard to postoperative outcomes in patients who are scheduled to undergo major oncologic surgery.[21,22]

Nevertheless, there are no specific recommendations for multimodal prehabilitation in pancreatic surgery. However, prehabilitation during neoadjuvant therapy for PDAC offers a window of opportunity to enhance physical reserve and reduce complication risk.[12–14] The principle of (multimodal) prehabilitation concepts is depicted in Figure 3.

A randomized trial from 2023 has demonstrated that even mild-moderate exercise programs can significantly improve six-minute walk distance.[23] Otherwise, the current status of effective prehabilitation programs in pancreatic surgery remains limited, and robust evidence from randomized trials is scarce. Consequently, clear recommendations regarding comprehensive, resource-intensive, multimodal prehabilitation are currently lacking in existing guidelines.[24]

The ERAS society guidelines for pancreatic surgery from

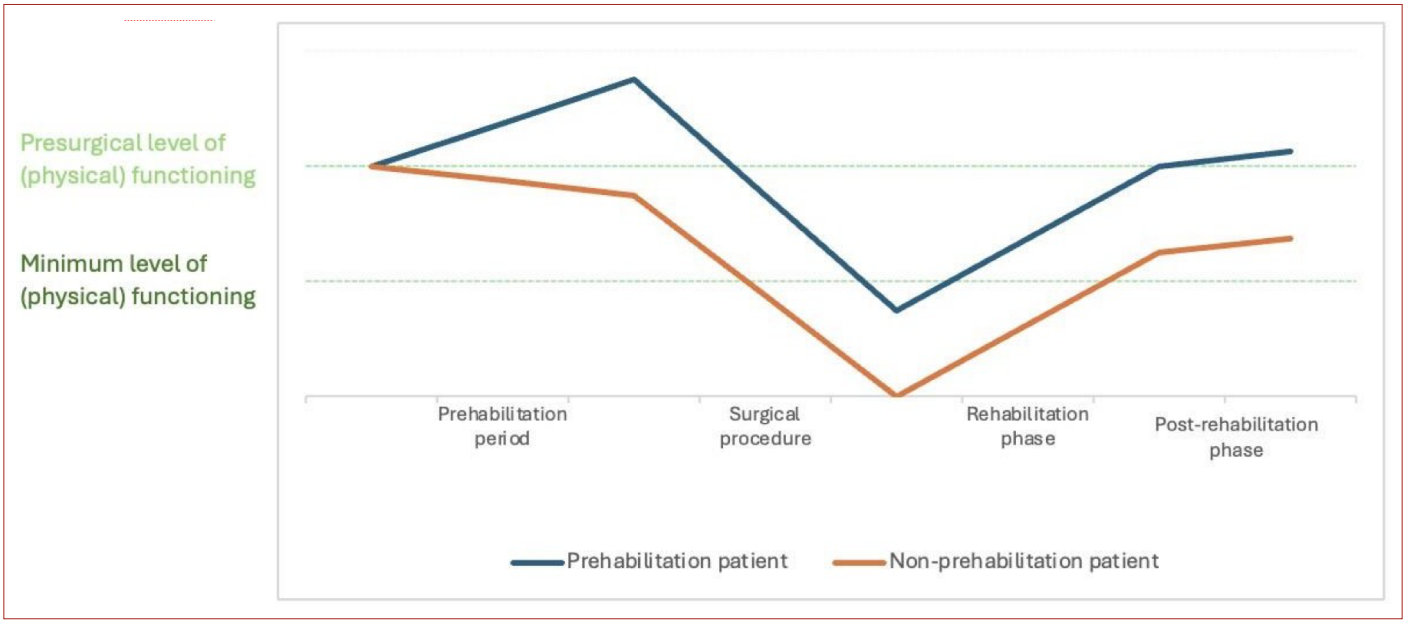

Figure 3. Concept of prehabilitation.

Functional recovery trajectory in prehabilitation vsersus non-prehabilitation patients. The graph illustrates the typical course of functional capacity in patients undergoing major surgery, comparing those who received prehabilitation (blue line) to those who did not (orange line). While both groups experience functional decline following surgery, prehabilitation patients enter the operation with a higher functional reserve and recover more rapidly, surpassing the minimum functional threshold earlier and approaching presurgical levels more consistently in the post-rehabilitation phase. Adapted from Banugo et al.[128]

2019,[25] furthermore, provide a structured framework for perioperative care, emphasizing multiple items that go in line with cornerstones of multimodal prehabilitation (Fig. 4):

- Smoking and alcohol cessation at least 4 weeks preoperatively
- Preoperative nutritional screening and supplementation in malnourished patients
- Encouragement of daily physical activity, including individualized exercise programs
- Patient education and counselling, including expectation management
- Avoidance of prolonged preoperative fasting and implementation of carbohydrate loading
- Standardized anesthesia and pain management protocols
- Early oral intake and early mobilization postoperatively

These ERAS (enhanced recovery after surgery) elements aim to reduce perioperative stress, preserve lean body mass, and improve functional recovery and overall morbidity profiles. Taken together, although robust evidence for pancreas-specific prehabilitation protocols is still emerging, the ERAS recommendations provide a structured, evidence-informed framework for perioperative care in pancreatic surgery. The integration of selected ERAS components offers a pragmatic opportunity to optimize patient condition both before and after pancreatic surgery.

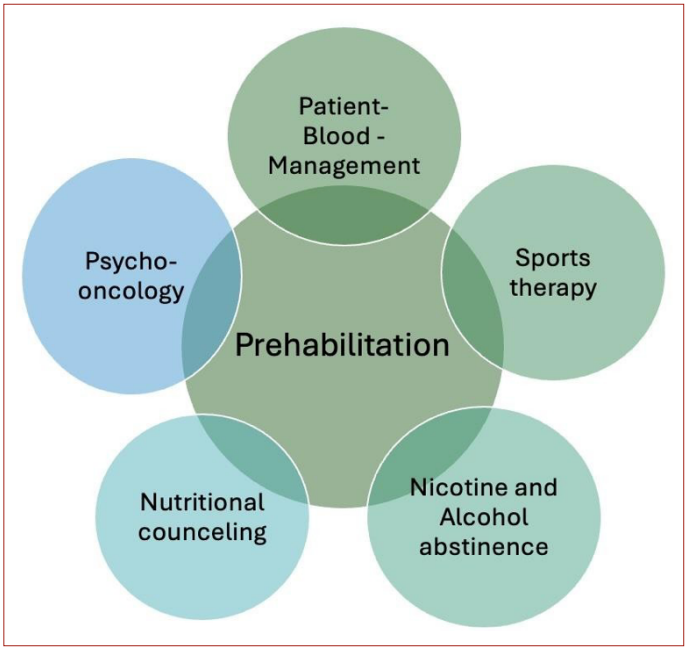

Figure 4. Core components of a multimodal prehabilitation program.

This schematic illustrates the multidimensional nature of modern prehabilitation in surgical oncology. Key components include sports therapy, nutritional counseling, nicotine and alcohol abstinence, psycho-oncologic support, and patient blood management. These interventions aim to optimize the patient's physiological and psychological status prior to major surgery and enhance postoperative recovery. Adapted from Flemming et al.[129]

Preoperative Biliary Drainage

Obstructive jaundice is a common clinical problem in patients with periampullary carcinoma including pancreatic head cancer, and may lead to cholangitis, liver dysfunction, or sepsis. In such scenarios, preoperative biliary drainage (PBD) becomes essential to stabilize the patient and ensure safe subsequent resection. Moreover, PBD is often required when neoadjuvant therapy is planned, as persistent cholestasis has been associated with increased toxicity and poorer treatment tolerance during systemic therapy.

The most commonly used technique for biliary decompression is endoscopic retrograde cholangio[pancreato]graphy (ERCP) with placement of either plastic or self-expanding metal stents. While widely available and effective in most patients, ERCP is associated with a significant risk of post-interventional infection due to retrograde contamination of the biliary tree, especially in the setting of stent occlusion or incomplete drainage.[26] Percutaneous transhepatic cholangiodrainage (PTCD) provides an alternative access route, particularly in patients with surgically altered anatomy, duodenal obstruction, or failed ERCP. Although more invasive, PTCD is associated with lower incidence of post-procedural infections and offers the advantage of external control and monitoring of bile.

Additional drainage strategies – such as endoscopic ultrasound-guided biliary drainage (EUS- BD), including choledochogastrostomy or choledochoduodenostomy, as well as surgical drainage via T-tube[27] – are increasingly applied in tertiary centers, particularly in anatomically challenging or complex cases.

The routine use of biliary drainage prior to surgery in asymptomatic patients remains controversial. The randomized multicenter DRAINAGE trial by van der Gaag et al.[26] demonstrated that routine ERCP with plastic stenting in jaundiced but otherwise stable patients undergoing pancreaticoduodenectomy led to a significantly higher rate of postoperative complications, particularly infectious and septic events, compared to primary surgery without drainage. These results strongly support upfront resection in patients without cholangitis or organ dysfunction.

Nonetheless, in defined clinical scenarios – particularly in patients with manifest cholangitis, liver dysfunction, planned neoadjuvant chemotherapy, or expected delay to surgery – preoperative drainage is clinically justified and often unavoidable. In this context, the optimal drainage strategy remains debated. A recent meta-analysis by Wang

et al.[28] comparing ERCP and PTCD in periampullary cancer patients found both methods to be overall comparable regarding drainage success, technical failure, and general complication rates. Importantly, evidence from retrospective cohort studies suggests that external drainage (e.g., PTCD or surgical drainage) may be associated with lower rates of postoperative cholangitis and pancreatic fistula compared to internal drainage (ERCP), possibly due to the higher bacterial load and bile contamination associated with endoscopic approaches (Reichert et al. unpublished, submitted).

Taken together, these findings underline the importance of individualized treatment planning based on clinical presentation, tumor resectability, timing of surgery, planned neoadjuvant therapy, and local expertise. The choice of an appropriate drainage modality with respect to postoperative morbidity remains the subject of ongoing clinical research.

Perioperative Antibiotic Prophylaxis

It is well established that single-dose perioperative antibiotic prophylaxis (PAP) effectively reduces the risk of surgical site infections in gastrointestinal surgery.[29,30] However, the specific PAP regimens applied in pancreatic surgery remain heterogeneous across institutions and countries.

A recent randomized controlled trial by D'Angelica et al.[31] challenged the use of narrow- spectrum antibiotics by demonstrating that broader-spectrum PAP with piperacillin/tazobactam not only reduced postoperative wound infections but also decreased the incidence of clinically relevant postoperative pancreatic fistula. These findings question the adequacy of smaller- spectrum regimens such as second-generation cephalosporins in high-risk pancreatic procedures.

Retrospective studies support this trend toward broader prophylaxis in selected patient populations, particularly in those with preoperative biliary drainage. Krüger et al. demonstrated significantly higher rates of bacterobilia in PBD patients, highlighting the altered microbial landscape and the increased risk of contamination with bile-resident pathogens.[32] Similarly, Dimitriou et al. emphasized the importance of adapting PAP regimens based on local resistance patterns and individual patient factors, especially in those with biliary drainage.[33] Droogh et al.[34], in a recent meta-analysis, went a step further by identifying a potential benefit of prolonged perioperative antibiotic prophylaxis specifically in patients with biliary drainage. Their findings suggest that this subgroup might profit from an extended PAP strategy beyond the traditional single-shot approach.

Nevertheless, the optimal duration and spectrum of PAP in patients with biliary contamination remain subjects of ongoing investigation.[35,36] Prospective data are required to determine whether prolonged or escalated PAP regimens reduce surgical site infections as well as postpancreatectomy complications such as in high-risk subgroups – without contributing to antimicrobial resistance.

Taken together, while broad-spectrum PAP appears beneficial in selected patient populations, especially those with biliary interventions, a universal escalation of antibiotic prophylaxis is not currently supported by guideline-level evidence. Instead, an individualized, risk-adapted approach – considering prior drainage, microbiological colonization, and institutional resistance data – should be pursued pending further prospective trials.

Minimally Invasive Versus Open Surgery

Distal Pancreatectomy

Minimally invasive distal pancreatectomy has evolved into a preferred approach for selected patients with lesions of the pancreatic body and tail, offering perioperative advantages without compromising oncologic outcomes. Originally met with scepticism due to technical complexity and limited early experience, minimally invasive distal pancreatectomy – either laparoscopic or robotic – has now reached the threshold of becoming standard of care in specialized centers.

The randomized LEOPARD trial, conducted across 14 Dutch high-volume centers, evaluated the clinical effectiveness of minimally invasive distal pancreatectomy versus open distal pancreatectomy in patients with resectable tumors of the pancreatic tail without vascular involvement. Time to functional recovery was significantly shorter in the minimally invasive group, and while rates of major complications (Clavien-Dindo ≥ III) were similar, patients undergoing minimally invasive distal pancreatectomy experienced less delayed gastric emptying and reported better postoperative quality of life.[37]

These findings were corroborated by large retrospective cohort studies: in an analysis of over 8,500 open procedures compared with 382 minimally invasive distal pancreatectomies, minimally invasive surgery was associated with lower rates of postoperative complications (30.1% vs. 39.0%, $p<0.001$), including a significant reduction in postpancreatectomy hemorrhage (13.6% vs. 20.6%, $p<0.001$), as well as shortened hospital stay.[38] Moreover, oncological equivalence was demonstrated in matched cohort studies: operative time, lymph node yield and margin status were comparable between laparoscopic (n=33) and open approaches (n=46). Even survival outcomes, rates of local recurrence and distant metastases showed no differences

between both groups.[39]

Importantly, the international DIPLOMA trial, a non-inferiority randomized controlled trial published in 2023, confirmed that minimally invasive resection (including robotic approaches) in PDAC achieves comparable oncologic results (R0 resection rates, lymph node harvest) while offering perioperative benefits such as reduced blood loss, faster recovery, and shorter length of stay.[40]

The clinical relevance of these findings is underscored in recent reflections by Diaz, Hays, and Hogg,[41] who emphasize that minimally invasive distal pancreatectomy for left-sided pancreatic cancer has moved beyond acceptance and should now be considered the preferred approach in suitable patients. However, they also highlight key prerequisites for safe implementation: structured training, high-volume centers, standardized perioperative care, and appropriate patient selection remain essential. Moreover, the broader adoption of robotic techniques is currently constrained by cost, platform availability, and training infrastructure.[41]

In summary, minimally invasive distal pancreatectomy is now firmly established as a safe, effective, and increasingly preferred approach for tumors of the pancreatic body and tail without vascular involvement. While technical expertise and access barriers remain, the convergence of evidence, training, and innovation will continue to drive the paradigm shift toward minimally invasive pancreatic surgery – offering improved recovery trajectories without compromising oncologic standards.

Pancreaticoduodenectomy

In contrast to minimally invasive distal pancreatectomy, the adoption of minimally invasive pancreaticoduodenectomy has been slower, mainly due to the complexity of the procedure and concerns regarding safety, complications, and oncologic adequacy. Nevertheless, accumulating data suggest that minimally invasive pancreaticoduodenectomy – particularly robotic-assisted approaches – may offer perioperative advantages in selected patients when performed by highly experienced surgeons in high-volume centers.[42]

A meta-analysis published in 2023 analysed data from a total of 40,230 patients across multiple, primarily non-randomized studies. The analysis revealed no significant differences in complication rates, mortality, lymph node yield, blood loss, reinterventions, or hospital readmissions, provided the procedures were performed by experienced surgeons.[42]

However, recent prospective trials present conflicting results. The EUROPA trial, a prospective randomized controlled study published in 2024, compared robotic assisted (RPD) with open pancreaticoduodenectomy (OPD) in 81 patients with resectable periampullary tumors. The 90- day Comprehensive Complication Index (CCI) was comparable between the groups (RPD: 34.0±23.5 vs. OPD: 36.5±27.7; p=0.713). However, the RPD group showed a higher rate of clinically relevant – grade B/C – pancreas-specific complications (58.6% vs. 33.3%; p=0.046).[43] These results suggest that while minimally invasive pancreaticoduodenectomy may be safe overall, certain complications may be more frequent due to the altered tissue handling or learning curve associated with minimally invasive techniques.

Earlier data from the LEOPARD-2 trial, a multicenter randomized study from the Netherlands, raised concerns about safety when the study was prematurely terminated due to an imbalance in 90-day mortality favoring the open group. This trial highlighted the importance of institutional experience, case volume, and structured training when implementing minimally invasive pancreaticoduodenectomy (van Hilst et al., 2019 → PMID: 30685489).

In their recent author reflections, Diaz, Hays, and Hogg (2025) emphasize that minimally invasive pancreaticoduodenectomy cannot yet be considered the new standard, unlike minimally invasive distal pancreatectomy. They stress that safe implementation requires significant institutional resources, highly specialized training, and adherence to standardized perioperative pathways. Moreover, the adoption of robotic platforms is still limited by cost, access, and the need for surgeon-specific credentialing. Ongoing and future randomized trials are expected to provide essential data on long-term oncologic outcomes, functional recovery, and complication rates.[41]

In summary, while minimally invasive pancreaticoduodenectomy is technically feasible and may offer specific perioperative benefits, it currently remains a procedure for selected patients in expert hands. Open pancreaticoduodenectomy continues to represent the gold standard in most settings. Further high-quality evidence is required to establish the role of minimally invasive pancreaticoduodenectomy in clinical practice and to define optimal indications, learning curves, and institutional prerequisites.

Perioperative Drainage Management

In pancreatic surgery, intraoperative drain placement remains a widely used strategy to detect and manage postoperative complications at an early stage. Drains enable monitoring of pancreatic enzyme concentrations in the peritoneal fluid, thereby facilitating the diagnosis as well as management of postoperative pancreatic fistula (POPF). They may also serve as an early indicator of other life-threatening complications such as intra-abdominal bleed-

ing or bile leakage.

However, the clinical benefit of intraoperatively placed routine drainage is subject to ongoing debate. A Cochrane review published in 2021 analyzed four randomized controlled trials comprising 1,110 patients undergoing pancreatic resection, with (n=560) or without (n=550) intraoperative drainage. The analysis found no significant differences between groups in terms of 30-day mortality, surgical site infections, surgical reintervention rates, length of hospital stay or quality of life. These findings suggest that routine drainage placement may not be universally beneficial in all patients undergoing pancreatic surgery.[44] A key limitation of these trials is the lack of stratification by risk factors such as pancreatic texture, duct size, or the type of resection. These anatomical and procedural factors are crucial, as they strongly influence the likelihood of POPF and other complications. The German POMGAT guideline acknowledges this heterogeneity and recommends an individualized drain strategy, rather than a general recommendation for or against intraoperative drainage.[24]

This routine drainage concept was recently corroborated by the PANDORINA trial, a multicenter, randomized non-inferiority trial investigating the safety of a no-drain policy in distal pancreatectomy.[45] In this large multicenter setting the rate of major morbidity was non- inferior in the no-drain group compared to the drain group in both the intention-to-treat as well as per-protocol analysis. Importantly, in the incidence of clinically relevant POPF (ISGPS grade B/C) was significantly lower in the no-drain group (12%) than in the drain group (27%). These results support the interpretation that a no-drain policy is not only safe but may reduce the incidence of clinically relevant fistula in selected patients undergoing distal pancreatectomy. Consequently, selective omission of prophylactic drains should be considered the new standard in eligible patients with low risk for POPF after distal pancreatectomy. However, this interpretation warrants careful consideration. As highlighted in the accompanying editorial by Constant and Doussot,[46] intraoperative randomization in PANDORINA was stratified using the Distal Pancreatectomy Fistula Risk Score, yet precise measurement of pancreatic duct diameter and parenchymal thickness may be more accurate when performed intraoperatively via ultrasound. Moreover, a subset of patients initially randomized to the no-drain group received intraoperative drains at the discretion of the surgeon, introducing an element of crossover and potential selection bias. This underscores the ongoing role of individualized intraoperative judgment, particularly in the presence of intraoperative bleeding, thick gland texture, or difficult anatomy. Furthermore, while superiority in terms of POPF was shown, this difference was driven predominantly by a reduction in grade B fistulas, for which the clinical impact is often moderate. Subclassification could provide more granularity in future studies. The PANDORINA study did not report this subclassification, limiting the interpretability of the clinical impact of drain omission.[45,46]

This evidence suggests that the use of intraoperative drains in pancreatic surgery should be carefully tailored to individual risk profiles and intraoperative findings. While routine drainage placement has not shown consistent benefit across unselected patient populations, its selective use remains critical in high-risk scenarios, such as soft pancreatic texture and small duct diameter. One of the most feared complications following pancreaticoduodenectomy is secondary hemorrhage due to arterial erosion in the context of a clinically relevant postoperative pancreatic fistula. In these cases, prophylactic drainage can be lifesaving by enabling early recognition of hemorrhagic or infected collections and facilitating prompt intervention. Conversely, current evidence supports the interpretation that in low-risk patients, prophylactic drain avoidance – or, alternatively, early drain removal – is beneficial and associated with a reduced incidence of major morbidity and clinically relevant postoperative pancreatic fistula.

Once a POPF is diagnosed, percutaneous image-guided drainage is the preferred first-line therapy. In selected anatomies, endoscopic ultrasound-guided approaches may be viable. If bleeding occurs, angiographic evaluation is essential to detect and manage pseudoaneurysms or arterial bleeding via transarterial embolization – an approach shown to be safer than surgical re-intervention in recent retrospective analyses.[47]

Taken together, these findings highlight a dynamic and individualized drainage strategy to reduce major morbidity, particularly in preventing progression from POPF to life-threatening complications:

- Avoid routine drainage in low-risk distal pancreatectomy
- Use prophylactic drains selectively in high-risk settings
- Implement early removal protocols in favorable postoperative courses
- Apply interventional techniques promptly for complication control

Evidence in Perioperative Medicine of Hepato-Biliary Surgery

Neoadjuvant Concepts Against Liver Cancer

Perioperative therapy for primary hepato-biliary tumors – particularly hepatocellular carcinoma (HCC) and cholan-

giocarcinoma (CCC) – has gained increasing attention in recent years. While adjuvant therapy remains the standard approach in many cases, selected patients may benefit from neoadjuvant or perioperative strategies aimed at improving resectability, downstaging advanced disease, and controlling micrometastatic spread.

Neoadjuvant and Bridging Concepts in Hepatocellular Carcinoma

Curative-intent therapy for hepatocellular carcinoma (HCC) primarily includes either liver resection or transplantation.[48,49] However, at initial diagnosis, up to 70% of patients are deemed unsuitable for surgery due to advanced tumor burden or impaired liver function.[49,50] For patients eligible for resection, long-term oncological outcomes remain unsatisfactory, with recurrence rates exceeding 50% in many series, primarily driven by intrahepatic relapse due to occult micrometastatic disease.[51]

Against this background, neoadjuvant strategies in HCC aim to achieve one of three objectives:

(i) bridging to transplantation in patients already within criteria but at risk of tumor progression;

(ii) downstaging of initially beyond-Milan tumors to transplant eligibility; and (iii) conversion therapy to enable resection of primarily unresectable tumors.[51–54] These multimodal strategies may include locoregional therapy (transarterial chemoembolization [TACE], hepatic arterial infusion chemotherapy [HAIC], stereotactic body radiation therapy [SBRT]), tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs).

While no neoadjuvant approach has yet been established as standard of care,[48,49] several promising developments have emerged. A recent meta-analysis identified the combination of a TKI, PD-1 inhibitor, and locoregional therapy as the most effective strategy for achieving secondary resectability, with improved overall survival and progression-free survival compared to non-converted-to-resection cases.[55]

Particularly noteworthy is a prospective early phase trial evaluating cabozantinib plus nivolumab in patients with locally advanced or borderline resectable HCC.[52] In this cohort of 15 patients, 12 (80%) underwent successful margin-negative resection, and 5 (42%) demonstrated a major pathological response. Importantly, this approach proved safe and feasible without delaying surgery. Immune profiling revealed enhanced infiltration of effector T cells and tertiary lymphoid structures in responders, suggesting that neoadjuvant immunotherapy may reshape the tumor immune microenvironment and reduce early recurrence risk.

Similarly, immune-oncology combinations such as atezolizumab/bevacizumab or durvalumab/tremelimumab – efficacy currently approved in the palliative setting for advanced HCC in the IMbrave050 study and in the HIMALAYA trial, respectively – have raised interest for potential use in the perioperative context.[56,57] However, there is currently no prospective clinical evidence supporting their routine application in the neoadjuvant setting. It remains to be seen whether these agents can be safely and effectively integrated into multimodal perioperative treatment strategies aimed at reducing micrometastatic disease and improving long-term outcomes.

In summary, emerging data suggest that selected patients with technically unresectable or borderline resectable HCC may benefit from multimodal neoadjuvant strategies. While preliminary results from early-phase trials are promising, the routine implementation of neoadjuvant systemic or combination therapy prior to liver resection awaits validation in large prospective studies.

Neoadjuvant and Perioperative Concepts in Cholangiocarcinoma

Due to different origin – intrahepatic, perihilar and distal – cholangiocarcinomas are anatomically and biologically heterogeneous malignancies with poor prognosis, even after curative-intent resection.[58,59] Surgical resection remains the cornerstone of treatment for resectable disease; however, only a minority of patients are eligible at diagnosis due to advanced tumor stage or unfavorable location.

Currently, there is no established recommendation for neoadjuvant therapy in patients with primarily resectable cholangiocarcinomas. However, the concept of preoperative systemic therapy is increasingly investigated in retrospective cohorts and prospective studies especially for patients with hilar or locally advanced intrahepatic disease. Its goals include tumor downstaging, increasing the R0 resection rate, and controlling occult micrometastatic disease, particularly in patients with borderline resectable or initially unresectable status. Recent retrospective series and early-phase studies suggest that neoadjuvant chemotherapy is feasible and can achieve secondary resectability in selected patients.[60–62] However, uniform criteria for anatomical resectability are lacking, and definitions vary across institutions and studies. In analogy to pancreatic cancer, proposed resectability criteria include the biliary, vascular and future liver remnant factor with tumor contact to the portal vein, hepatic arteries, and bile duct involvement (Fig. 5), although prospective validation is still pending.[63–65] Neoadjuvant systemic treatment strategies are often extrapolated from the advanced-stage setting. The combination of gemcitabine and cisplatin (Gem/Cis) is currently the standard backbone, based on the ABC-02 trial.[66] The addition of checkpoint inhibition with durvalumab or pem-

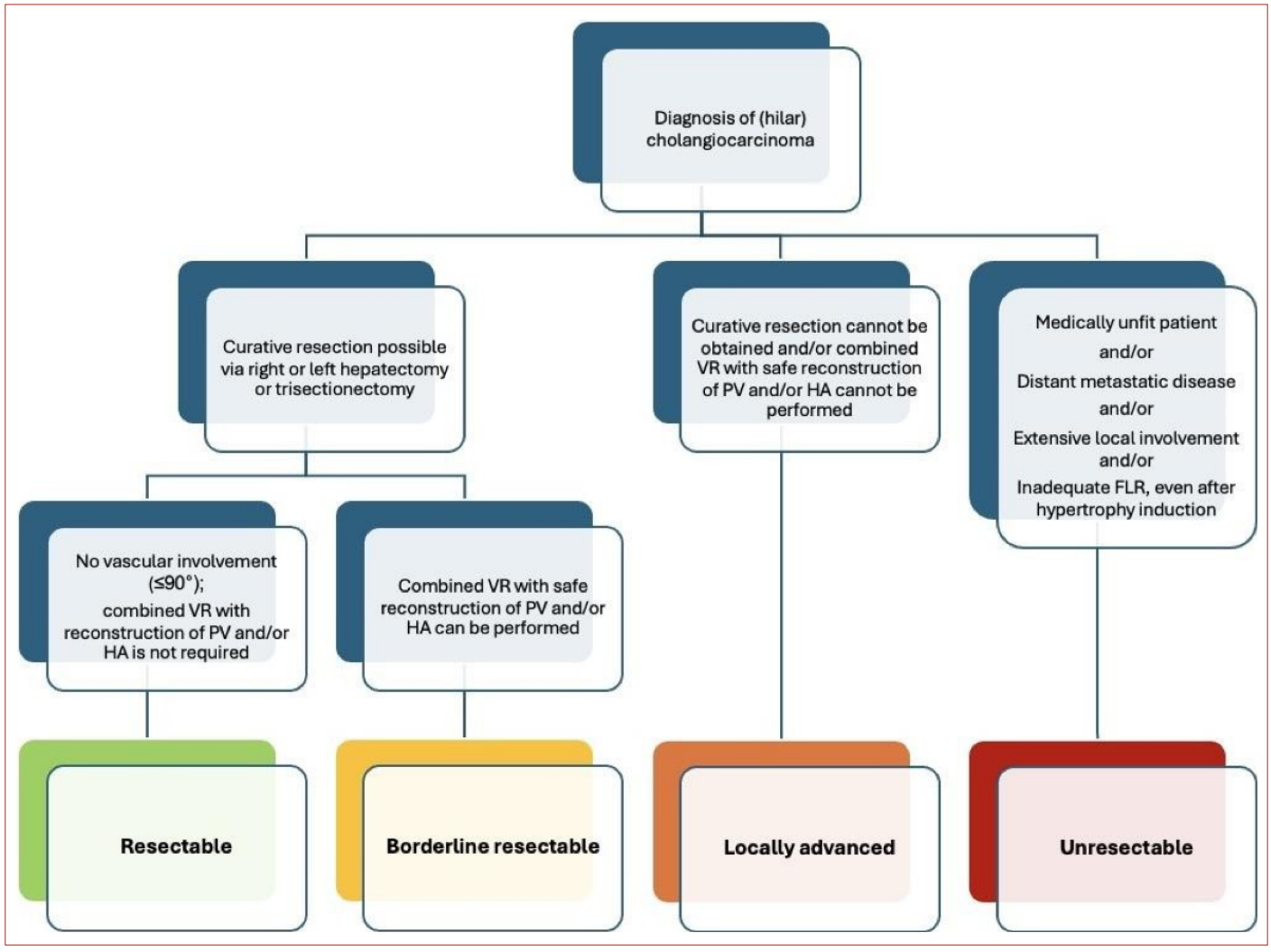

Figure 5. Resectability criteria of (perihilar) cholangiocarcinoma.

This flowchart illustrates a clinical decision algorithm for resectability in patients with (perihilar) cholangiocarcinoma. Tumors without vascular involvement (≤90° contact to portal vein [PV] or hepatic artery [HA]) are considered resectable. Borderline resectable cases allow for safe vascular reconstruction. Locally advanced tumors lack options for curative resection or safe reconstruction of PV/HA. Unresectability is defined by distant metastases, inadequate future liver remnant (FLR) despite hypertrophy induction, or extensive local disease. Medical fitness also factors into the resectability assessment. TSN = Trisectionectomy, VR = vascular resection.[64,65,130]

brolizumab has shown a significant improvement in progression-free and overall survival in the phase III TOPAZ-1 or KEYNOTE-966 trials, leading to its approval for first-line treatment in advanced biliary tract cancer.[67,68]

As demonstrated in the retrospective cohort study by ten Haaft et al., conversion chemotherapy with gemcitabine and cisplatin enabled secondary resectability in approximately 26% of patients with initially unresectable perihilar cholangiocarcinoma.[61] These findings support the feasibility of systemic therapy as a means to downstage tumors in anatomically complex or locally advanced disease. Prospective evidence further underlines the potential value of neoadjuvant chemotherapy: the recently presented GAIN trial, a multicenter randomized phase III study, investigated gemcitabine and cisplatin as neoadjuvant treatment for patients with biliary tract cancer. The trial demonstrated a significant improvement in overall survival (27.8 vs. 14.6 months) and a higher R0 resection rate (62.5% vs. 33.3%) compared to upfront surgery followed by adjuvant therapy.[60]

Building on these findings, the triplet regimen gemcitabine/cisplatin/PD (-L) 1 inhibition – already established in the palliative setting – is currently under investigation in several neoadjuvant trials for patients with high-risk resectable or borderline resectable CCC. However, robust comparative data for this immunochemotherapeutic combination in the perioperative setting are still lacking. Thus, while early clinical evidence supports the feasibility and potential efficacy of neoadjuvant chemotherapy in selected pa-

tients with cholangiocarcinoma, its routine implementation remains investigational. Future prospective studies are required to define precise selection criteria, determine the optimal regimen and duration, and assess long-term oncological outcomes. Until then, integration of neoadjuvant strategies should be guided by multidisciplinary evaluation in experienced centers.

Preoperative Optimization

Risk Stratification

Major liver resections carry significant morbidity and mortality, particularly in patients with impaired hepatic function or reduced cardiopulmonary capacity. A study of liver resections by Dunne et al. demonstrated that a low anaerobic threshold (<11 ml/kg/min) during preoperative cardiopulmonary exercise testing defined high risk patients.[69,70] This was associated with increased postoperative complications and prolonged hospital stay.[71] Other relevant predictors include advanced age, comorbidities, low skeletal muscle mass or sarcopenia, and poor performance status, e.g., ECOG ≥2. Particularly in patients with chronic liver disease, portal hypertension, and impaired synthetic liver function (e.g., elevated bilirubin and international normalized ratio and reduced platelet count), careful functional assessment is essential[72] and liver function assessment can guide surgical decision-making.

Taken together, structured risk stratification – including assessment of liver function, nutritional and physical reserve, and cardiopulmonary fitness – is crucial for selecting suitable candidates for (extended) liver resection and tailoring perioperative management accordingly.

Preoperative Optimization, Prehabilitation and ERAS

Poor preoperative functional status is a key predictor of adverse outcomes in hepato-biliary surgery. Multiple studies have demonstrated that low skeletal muscle mass with sarcopenia, reduced cardiopulmonary fitness, and malnutrition are associated with increased postoperative morbidity, delayed recovery, and prolonged length of stay following liver resection.[69–71]

Multimodal prehabilitation aims to improve patients' physical reserve and nutritional status before major oncologic surgery. A systematic review by Lambert et al. showed that prehabilitation interventions can reduce postoperative length of stay undergoing abdominal procedures including liver surgery as a global indicator of patient recovery.[73] While robust, liver-specific evidence for structured prehabilitation remains limited, high-risk patients – particularly those with impaired cardiopulmonary function, sarcopenia, or malnutrition – may benefit from individualized prehabilitation programs prior to major hepatic resections.[70] Increasingly applied neoadjuvant treatment intervals, e.g., before surgery for colorectal liver metastases or locally advanced primary hepato-biliary cancers, offer a practical window of opportunity to implement such strategies.

The 2022 ERAS guidelines for liver surgery[74] outline key elements of perioperative care, many of which align with the principles of prehabilitation (Fig. 4):

- Encouragement of daily physical activity, and implementation of supervised prehabilitation programs in high-risk patients
- Smoking and alcohol cessation for at least 4 weeks preoperatively
- Preoperative nutritional screening and tailored supplementation in malnourished or sarcopenic patients
- Preoperative biliary drainage in selected patients with obstructive jaundice
- Patient education and shared decision-making, including expectation management
- Minimization of preoperative fasting and use of carbohydrate loading
- Standardized anesthesia and intraoperative fluid management protocols
- Early enteral nutrition and early mobilization after surgery

In summary, although data from randomized trials on liver-specific prehabilitation remain sparse, current ERAS recommendations provide a structured, evidence-informed framework for perioperative care in hepato-biliary surgery. The integration of selected ERAS components and individualized prehabilitation – especially in high-risk patients – may optimize functional status, reduce complication rates, and improve overall postoperative recovery.

Management of Malignant Biliary Obstruction and Preoperative Biliary Drainage

Malignant biliary obstruction is a frequent problem in patients with biliary tract cancer, i.e. cholangiocarcinoma. Jaundice caused by biliary obstruction usually develop at an advanced tumor stage.[75] Obstruction of biliary tracts and occlusion of biliary drainages with consecutive obstructive cholestasis frequently lead to retrograde bile infection, sepsis and probably liver failure. Some studies found that preoperative cholangitis due to biliary obstruction is a negative independent prognostic factor for long-term survival in patients undergoing surgery for extrahepatic bile duct tumors.[76] Acute cholangitis can cause a rapid decline in the patients' condition due to persistent infection. Therefore, the Tokyo Guidelines 2018 recommend a prompt and adequate therapy which consists of antibiotics and interventions for biliary drainage, depending on the severity of cholangitis

and patients' clinical condition.[77] However, there is no clear recommendation for the necessity of biliary drainage in resectable and clinically stable patients with biliary obstruction. According to The European Society of Gastrointestinal Endoscopy (ESGE), biliary drainage should be performed in patients with cholangitis, severe jaundice, before neoadjuvant therapy or in cases of delayed surgery.[78]

Therefore, endoscopic drainage or percutaneous transhepatic biliary drainage (PTBD) are established options for temporary treatment in patients with biliary obstruction due to malignancy with severe jaundice and acute cholangitis prior to surgery or before implementation of a neoadjuvant therapy.[79,80] However currently, a potential superiority of either interventional procedure remains unclear.

Coelen et al. investigated complication-rates associated with preoperative biliary drainage via endoscopic stenting or PTBD in a multicenter randomized controlled trial.[81] Their study was terminated prematurely due to a higher mortality rate in patients that were treated with PTBD.[81] However, severe preoperative complications associated with biliary drainage were similar between both groups (63 % in patients with PTBD vs 67 % in patients with endoscopic biliary drainage).[81] But, these results are based on a relatively small sample size (n=54).[81] Moll et al. investigated the superiority of the respective procedures in a meta-analysis and found that PTBD is superior to EBD in the context of crossover rate, overall post-drainage complications, post-drainage pancreatitis and palliation.[82] However, Kishi et al. found an association of a higher morbidity-rate post major hepatectomy in patients with preoperative PTBD.[83] Thus, there is no clear consensus regarding the preference of either method for biliary drainage and authors recommend an individualized approach for the choice of the favored procedure.[82]

Perioperative Antibiotic Prophylaxis

In patients with malignant obstructive jaundice and preoperative bile drainage, bile duct infection is crucial. The Tokyo Guidelines 2018 recommend a duration of antibiotic therapy for 4 to 7 days after interventional biliary drainage.[77] A recent study by Srinu et al. demonstrated non-inferior outcomes for a shorter duration of antibiotic therapy.[84] Clinical cure as a primary endpoint in patients with a 4-days duration of antibiotic administration for acute cholangitis was seen in 77.79 % and in 79.66 % of patients with an 8-days duration. Additionally, they found no difference in recurrence of cholangitis, length of stay and overall mortality in both groups.[84] The microbial spectrum of ascending cholangitis mainly consists of E. coli, Klebsiella spp. and Enterococcus spp.[85] The antimicrobial treatment of choice is in consideration of the most common pathogens and thus empirical. The current Tokyo guidelines recommend third generation cephalosporines, piperacillin/tazobactam or carbapenems for empirical treatment, depending on standard protocols in the respective institution.[85]

Minimally Invasive Major Hepatectomy

Minimally invasive hepato-biliary surgery has evolved to a dynamic and rapidly expanding field within hepato-biliary oncology. Recent technological and technical advancements – including enhanced imaging, energy devices, and refined surgical techniques – have enabled laparoscopic and robotic approaches even for complex (anatomical) hepato-biliary resections.

Today, minimally invasive liver surgery is increasingly used for both benign and malignant liver lesions, including hepatocellular carcinoma, colorectal liver metastases, and selected cases of cholangiocarcinoma. In expert centers, even complex procedures such as anatomical segmentectomies, extended hepatectomies, repeat hepatectomies and laparoscopic ALPPS (associating liver partition and portal vein ligation for staged hepatectomy) have become feasible with acceptable morbidity and oncological outcomes.[86–89]

Recent literature have confirmed that laparoscopic liver resections – when performed by experienced teams - are associated with reduced blood loss, lower complication rates, shorter hospital stay, and earlier recovery, while maintaining oncological equivalence to open approaches in terms of R0 resection rates and long-term survival[90–92] Robotic liver surgery, although less widespread, offers ergonomic and visual advantages and has shown benefits particularly in complex resections.[86,93–95]

Minimally invasive liver surgery remains technically demanding and should be performed in specialized centers with appropriate expertise, especially in patients with underlying liver disease, portal hypertension, or prior abdominal surgery. In summary, minimally invasive liver surgery represents a significant advance in hepato-biliary oncology and continues to expand its role across the spectrum of benign and malignant indications. With growing experience and increasing standardization, minimally invasive hepato-biliary surgery is poised to become a cornerstone of modern surgery – even for complex resections – in appropriately selected patients.

Management and Classification of Post-Hepatectomy Specific Complications

Despite advances in perioperative management and surgical techniques, the rate of postoperative complications after hepatectomy remains between 38 % to 47 % with lower rates reported by high-volume centers[90–92] Various studies suggest an association of postoperative complica-

tions with preoperative Child-Pugh-class, time of portal occlusion during surgery, duration of operation, volume of blood loss and extent of hepatectomy.[96–98]

Perioperative Drainage Management and Biliary Leakage

Bile leakage is a frequent and potentially serious complication following hepatic resection. Its incidence ranges from 4–12 % after liver resection without biliary reconstruction[99–102] and from 0.4–8 % in procedures involving biliary-enteric anastomosis, such as hepaticojejunostomy.[103]

The International Study Group of Liver Surgery (ISGLS) defines bile leakage as either:

- a bilirubin concentration in the intra-abdominal drain fluid at least three times higher than the corresponding serum level beyond postoperative day 3, or
- the need for interventional or surgical management due to biliary collections or bile peritonitis.[104]

To standardize clinical severity, the ISGLS proposes a three-tier grading system (A–C) based on the clinical consequences and need for intervention (Table 1).[104] Management of bile leakage is guided by clinical presentation and ISGLS grade. While Grade A leaks typically resolve without additional measures, Grade B and C leaks may require step-up strategies involving imaging, interventional radiology, or surgery. Early identification and appropriate classification are critical to initiate timely treatment, avoid secondary complications such as sepsis, and reduce failure-to-rescue.

The use of prophylactic intra-abdominal drains in liver surgery has been critically reassessed in recent years. A comprehensive meta-analysis including over 5,000 patients and summarized in the 2023 German guideline for perioperative medicine evaluated the outcomes of prophylactic drainage in hepatic surgery.[24,105] The analysis revealed that in uncomplicated liver resections, prophylactic drains were associated with higher rates of bile leakage, increased overall morbidity, and longer hospital stays. Notably, patients with drains were more likely to require subsequent percutaneous drainage interventions, without clear benefit regarding wound infections or postoperative bleeding. These findings were supported by a recent randomized controlled trial from Japan and by a Cochrane review, both of which concluded that omitting drains in uncomplicated resections is safe and may reduce complications.[106,107] In contrast, for complex liver resections involving biliary and/or vascular reconstruction, the data remain insufficient to make definitive recommendations. In such high-risk cases, prophylactic drainage may still be considered on an individual basis, particularly when the anticipated risk of intra-abdominal collections or bile leakage is elevated.[24]

The 2023 ERAS Guidelines for Liver Surgery[74] support these findings by advising against routine prophylactic drainage in standard hepatic resections. Instead, the ERAS recommendation emphasizes a selective and individualized approach to drain placement, reserving it for cases where the surgical complexity or intraoperative findings suggest an increased risk of postoperative complications. This strategy aligns with the broader ERAS philosophy of reducing unnecessary interventions and optimizing recovery.

In summary, routine prophylactic drainage should be avoided in uncomplicated liver resections, whereas selective use remains appropriate in complex procedures with biliary reconstruction. Adhering to evidence-based drainage strategies may help minimize complications, reduce hospital stays, and ultimately improve perioperative outcomes.

Post-Hepatectomy Portal Vein Thrombosis

Portal vein thrombosis is a potentially severe complication following liver resection, particularly in patients with pre-existing portal hypertension. It impairs liver regeneration by reducing portal venous inflow and increasing intrahepatic vascular resistance, thereby contributing to post- hepatectomy liver failure and acute portal hypertension.[108–111] Retrospective studies report an incidence of up to 9.1 % after hepatectomy, with higher rates observed following extended right hepatectomies and prolonged (repetitive) Pringle maneuvers exceeding 75 minutes.[111,112] In this context, portal vein flow interruption, technical alterations of inflow hemodynamics, and postoperative hypercoagulability act synergistically to increase thrombotic risk. Management of portal vein thrombosis includes early anticoagulation, endovascular recanalization, or surgical thrombectomy, the latter being indicated particularly in cases of complete occlusion of the main portal vein trunk.[113] Timing is critical: patients undergoing thrombectomy within five postoperative days have significantly better outcomes compared to those with delayed intervention.[114]

The ERAS Society Guidelines for liver surgery recommend routine thromboprophylaxis in patients undergoing hepatectomy due to the high incidence of thromboembolic complications.[74] While the evidence is largely extrapolated from colorectal and general abdominal surgery, this recommendation gains relevance in patients with underlying cirrhosis or splenomegaly, where portal venous flow may be precariously balanced. Perioperative risk stratification should therefore consider the extent of resection, duration of vascular occlusion, baseline portal pressure, and hypercoagulable states. In patients with cirrhosis or small-for-size remnants, intraoperative Doppler assessment and early postoperative duplex sonography are valuable tools for early detection of impaired portal flow.

Small-for-Size and Posthepatectomy Liver Failure

Small-for-size-syndrome (SFSS) is defined as insufficient residual liver-tissue post resection or liver transplantation and thus impaired recovery of a normal liver function.[115] After extended liver resection SFSS occurs in disproportioned relation of remaining liver-mass to body surface, weight and organ-condition prior to surgery.

The increased portal blood-flow leads to hyperperfusion through the relatively small liver mass and subsequent portal hypertension and concurrent reduction in arterial perfusion.[115] These mechanisms induce biliary injury and dysfunction which are aggravated by inflammatory and immunologic responses triggered by ischemia-reperfusion injury.[116] SFSS is associated with prolonged cholestasis, coagulopathy i.e., a persistent INR > 1.5, ascites, portal hypertension and gastrointestinal bleeding with manifestation during the first 1 to 2 weeks post- surgery as well as death from recurrent sepsis after 4-6 weeks.[117,118]

Generally, patients with chronic liver disease or fibrosis are at risk for SFSS with a future liver remnant of less than 30 %, while cirrhotic patients are at risk with a future liver remnant less than < 40 %.[119] In patients with chronic liver disease and fibrosis, indications for extensive hepatectomy should be reviewed critically, as complication rates are increased.[120,121]

To adequately indicate the future liver remnant, baseline liver volume and function need to be assessed in biochemical tests and high-quality imaging, i.e. computed tomography-based volumetry.[119]

Procedures to increase future liver remnant consider the risk of SFSS and postoperative liver failure. The decision for either extensive liver resection or palliative treatment for malignant liver diseases remains challenging. In recent years, multiple strategies to induce liver hypertrophy and increase of future liver remnant have been established.[122] The optimal procedure requires a fast and sufficient hypertrophy induction outracing simultaneous tumor progression, increased R0-resection rates and relatively low morbidity and mortality. Conventional procedures of liver hypertrophy-induction are surgical portal vein ligation (PVL) and interventional portal vein embolization (PVE).

A novel strategy to induce rapid liver hypertrophy in primarily non-resectable liver tumors is a two-stage hepatectomy, associating liver partition and portal-vein-ligation for staged hepatectomy (ALPPS).[122] This procedure is more favorable in comparison to PVL and PVE that fail to induce sufficient hypertrophy in about 14 % of patients mainly due to intraparenchymal portovenous collaterals bridging segmental borders.[122] Generally, ALPPS is indicated in marginally resectable or locally advanced unresectable liver tumors of patients with a FLR of less than 30 % in healthy livers or less than 40 % in diseased livers.[122] Li et al. investigated the potential superiority of ALPPS compared to PVE and TACE in patients with initially unresectable HBV-related HCC in a cohort of 76 patients. They found a significantly shorter interval between stage 1 and stage 2 operations and a significantly higher rate of R0- resections in patients treated with ALPPS.[123] However, they reported a significantly higher rate of major complications in the ALPPS group.[123] As other studies confirm the high morbidity and mortality rate in patients undergoing ALPPS, the procedure is considered as a high-risk alternative to conventional methods of hypertrophy-induction.[124,125]

Recently, the retrospective observational DRAGON0 study demonstrated that combined PVE combined with hepatic vein embolization offers a resection-rate comparable to ALPPS with a safety profile similar to PVE alone.[126] Further, they subsequently reported a significantly higher overall-survival in patients treated with this combined procedure than in patients treated with PVE alone.[127]

In patients with insufficient hypertrophy despite PVE and hepatic vein embolization, a parenchymal split may be used to disrupt intraparenchymal collaterals between liver segments and thereby induce ALPPS-like hypertrophy. While this approach may increase future liver remnant and enhance resectability, its application in borderline cases – especially in patients with compromised or cirrhotic liver parenchyma – remains highly individualized and must be carefully weighed in a multidisciplinary context. These complex cases often require patient- tailored strategies based on detailed risk–benefit assessment.

Conclusion and Outlook

Perioperative medicine in oncologic HPB surgery has undergone a paradigm shift from standardized protocols to personalized, risk-adapted strategies. Future research should focus on validating tailored neoadjuvant approaches, refining ERAS-based interventions, and establishing standardized protocols for multimodal prehabilitation. The integration of advanced imaging, and minimally invasive techniques – including robotic liver surgery – offers exciting perspectives but requires ongoing clinical validation. Ultimately, multidisciplinary collaboration remains the cornerstone of safe and effective perioperative management in this high-risk patient population.

Disclosures

Authorship Contributions: Concept – A.H., M.S., M.R.; Design – J.B., A.M.R.; Supervision – A.H., M.S., M.R.; Materials – A.H., M.S.; Data collection/processing – J.B., A.M.R.; Analysis/interpretation – J.B., A.M.R., M.R.; Literature search – J.B., A.M.R.; Writing – J.B., A.M.R.; Critical review – A.H., M.S., M.R.

References

1. Mantke R, Weber U, Schildberg C, Hunger R, Büchler M. Mortality after total pancreatectomy in an observational nationwide cohort study. Br J Surg 2025;112.
2. Mantke R, Seliger B, Ogino S, Büchler MW, Hunger R. Not only caseload but also patient selection predicts mortality after pancreatic resection. Ann Surg Open 2025;6:e536.
3. Krautz C, Nimptsch U, Weber GF, Mansky T, Grützmann R. Effect of hospital volume on morbidity and mortality following pancreatic surgery in Germany. Ann Surg 2018;267:411–7.
4. Krautz C, Gall C, Gefeller O, Nimptsch U, Mansky T, Brunner M, et al. In-hospital mortality and failure to rescue following hepatobiliary surgery in Germany. BMC Surg 2020;20:171.
5. Koch-Institut. Krebsdatenbankabfrage. 2018. Available at: https://www.krebsdaten.de/Krebs/DE/Home/homepage_node.html. Accessed Nov 5, 2025.
6. Demir IE, Jäger C, Schlitter AM, Konukiewitz B, Stecher L, Schorn S, et al. R0 versus R1 resection after pancreaticoduodenectomy for pancreatic cancer. Ann Surg 2018;268:1058–68.
7. S3-Leitlinie Exokrines Pankreaskarzinom. Version 3.1. 2024.
8. Gillen S, Schuster T, Zum Büschenfelde CM, Friess H, Kleeff J. Neoadjuvant therapy in pancreatic cancer: systematic review and meta-analysis. PLoS Med 2010;7:e1000267.
9. Dickerson LD, Gittens J, Brunning C, Jackson R, Schmid MC, Mielgo A, et al. Neoadjuvant treatment vs upfront surgery in pancreatic cancer: meta-analysis. BJS Open 2025;9.
10. National Institute for Health and Care Excellence. Pancreatic cancer guideline. 2018. Available from: www.nice.org.uk/guidance/ng85. Accessed Nov 5, 2025.
11. NCCN Clinical Practice Guideline: Pancreatic cancer. 2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed Jun 8, 2025.
12. Takaori K, Bassi C, Biankin A, Brunner TB, Cataldo I, Campbell F, et al. IAP/EPC consensus for pancreatic cancer treatment. Pancreatology 2016;16:14–27.
13. Conroy T, Pfeiffer P, Vilgrain V, Lamarca A, Seufferlein T, O'Reilly EM, et al. ESMO guideline for pancreatic cancer. Ann Oncol 2023;34:987–1002.
14. Siewert JR, Rothmund M, Schumpelick V. Onkologische Chirurgie. 2010.
15. Chun YS, Cooper HS, Cohen SJ, Konski A, Burtness B, Denlinger CS, et al. Pathologic response to preoperative therapy in pancreatic cancer. Ann Surg Oncol 2011;18:3601–7.
16. Jang JY, Han Y, Lee H, Kim SW, Kwon W, Lee KH, et al. Neoadjuvant chemoradiation vs upfront surgery for borderline resectable pancreatic cancer. Ann Surg 2018;268:215–22.
17. Versteijne E, Suker M, Groothuis K, Akkermans-Vogelaar JM, Besselink MG, Bonsing BA, et al. PREOPANC trial: chemoradiotherapy vs immediate surgery. J Clin Oncol 2020;38:1763–73.
18. Kim SY, Weinberg L, Christophi C, Nikfarjam M. Outcomes of pancreaticoduodenectomy in patients ≥80 years. HPB 2017;19:475–82.
19. Tas F, Sen F, Odabas H, Kilic L, Keskin S, Yildiz I. Performance status as prognostic factor in pancreatic cancer. Int J Clin Oncol 2013;18:839–46.
20. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-del Castillo C, Hackert T, et al. Consensus definition of borderline resectable pancreatic ductal adenocarcinoma. Pancreatology 2018;18:2–11.
21. Molenaar CJ, van Rooijen SJ, Fokkenrood HJ, Roumen RM, Janssen L, Slooter GD. Prehabilitation vs none for colorectal cancer surgery. Cochrane Database Syst Rev 2022;5.
22. McIsaac DI, Gill M, Boland L, Hutton B, Branje K, Shaw J, et al. Prehabilitation before surgery: umbrella review. Br J Anaesth 2022;128:244–57.
23. Ngo-Huang A, Parker NH, Bruera E, Lee RE, Simpson R, O'Connor DP, et al. Home-based prehabilitation improves function in pancreatic cancer. Integr Cancer Ther 2019;18:1–8.
24. S3-Leitlinie Perioperatives Management bei gastrointestinalen Tumoren. 2023.
25. Melloul E, Lassen K, Roulin D, Grass F, Perinel J, Adham M, et al. ERAS recommendations for pancreatoduodenectomy. World J Surg 2020;44:2056–84.
26. van der Gaag NA, Rauws EAJ, van Eijck CHJ, Bruno MJ, van der Harst E, Kubben FJGM, et al. Preoperative biliary drainage for pancreatic cancer. N Engl J Med 2010;362:129–37.
27. Klotz R, Hank T, Berente MP, Joos M, Hinz U, Pianka F, et al. Preoperative surgical vs endoscopic bile duct drainage. Ann Surg 2024.
28. Wang Y, Zhao X, She Y, Kang Q, Chen X. Efficacy of biliary drainage in malignant jaundice: meta-analysis. Front Oncol 2024;14:1–8.
29. Dellinger EP, Gross PA, Barrett TL, Krause PJ, Martone WJ, McGowan JE, et al. Antimicrobial prophylaxis in surgery: quality standard. Clin Infect Dis 1994;18:422–7.
30. Cruse PJE, Foord R. Epidemiology of wound infection: 10-year prospective study. Surg Clin North Am 1980;60:27–40.
31. D'Angelica MI, Ellis RJ, Liu JB, Brajcich BC, Gönen M, Thompson VM, et al. Piperacillin–tazobactam vs cefoxitin as prophylaxis for pancreatoduodenectomy. JAMA 2023;329:1579.
32. Krüger CM, Adam U, Adam T, Kramer A, Heidecke CD, Makowiec F, et al. Bacterobilia in pancreatic surgery and implications for prophylaxis. World J Gastroenterol 2019;25:6238–47.
33. Dimitriou I, Bultmann U, Niedergethmann M. Antibiotic prophylaxis in pancreas resections with or without bile drainage. Chirurg 2019;90:557–63.
34. Droogh DHM, Groen JV, de Boer MGJ, van Prehn J, Putter H, Bonsing BA, et al. Prolonged antibiotic prophylaxis after pancreatoduodenectomy: meta-analysis. Br J Surg 2023;110:1458–66.
35. Schwarz L, Gillibert A, Rondeaux J, Lacroix E, Sa Cunha A, Joannes-

Boyau O. Postoperative anti-infective strategy after biliary stent in pancreatoduodenectomy: protocol. BMC Surg 2024;24:237.
36. Droogh DHM, de Boer MGJ, van Prehn J, Putter H, Bonsing BA, Bosscha K, et al. SPARROW trial protocol for postoperative infections after Whipple. Trials 2025;26:88.
37. De Rooij T, van Hilst J, van Santvoort H, Boerma D, van Den Boezem P, Daams F, et al. Minimally invasive vs open distal pancreatectomy (LEOPARD). Ann Surg 2019;269:2–9.
38. Tran Cao HS, Lopez N, Chang DC, Lowy AM, Bouvet M, Baumgartner JM, et al. Perioperative outcomes in minimally invasive distal pancreatectomy. JAMA Surg 2014;149:237–43.
39. Bauman MD, Becerra DG, Kilbane EM, Zyromski NJ, Schmidt CM, Pitt HA, et al. Laparoscopic distal pancreatectomy for pancreatic cancer. Surg Endosc 2018;32:53–61.
40. Korrel M, Jones LR, van Hilst J, Balzano G, Björnsson B, Boggi U, et al. Minimally invasive vs open distal pancreatectomy (DIPLOMA). Lancet Reg Health Eur 2023;31:100673.
41. Diaz A, Hays S, Hogg ME. Minimally invasive pancreatic resection: past, present, and future. Ann Surg Oncol 2025;36.
42. Yan Y, Hua Y, Chang C, Zhu X, Sha Y, Wang B. Laparoscopic vs open pancreaticoduodenectomy: meta-analysis. Front Oncol 2023;12:1–12.
43. Klotz R, Mihaljevic AL, Kulu Y, Sander A, Klose C, Behnisch R, et al. Robotic vs open partial pancreatoduodenectomy (EUROPA). Lancet Reg Health Eur 2024;39:1–10.
44. He S, Xia J, Zhang W, Lai M, Cheng N, Liu Z, et al. Prophylactic abdominal drainage after pancreatic surgery. Cochrane Database Syst Rev 2021;2021.
45. van Bodegraven EA, Balduzzi A, van Ramshorst TME, Malleo G, Vissers FL, van Hilst J, et al. Prophylactic drainage after distal pancreatectomy (PANDORINA). Lancet Gastroenterol Hepatol 2024;9:438–47.
46. Constant M, Doussot A. Commentary on PANDORINA trial. Hepatobiliary Surg Nutr 2024;13:675–7.
47. Bruder L, Schawe L, Gebauer B, Frese JP, de Bucourt M, Beyer K, et al. Treatment for visceral artery erosions after pancreatitis or surgery. Curr Oncol 2022;29:2472–82.
48. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL, et al. EASL guideline for hepatocellular carcinoma. J Hepatol 2018;69:182–236.
49. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD guidance for hepatocellular carcinoma. Hepatology 2023;78:1922–65.
50. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet 2022;400:1345–62.
51. Llovet JM, Pinyol R, Yarchoan M, Singal AG, Marron TU, Schwartz M, et al. Neoadjuvant and adjuvant immunotherapies in hepatocellular carcinoma. Nat Rev Clin Oncol 2024;21:294–311.
52. Ho WJ, Zhu Q, Durham J, Popovic A, Xavier S, Leatherman J, et al. Neoadjuvant cabozantinib and nivolumab convert unresectable HCC to resectable. Nat Cancer 2021;2:891–903.
53. Sidali S, Trépo E, Sutter O, Nault J. New concepts in hepatocellular carcinoma treatment. United European Gastroenterol J 2022;10:765–74.
54. Vogel A, Chan SL, Dawson LA, Kelley RK, Llovet JM, Meyer T, et al. ESMO guideline for hepatocellular carcinoma. Ann Oncol 2025;36:491–506.
55. Xu H, Zhang H, Li B, Chen K, Wei Y. Conversion therapy for unresectable hepatocellular carcinoma: meta-analysis. BMC Cancer 2024;24:1–12.
56. Qin S, Chen M, Cheng AL, Kaseb AO, Kudo M, Lee HC, et al. Atezolizumab plus bevacizumab after resection/ablation in high-risk HCC (IMbrave050). Lancet 2023;402:1835–47.
57. Sangro B, Chan SL, Kelley RK, Lau G, Kudo M, Sukeepaisarnjaroen W, et al. Four-year survival update: HIMALAYA trial. Ann Oncol 2024;35:448–57.
58. Sturesson C, Soreide K. Preoperative management in perihilar cholangiocarcinoma. Br J Surg 2025;112.
59. Banales JM, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, et al. Cholangiocarcinoma mechanisms and management. Nat Rev Gastroenterol Hepatol 2020;17:557–88.
60. Goetze TO, Bechstein WO, Bankstahl US, Keck T, Königsrainer A, Lang SA, et al. Neoadjuvant gemcitabine–cisplatin before radical resection vs surgery alone in gallbladder carcinoma. BMC Cancer 2020;20:122.
61. ten Haaft BHEA, Sickmann MMT, Nooijen LE, Ali M, Wilmink JW, Klümpen HJ, et al. Gemcitabine–cisplatin induction for perihilar cholangiocarcinoma (IMPACCA). Eur J Surg Oncol 2025;51:109358.
62. van Keulen A, Franssen S, van der Geest LG, de Boer MT, Coenraad M, van Driel LMJW, et al. Nationwide treatment and outcomes of perihilar cholangiocarcinoma. Liver Int 2021;41:1945–53.
63. Matsuyama R, Mori R, Ota Y, Homma Y, Yabusita Y, Hiratani S, et al. Neoadjuvant gemcitabine plus S1 for borderline resectable perihilar cholangiocarcinoma. Ann Surg Oncol 2022;29:2393–405.
64. Nooijen LE, de Boer MT, Braat AE, Dewulf M, den Dulk M, Hagendoorn J, et al. National resectability classification for perihilar cholangiocarcinoma: Delphi consensus. Eur J Surg Oncol 2025;51:107117.
65. Kuriyama N, Usui M, Gyoten K, Hayasaki A, Fujii T, Iizawa Y, et al. Neoadjuvant chemotherapy followed by surgery for perihilar cholangiocarcinoma. BMC Cancer 2020;20:405.
66. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine vs gemcitabine in biliary tract cancer. N Engl J Med 2010;362:1273–81.
67. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab + gemcitabine/cisplatin in biliary cancer (KEYNOTE-966). Lancet 2023;401:1853–65.
68. Oh DY, He AR, Bouattour M, Okusaka T, Qin S, Chen LT, et al. Durvalumab + gemcitabine/cisplatin in biliary cancer (TOPAZ-1). Lancet Gastroenterol Hepatol 2024;9:694–704.

69. Dunne DFJ, Jones RP, Lythgoe DT, Pilkington FJ, Palmer DH, Malik HZ, et al. Cardiopulmonary exercise testing before liver surgery. J Surg Oncol 2014;110:439–44.
70. Dunne DFJ, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, et al. Randomized trial of prehabilitation before liver resection. Br J Surg 2016;103:504–12.
71. Kasivisvanathan R, Abbassi-Ghadi N, McLeod ADM, Oliver A, Rao Baikady R, Jhanji S, et al. Cardiopulmonary exercise testing predicts morbidity after hepatectomy. HPB 2015;17:637–43.
72. Ostojic A, Mahmud N, Reddy KR. Surgical risk stratification in cirrhosis. Hepatol Int 2024;18:876–91.
73. Lambert JE, Hayes LD, Keegan TJ, Subar DA, Gaffney CJ. Impact of prehabilitation on cancer surgery outcomes. Ann Surg 2021;274:70–7.
74. Joliat G, Kobayashi K, Hasegawa K, Thomson J, Padbury R, Scott M, et al. ERAS recommendations for liver surgery 2022. World J Surg 2023;47:11–34.
75. Cimen S, Cimen S, Molinari M. Loco-regional palliation of unresectable cholangiocarcinoma. Ann Palliat Med 2014;3.
76. Akita M, Ajiki T, Matsumoto T, Shinozaki K, Goto T, Asari S, et al. Preoperative cholangitis affects survival in extrahepatic bile duct cancer. J Gastrointest Surg 2017;21:983–9.
77. Miura F, Okamoto K, Takada T, Strasberg SM, Asbun HJ, Pitt HA, et al. Tokyo Guidelines 2018: acute biliary infection management. J Hepatobiliary Pancreat Sci 2018;25:31–40.
78. Dumonceau JM, Tringali A, Papanikolaou IS, Blero D, Mangiavillano B, Schmidt A, et al. ESGE guideline for endoscopic biliary stenting. Endoscopy 2018;50:910–30.
79. Salgado SM, Gaidhane M, Kahaleh M. Endoscopic palliation of malignant biliary strictures. World J Gastrointest Oncol 2016;8:240–7.
80. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, et al. Guideline for diagnosis and treatment of cholangiocarcinoma. Gut 2012;61:1657–69.
81. Coelen RJS, Roos E, Wiggers JK, Besselink MG, Buis CI, Busch ORC, et al. Endoscopic vs percutaneous drainage in resectable perihilar cholangiocarcinoma. Lancet Gastroenterol Hepatol 2018;3:681–90.
82. Moll CF, de Moura DTH, Ribeiro IB, Proença IM, do Monte Junior ES, Sánchez-Luna SA, et al. Endoscopic vs percutaneous drainage for PCCA: meta-analysis. Clinics 2023;78:1–12.
83. Kishi Y, Shimada K, Nara S, Esaki M, Kosuge T. Type of biliary drainage predicts outcome after major hepatectomy. Langenbecks Arch Surg 2016;401:503–11.
84. Srinu D, Shah J, Jena A, Jearth V, Singh AK, Mandavdhare HS, et al. Conventional vs short antibiotics in moderate–severe cholangitis. Am J Gastroenterol 2024;119:1–8.
85. Gomi H, Solomkin JS, Schlossberg D, Okamoto K, Takada T, Strasberg SM, et al. Tokyo Guidelines 2018: antimicrobial therapy. J Hepatobiliary Pancreat Sci 2018;25:3–16.
86. Birgin E, Abdelhadi S, Seyfried S, Rasbach E, Rahbari M, Téoule P, et al. Robotic or laparoscopic repeat hepatectomy after open hepatectomy. Surg Endosc 2024;38:1296–305.
87. Dincer HA. Advances in minimally invasive liver surgery. North Clin Istanb 2024;11:586–92.
88. Loke S, Ong BDC, Ng J, Kow AWC. Minimally invasive ALPPS: systematic review. Int J Surg 2025;111:2283–90.
89. Birgin E, Heibel M, Hetjens S, Rasbach E, Reissfelder C, Téoule P, et al. Robotic vs laparoscopic hepatectomy (ROC'N'ROLL). Lancet Reg Health Eur 2024;43:100972.
90. Taketomi A, Kitagawa D, Itoh S, Harimoto N, Yamashita Y, Gion T, et al. Trends in morbidity and mortality after hepatic resection for HCC. J Am Coll Surg 2007;204:580–7.
91. Imamura H. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198.
92. Benzoni E, Molaro R, Cedolini C, Favero A, Cojutti A, Lorenzin D, et al. Liver resection for HCC: causes and risk factors for postoperative complications. Hepatogastroenterology 2007;54:186–9.
93. Téoule P, Dunker N, Gölz V, Rasbach E, Reissfelder C, Birgin E, et al. Laparoscopic hepatectomy in posterosuperior segments: risk factors for complications. Surg Endosc 2025;39:3691–701.
94. Birgin E, Rahbari NN. Robotic anatomical segment VIII resection for hepatocellular carcinoma. Ann Surg Oncol 2025;32:3544.
95. Birgin E, Heibel M, Téoule P, Reißfelder C, Rahbari NN. Robotic sectionectomy vs robotic hemihepatectomy: perioperative outcomes. J Robot Surg 2024;18:197.
96. Hoffmann K, Hinz U, Stravodimos C, Knoblich T, Schön MR, Büchler MW, et al. Risk assessment for liver resection. Surgery 2018;164:998–1005.
97. Masi G, Loupakis F, Pollina L, Vasile E, Cupini S, Ricci S, et al. Long-term outcome in unresectable metastatic colorectal cancer treated with FOLFOXIRI and surgery. Ann Surg 2009;249:420–5.
98. Adam R, Pascal G, Castaing D, Azoulay D, Delvart V, Paule B, et al. Tumor progression while on chemotherapy. Ann Surg 2004;240:1052–64.
99. Yamashita YI, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Shimada M, et al. Bile leakage after hepatic resection: experience in 781 patients. Ann Surg 2000;233:1–6.
100. Erdogan D, Busch ORC, van Delden OM, Rauws EAJ, Gouma DJ, van Gulik TM. Management of bile leakage after partial liver resection. Dig Surg 2008;25:60–6.
101. Guillaud A, Pery C, Campillo B, Lourdais A, Laurent S, Boudjema K. Predictors of clinically relevant bile leakage after liver resection. HPB 2013;15:224–9.
102. Tanaka S, Hirohashi K, Tanaka H, Shuto T, Lee SH, Kubo S, et al. Bile leakage after hepatic resection for malignant liver tumors. J Am Coll Surg 2002;195:1–6.
103. de Castro SMM, Kuhlmann KFD, Busch ORC, van Delden OM, Laméris JS, van Gulik TM, et al. Biliary leakage after hepaticojejunostomy. J Gastrointest Surg 2005;9:1163–73.
104. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti

L, et al. Definition and grading of bile leakage after hepatobiliary surgery. Surgery 2011;149:680–8.
105. Dezfouli SA, Ünal UK, Ghamarnejad O, Khajeh E, Ali-Hasan-Al-Saegh S, Ramouz A, et al. Prophylactic drainage in liver resection: meta-analysis. Sci Rep 2021;11:3095.
106. Gurusamy KS, Samraj K, Davidson BR. Routine abdominal drainage in uncomplicated liver resection. Cochrane Database Syst Rev 2007;2007:CD006232.
107. Arita J, Sakamaki K, Saiura A, Konishi M, Sakamoto Y, Hashimoto M, et al. Drain placement after liver resection increases severe complications. Ann Surg 2021;273:224–31.
108. Wu TJ, Dahiya D, Lee CS, Lee CF, Chou HS, Chan KM, et al. Portal venous hemodynamics and liver regeneration post-transplant. Liver Transpl 2011;17:1035–45.
109. Marubashi S, Sakon M, Nagano H, Gotoh K, Hashimoto K, Kubota M, et al. Effect of portal hemodynamics on liver regeneration in rat model. Surgery 2004;136:1028–37.
110. Abshagen K, Eipel C, Vollmar B. Hemodynamic signal driving liver regeneration: critical appraisal. Langenbecks Arch Surg 2012;397:579–90.
111. Yoshiya S, Shirabe K, Nakagawara H, Soejima Y, Yoshizumi T, Ikegami T, et al. Portal vein thrombosis after hepatectomy. World J Surg 2014;38:1.
112. Onda S, Furukawa K, Shirai Y, Hamura R, Horiuchi T, Yasuda J, et al. Classification-oriented treatment strategy for portal vein thrombosis after hepatectomy. Ann Gastroenterol Surg 2020;4:701–9.
113. Wakizaka K, Shichi S, Aiyama T, Asahi Y, Nagatsu A, Orimo T, et al. Risk factors and management of portal vein thrombosis after hepatectomy. Ann Surg Open 2024;5:e523.
114. Kuboki S, Shimizu H, Ohtsuka M, Kato A, Yoshitomi H, Furukawa K, et al. Portal vein thrombosis after hepatectomy: incidence, risk factors and management. Am J Surg 2015;210:878–85.
115. Papamichail M, Pizanias M, Heaton ND. Minimizing small-for-size syndrome after liver surgery. Hepatobiliary Pancreat Dis Int 2022;21:113–33.
116. Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. Am J Physiol Gastrointest Liver Physiol 2003;284:G15–26.
117. Golriz M, Majlesara A, El Sakka S, Ashrafi M, Arwin J, Fard N, et al. Small-for-size and flow syndrome: alternative description for posthepatectomy liver failure. Clin Res Hepatol Gastroenterol 2016;40:267–75.
118. Eshkenazy R, Dreznik Y, Lahat E, Zakai BB, Zendel A, Ariche A. Small-for-size liver remnant after resection: prevention and management. Hepatobiliary Surg Nutr 2014;3:303–12.
119. Narula N, Aloia TA. Portal vein embolization in extended liver resection. Langenbecks Arch Surg 2017;402:727–35.
120. Nakamura N, Hatano E, Iguchi K, Seo S, Taura K, Uemoto S. Posthepatectomy liver failure affects long-term function after HCC resection. World J Surg 2016;40:929–36.
121. Papamichail M, Pizanias M, Heaton ND. Minimizing small-for-size syndrome after liver surgery. Hepatobiliary Pancreat Dis Int 2022;21:113–33.
122. Zhang GQ, Zhang ZW, Lau WY, Chen XP. ALPPS: increasing resectability in liver surgery. Int J Surg 2014;12:437–41.
123. Li PP, Huang G, Jia NY, Pan ZY, Liu H, Yang Y, et al. ALPPS vs sequential TACE and PVE in HBV-HCC. Hepatobiliary Surg Nutr 2022;11:38–51.
124. Schadde E, Ardiles V, Slankamenac K, Tschuor C, Sergeant G, Amacker N, et al. ALPPS vs conventional staged hepatectomy in unresectable tumors. World J Surg 2014;38:1.
125. Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, et al. Early survival and safety of ALPPS: International ALPPS Registry. Ann Surg 2014;260:1–7.
126. Heil J, Korenblik R, Heid F, Bechstein WO, Bemelmans M, Binkert C, et al. Portal vs portal+hepatic vein embolization (DRAGON). Br J Surg 2021;108:834–42.
127. Korenblik R, Heil J, Smits J, James S, Olij B, Bechstein WO, et al. Liver regeneration after portal+hepatic vein embolization improves survival vs PVE alone. Br J Surg 2024;111:1–6.
128. Banugo P, Amoako D. Prehabilitation. BJA Educ 2017;17:401–5.
129. Flemming S. App-based prehabilitation: adherence and implementation. Chirurgie 2025;96:459–63.
130. Schulick RD. Criteria of unresectability in liver surgery. HPB 2008;10:122–5.
131. Rahbari NN, Garden OJ, Padbury R, Maddern G, Koch M, Hugh TJ, et al. Post-hepatectomy haemorrhage: ISGLS definition and grading. HPB 2011;13:528–35.
132. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: ISGLS definition and grading. Surgery 2011;149:713–24.
133. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: ISGLS definition. Surgery 2011;149:680–8.
134. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. ISGPS update on postoperative pancreatic fistula definition (2016). Surgery 2017;161:584–91.
135. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying after pancreatic surgery: ISGPS definition. Surgery 2007;142:761–8.
136. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage: ISGPS definition. Surgery 2007;142:20–5.
137. Marchegiani G, Barreto SG, Bannone E, Sarr M, Vollmer CM, Connor S, et al. Postpancreatectomy acute pancreatitis (PPAP) definition. Ann Surg 2022;275:663–72.
138. Noll et al. Perioperative multidrug-resistant bacteria impair clinical outcome after pancreatic surgery: Missed targets of antibiotic prophylaxis. Surgery 2025:188:109717.