Is enhancing recovery after pancreatic cancer surgery even possible?—a narrative review

Monish Karunakaran[1,2], Savio George Barreto[3,4]

[1]Department of Gastrointestinal Surgery, Gastrointestinal Oncology, and Bariatric Surgery, Medanta Institute of Digestive and Hepatobiliary Sciences, Medanta, The Medicity, Gurgaon, India; [2]Department of Liver Transplantation and Regenerative Medicine, Medanta, The Medicity, Gurgaon, India; [3]College of Medicine and Public Health, Flinders University, South Australia, Australia; [4]Division of Surgery and Perioperative Medicine, Flinders Medical Center, Bedford Park, Adelaide, South Australia, Australia

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Correspondence to: Savio George Barreto. Department of Surgery, Flinders Medical Centre, Bedford Park, South Australia, 5042, Australia. Email: georgebarreto@yahoo.com; savio.barreto@sa.gov.au.

Objective: This narrative review traces the evolutionary journey of ERAS® with emphasis on challenges specific to pancreatic cancer. This article will also attempt to explore the barriers to routine ERAS® implementation and offers possible solutions to increasing its uptake and compliance rates.

Background: Enhanced Recovery After Surgery (ERAS®) represents a paradigm shift in the perioperative management of surgical patients using a multi-modality approach each of which is based on best available evidence. ERAS® has come a long way since its inception and can now be regarded as one of the promising ways forward in the perioperative management of patients undergoing pancreatic surgery.

Methods: We identified 37 studies on the impact of ERAS® in pancreatic surgery, published over the last 2 decades. Implementation of ERAS® helped in shortening the length of stay without an increase in hospital re-admissions, morbidity, or mortality. Compliance to ERAS® is relatively low following pancreatic surgery, with a reported median compliance of 52%. Elderly patients or those with higher BMI, higher ASA scores, hypoalbuminemia, cardiac comorbidities or longer operative duration are more prone for deviations.

Conclusions: ERAS pathways have been successful in achieving their intended outcomes, despite low compliance. Complementing existing ERAS® pathways with prehabilitation measures, risk-stratified clinical pathways and the accessibility to step-down care facilities following discharge may facilitate its wider utilisation.

Keywords: Outcomes; enhanced recovery; pancreatic surgery; quality; compliance

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ERAS®: the road travelled so far!

Introduced by Kehlet *et al.* in 1997 (1), Enhanced Recovery After Surgery (ERAS®) is a holistic, multi-pronged, interdisciplinary framework which utilizes evidence-based practices to decrease surgical stress, maintain physiologic homeostasis, and facilitate recovery of patients (2). Pioneering work by Kehlet *et al.* (3) showed that patients undergoing open sigmoid resection could be discharged in 2 days, at a time when the average length of stay was around 10 days in most of the centres. The concept survived initial scepticism, and its acceptance increased as it became evident that outcomes improved with standardized implementation of ERAS® protocols (4). Encouraged by the dramatic reduction in hospital stay, without compromising patient outcomes, and an increase in functional recovery following structured synchronous implementation of an ERAS® program in elective colonic surgery in Netherlands, led to the founding of the ERAS® Society in 2010 (5). This society is an international non-profit academic society aiming wider dissemination and periodic appraisal of the ERAS® guidelines.

Although the initial experience with ERAS® was largely based on reports of its use and success in colorectal surgery, other surgical subspecialties began to adapt these principles with the overarching aim of enhancing patient recovery. It is important to note that the benefits of ERAS®, compared to conventional care, in terms length of hospitalization and reduced overall complications continued to be appreciated in colorectal cancer surgery despite the uniform adoption of laparoscopic surgery (6). Recent meta-analyses in oesophageal and gastric cancer have also demonstrated the benefits of adoption of the principles of ERAS® on the length of hospital stay and time to functional recovery without negatively influencing overall morbidity rates (7,8). In *Urology*, Orejón *et al.* (9) noted a reduced utilization of Intensive Care Unit stay as well as the need for transfusion of blood products following radical cystectomy for bladder cancer. Similarly, the benefits of ERAS® on patient satisfaction, along with reduced length of hospital stay and overall costs have been documented following its adoption for gynaecological malignancies (10). The use of ERAS® has been successfully trialed in thoracic surgery with increasing compliance found to correlate with improved outcomes in lung resections for cancer (11) while it even enabled same-day discharge following mastectomy for breast cancer (12). We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/ 10.21037/cco-21-36).

Rationale and perceived benefits of ERAS®

The scope of ERAS® extends beyond its commonly perceived aim of shortening hospital stay (13). It emphasizes the creation of a supportive environment for the patient to have an optimal perioperative experience that, in turn, reduces surgical stress (14). ERAS® guidelines encompass precisely defined elements for all stages of perioperative care (15), with the derived benefits attributed to either a significant improvement in one or two influential individual elements, summation of marginal gains achieved by adherence to the entire pathway, or a combination of both (16).

Surgical stress is borne out of a combination of catabolic-neuroendocrine and inflammatory-immunological responses, culminating in a state of insulin resistance (17). This causes accelerated protein breakdown and increased production of endogenous hepatic glucose (18), which is partly utilized by the cells for glycolysis with the rest directed towards the generation of oxygen radicals with resultant inflammation (19). Practices like carbohydrate loading (20) and early initiation of oral/enteral feeds (21) are based on this understanding, which may mitigate insulin resistance (22,23). Early enteral feeds also maintain the gut-mucosal barrier, which may help in the reduction of infectious complications (24). Pain contributes to the insulin resistance by sympathetic stimulation and systemic release of pro-inflammatory cytokines (25). Pain relief with neuraxial blockade decreases insulin resistance by attenuation of hormonal response (cortisol and epinephrine), an effect which is not shown by opioids or non-steroidal anti-inflammatory drugs (NSAIDs) (26). Similarly, normothermia diminishes the perioperative release of catecholamines and decreases loss of body nitrogen (27). Though the underlying mechanisms are yet to be elucidated, early mobilization ameliorates fatigue and facilitates functional recovery (28), in addition to reducing thrombo-embolic complications. Post-operative ileus is multifactorial in origin and the causative factors include neural sympathetic inhibitory reflexes, opioids, intestinal inflammatory responses and perioperative fluid excess (29-31). Care bundles consisting of chewing gum (32), epidural analgesia (33), restrictive fluid supplementation (34), avoidance of nasogastric tubes (35), early initiation of oral diet and mobilization (36) and pharmacological measures like peripheral opioid antagonists (37) have contributed to expedite the recovery from postoperative ileus. These observations are of increasing relevance to pancreatic surgery because, contrary to the experience from colorectal surgery, available evidence in pancreatic surgery does not endorse the role of minimal access surgery in reducing the stress response (38).

Though ERAS® pathways appear to have improved surgical outcomes (39), further research is warranted to help decipher the mechanisms underlying the inflammatory and neuro-humoral surgical stress responses (40), the optimal choice of perioperative fluid management (which is neither liberal nor too restrictive) (41,42), mechanisms and prevention of orthostatic intolerance (43), postoperative cognitive dysfunction including sleep promotion (44), a reduction in the neuro-inflammatory response (45) and measures to improve compliance to pathways (46). It is also important to realize that the ultimate success of an ERAS®

program depends on clinical initiative and leadership, inter-departmental coordination, and continuous audit of the compliance and outcomes (47) to inform strategies for improving the process.

ERAS® in pancreatic surgery

Pancreatic cancer is a deadly disease, which currently ranks fourth in cancer-related mortality and is expected to ascend to second position in the Western world by 2030 (48). Given the complex nature of the technicality of pancreatic surgery, it is commendable that overall perioperative mortality has been reduced to <3%, at some high-volume centres (49). However, high post-operative morbidity continues to challenge pancreatic surgeons (50). This area of pancreatic surgery certainly lends itself to further improvement (51). Clinical pathways, inspired by the ERAS® guidelines (52,53), have been implemented to standardize care and contain costs.

It has been postulated that the inherently complex nature of pancreatic surgery, with its attendant higher rates of post-operative morbidity, being performed on a relatively weak patient likely contributed to the reluctance among pancreatic surgeons to adopt ERAS® pathways as overwhelmingly as was noted with other surgeons (52). The typical pancreatic cancer patient is generally malnourished due to a combination of poor intake, pancreatic exocrine insufficiency and malignant cachexia (54). Tumours in the head of pancreas usually present with obstructive jaundice, which in turn predisposed to cholangitis, sepsis, coagulopathy and renal failure. Sepsis is further compounded by secondary gut failure with increased bacterial translocation via the portal system or significant biliary colonization (55,56). Vitamin K malabsorption leads to hypoprothrombinemia and a prolonged PT (57). Furthermore, new-onset diabetes mellitus, believed to be due to increased tumoral production of amylin and destruction of β-islets, occurs in about 70% of patients (54). All of these factors serve to challenge the recovery of pancreatic cancer patients who are amenable to surgery. In light of these challenges, there appears a need to need to review the level of integration of ERAS protocols into the perioperative care of pancreatic cancer patients, identify potential barriers to its widespread implementation and search for possible solutions to overcome these hurdles.

The authors performed a literature search of the major reference databases (PubMed, Embase, Scopus and Google Scholar) in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (58) guidelines, to identify studies published between January 2000 to January 2021 that reported on the impact of Clinical/ERAS® pathways on outcomes following pancreatoduodenectomy (PD). Articles were searched using MeSH (Medical Education Subject Headings) keywords: "Enhanced recovery OR Clinical pathways", Pancreaticoduodenectomy OR Pancreatoduodenectomy, "Pancreatic cancer OR Pancreatic carcinoma OR Pancreatic adenocarcinoma". Studies with a clearly defined clinical pathway for peri-operative care were included, while those without a description of clinical care pathways elements and non-English language studies were excluded. Study selection process and PRISMA flow diagram for identifying studies are shown in *Figure 1*. The search strategy identified 37 studies (https://cdn.amegroups.cn/static/public/cco-21-36-1.pdf) (59-83) published (84-96) in the last 2 decades, including 4 RCTs (81,83,87,88). On comparing the components (pre-, intra- and post-operative) of the pathways in these studies, we found considerable heterogeneity amongst institutional protocols. This may be attributed to the practice of "glocalization", which refers to simultaneous occurrence of both universalizing and particularizing tendencies in a contemporary system (97). Again, we noted a low representation of pre- (59,61,62,67,72,73,76,78,80,81,94,95) and intra-operative (59-62,64,67,70,72,73,76,78,80,94,95) components in many of the institutional pathways. It is quite possible that some routine practices would not have been itemized as pathway components. However, we believe that operationalizing care by means of pathway components can bring in standardization as well as improve adherence. Similar to the results observed in other surgical populations (98), majority of the studies reported that primary length of stay was significantly shorter (59,61-64,66,67,69,70,73,75-78,80,81,83,87) in the enhanced recovery arm without an increase in complication rates (59-63,65,67,69,70,73,74,76,77,80,81,83,87), hospital re-admissions (59-65,67,73,74,76,79,83,87) or mortality (59-62,65-67,69,70,74,76,79,81). At the same time, we would like to make the reader cognizant to the fact that most of these studies have compared the outcomes of ERAS® pathway with traditional, often historical, care pathways which often does not account for the secular trends and fails to capture the entire magnitude of benefit.

Though ERAS® implementation can be believed to have brought about quality improvement, one should not forget that compliance (overall median compliance of 52%

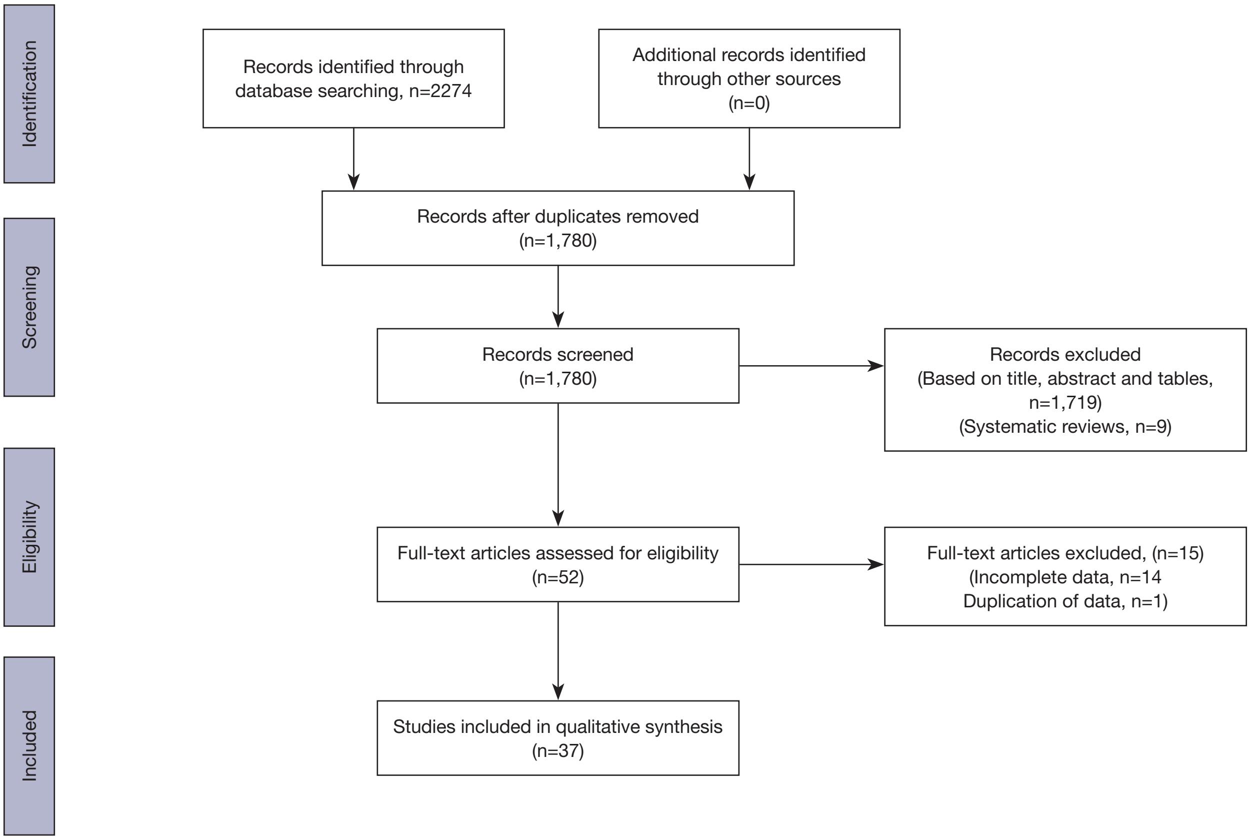

Figure 1 PRISMA diagram for study selection.

Table 1 Compliance to ERAS®/clinical pathway components following pancreatic surgery

Study	Study design	n	Number of clinical pathway components (post-op)	Overall compliance (%)
Williamsson *et al.* 2019 (Sweden) (99)	Retrospective	160	8	52
Roulin *et al.* 2020 (Multicentre) (91)	Prospective	390	9	30
Capretti *et al.* 2020 (Italy) (93)	Prospective	205	6	68.4
Karunakaran *et al.* 2020 (India) (100)	Retrospective	162	8	53
St-Amour *et al.* 2020 (Switzerland) (101)	Retrospective	89	Not mentioned	36

across studies) to these pathways in pancreatic surgery has not been as robust as with other surgical subspecialties (91,93,96,99,100) (*Table 1*). The lack of compliance is mainly seen with the postoperative component of the pathways, which not only display maximal variance, but have also been noted to best correlate with the final outcomes (91). Braga *et al.* (65) highlighted that patients with early postoperative low compliance to the ERAS® pathway had a higher incidence of complications. Karunakaran *et al.* (100) showed that less than 10% of patients following PD display a 100% compliance and deviation from >50% of clinical pathway components is associated with an increased risk of 90-day (but not 30-day) readmission, which signals the importance of continued close surveillance in these patients (102).

Most studies have used length of hospital stay (LoS) to evaluate the performance of their care pathways. Taking a closer look at the relationship between adherence to individual pathway components and LoS, failure to remove

Table 2 Factors predicting deviations from ERAS®/clinical pathways

Study (author and year, reference)	Factors	
	Pre-operative	Intra-operative
Tankel *et al.*, 2020 (Israel) (92)	Male gender	Longer operative duration
Capretti *et al.*, 2020 (Italy) (93)	Age; higher BMI	Longer operative duration; pancreatic texture
Karunakaran *et al.*, 2020 (India) (100)	Higher BMI; hypoalbuminemia; cardiac co-morbidities	Longer operative duration
Zhang *et al.*, 2020 (China) (103)	Age >70 years; hypoalbuminemia; high ASA score	

ASA, American Society of Anesthesiologists; BMI, body mass index.

the naso-gastric tube (NGT) on POD2 (103), intolerance to liquid diet on post-operative day (POD) 3 (103), inability to tolerate solid food by POD 5 (94,100), re-insertion NGT (100), need to continue antibiotics beyond POD 2 (100) and inability to remove drain on the designated day (94) were predictors of longer hospitalization. This leads one to infer that post-operative pancreatic fistula (POPF), delayed gastric emptying (DGE), and infectious complications are major causes of deviations. These, in turn, lead to a prolonged LoS. The utility of Clinical pathways in this patient cohort is to serve the early identification of complications thereby reducing 'failure to rescue' rates (104).

Barriers to ERAS® implementation and possible solutions

Compliance may be deconstructed into two components: provider (Surgeon-related) compliance and recipient (patient-related) compliance. Despite its proven benefits, the universal acceptance of ERAS® has also been impacted by the fact that it challenges many deeply-entrenched surgical dogmas (105). It is important to address these concerns that drive a resistance to change because the benefits of ERAS®, e.g., decrease in complications and reduced LoS depends on the degree of compliance (106). Pędziwiatr *et al.* (107) highlighted that a multidisciplinary team needs at least 40 cases and 6 months to reach satisfactory level of adherence to the protocol. For initiation of a program, ERAS® society recommends the incorporation of ERAS® Implementation Process (EIP), a systematic training program which consists of four specific workshops over 8–10 months (108), in the training of the team involved in delivering strategies aimed at enhancing recovery. Based on the "breakthrough method" (109), measurable goals are defined, actions and plans are put into practice, outcomes assessed, followed by appropriate adjustments [Plan-Do-Study-Act (PDSA)]. This process is repeated multiple times over the implementation and maintenance phases. ERAS Interactive Audit System (EIAS), an online interactive software, can be used to assess compliance with the guidelines, length of stay, readmissions, and complications (108). Measures to increase clinician involvement, identification of local evidence-practice gaps, adaptation of evidence to the local circumstances, periodic staff education sessions, incorporation of reminder systems, and audit and feedback are paramount to ensure optimal compliance (110). However, one must also be aware of the findings of Roulin *et al.* (111) who noted that reasons for non-compliance in the long-term are usually medically justified and were mostly observed in the postoperative period.

When developing ERAS®/clinical pathways, it is important for the team to understand, and develop strategies to address, patient-related factors that have been shown to impact on compliance. It has become increasingly clear that the patients who are able to adhere to the ERAS® pathways have significantly better outcomes that those do not. The corollary is even more important, namely, being able to identify the subset of patients who are likely to deviate from the pathways (92,93,100,103) (*Table 2*). This knowledge can possibly usher in optimization measures with the overarching aim of improving outcomes. POPF is one of the major determinants of post pancreatectomy morbidity and mortality (112). Main pancreatic duct diameter <3 mm (113) and soft texture of the pancreatic remnant are important risk factors for the development of POPF (114). Higher body mass index (BMI) is a known predisposing factor for increased intra-operative bleeding (115) and longer operative duration (116) during PD, surgical site infections (117,118) and longer hospitalization (119,120) following PD. Inclusion of BMI in 3 scoring systems (121-123) predicting POPF testifies its importance. Furthermore, certain racial groups, especially Asians are known to incur greater metabolic injury even at lower BMI (124). This, along with other adverse factors like hypoalbuminemia (100,125,126) and pre-existing comorbidities especially cardiac (100), prepare a conducive milieu for the complications to develop.

The overriding question is can these hurdles be overcome? If so, what interventions can be instituted? Prehabilitation programs promise, at least in principle, to increase the overall fitness of a pancreatic cancer patient and thus improve their surgical candidacy by improving their ability to withstand the postoperative stress response (127). Studies examining the role prehabilitation in pancreatic cancer have been detailed in *Table 3*. Three studies specifically looked at the impact of prehabilitation on post-operative outcomes following pancreatic cancer surgery (130,131,133). While all of them reported a significant decrease in the LoS in the prehabilitation arm [Ausania *et al.* (133) 11.4 *vs.* 13.2 days, P=0.049; Nakajima *et al.* (131) 23 *vs.* 30 days, P=0.045; Kitahata *et al.* (130) 16 *vs.* 24 days, P=0.001], there were no differences in major or minor complications, except for a significant decrease in DGE (1% *vs.* 9%, P=0.01) (133) and post-operative pulmonary complications (0.9% *vs.* 4.3%, P=0.011) (130) in the prehabilitation group. Bundred *et al.* (139) advocate on developing tele-prehabilitation programs consisting of home-based standardized exercise, nutritional and psychological interventions with remote monitoring and emphasize on nutritional interventions in patients with sarcopenia or sarcopenic obesity. With the available data, it appears safe to assume that prehabilitation interventions in pancreatic cancer surgery are feasible and safe (139). However, current literature suffers from some common deficiencies including small sample sizes with no standardized pre-intervention frailty assessment, focus on sarcopenia, a component of cachexia, rather than cachexia itself (140), heterogeneity in protocols with varying combinations of nutritional and exercise interventions and the end points are often surrogate markers of frailty improvement, rather than their effect on resectability rates, post-operative outcomes or disease free survival or overall survival. Out of the general concerns in universally recommending prehabilitation prior to pancreatic cancer surgery, the most important ones are the lack of direct association between prehabilitation and improved perioperative outcomes (141) and the inherent risk of such an approach potentially delaying surgery in a cancer that is fraught with a risk of rather rapid progression. Prehabilitation tends to be shorter in patients undergoing upfront surgery (130,131,133), while it ranged from 2 to 6 months with neoadjuvant therapy (129,132). The adoption of neoadjuvant treatment protocols even for patients with resectable cancers may offer an opportunity to trial the safe implementation of prehabilitation.

Future directions

The acceptance of ERAS® in pancreatic surgery has been slow. However, there has been a growing movement towards adopting specific components (post-surgical clinical pathways) of ERAS® tailored to the problems inherent to pancreatic cancer surgery. The importance of a higher level of engagement, to bridge the gap between our knowledge of surgical pathophysiology, surgeon attitudes and actual peri-operative practices is warranted if we are to truly incorporate ERAS® into pancreatic surgery. We need to clarify the minimum acceptable level of compliance following PD to improve outcomes and focus on measures to increase compliance (107). We need to incorporate patient-reported outcome measures (PROM) (142) to understand some of the barriers and increase patient participation and to enhance their experience. ERAS® pathways have shifted a significant portion of patient convalescence from the hospital to an external outpatient setting, which makes it pertinent to examine different barriers to post-discharge functional recovery and the choice of (pre- and postoperative) rehabilitation, preferably customized to the procedure and the patient. We suggest a 3-pronged approach in the efforts towards improving the compliance rates to ERAS® or clinical pathways: Patient Prehabilitation, Periodic Provider (Treating team) education and training, and Progressive Refinement of the Clinical Pathways. Refinement measues may include devising Personlized or Risk-Stratified Clinical Pathways (74,143), with the "risk" being estimated based on factors such as peroperative BMI, co-morbidities or likelihood of post-operative pancreatic fistula, as well as addition of complimentary elements to the pathways like "Perioperative Surgical Home" (PSH) (144) and/or tele-discharge program (145) with "virtual" visits in the post-operative period would make ERAS® safer, leading to increased acceptance and sustained improvements in patient care. From a clinician's or policymaker's perspective, we certainly need to dissect out the economic implications of ERAS protocols, as concrete proof of financial gains in terms of grossly positive projected return on investment (108), in

Table 3 Summary of studies exploring the role of prehabilitation in pancreatic cancer patients

Study	Study design	n	Study objectives	Time to surgery (weeks)	Fitness measure	Nutritional assessment	HR-QOL	Exercise description (per day)	Nutritional therapy	Inferences
Ngo-Huang *et al.*, 2019 (United States) (128)	P	15	Gain of muscle mass or fitness prior to surgery	16±9[¥]	6 MWT, 5 times sit-to-stand, 3 meters walk test, hand-grip strength	NR	FACT-Hep [134]	Aerobic and resistance training (1 hour)	High-protein supplement drink within an hour of exercises	Prehabilitation improves physical function during preoperative treatment for pancreatic cancer, which was associated with improved HRQOL and functional outcomes
Parker *et al.*, 2019 (United States) (129)	P	58	QOL and exercise adherence	8–24***	PAR-Q questionnaire [137]	NR	IPAQ-SF [138]	Aerobic and resistance training 2 hours/week)	Nil	Adherence to strengthening exercise was low
Kitahata *et al.*, 2018 (Japan) (130)	R	576	Post op outcomes	1*	Physiotherapist individual assessment	NR	NR	Cardio-respiratory functional capacity, strength and respiratory training	Nil	Patients undergoing prehabilitation had reduced postop pulmonary complications and shorter LoS after PD
Nakajima *et al.*, 2019 (Japan) (131)	R	76	Post op outcomes	4.6*	6 MWT, 10-min walk speed	Weight, BMI, serum albumin, PNI [133]	NR	Aerobic training (30 minutes)	Leucine rich essential amino acids	6-min walk distance significantly increased during the waiting period. Postop LoS was shorter in the prehabilitation group (P=0.045), though overall rate of complications did not differ
Florez Bedoya *et al.*, 2019 (United States) (132)	P	23	Changes in tumour vasculature	22.3**	NR	NR	NR	Aerobic and resistance training (1 hour)	Nil	Moderate treadmill exercise remodels tumor vasculature (pre-habilitation group had total vessels per field, higher microvessel density, more elongated vessels with open lumens)
Ausania. *et al.*, 2019 (Spain) (133)	RCT	18	Post op outcomes	2.6*	10-meters walk test, spirometry, pulse oximetry barthel index [135]	SGA [136], anthropometry, bioimpedance, serum albumin/ pre-albumin	NR	Aerobic training (1 hour)	Pancreatic and multivitamin supplements	Though a reduction in DGE was observed, pre-habilitation did not reduce overall complications

*, no NAT; **, NACT; ***, NACRT; ¥, either NACT or NACRT. PNI (134) = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count in the peripheral blood). FACT-Hep (135) is a validated questionnaire consisting of 27-question FACT-General (FACT-G) subscale and the 18-question hepatobiliary subscale which measures well-being in 4 domains: physical, social/family, emotional, and functional. Barthel index (136) is an ordinal scale that measures functional independence in the domains of personal care and mobility (toileting, bathing, eating, dressing, continence, transfers, and ambulation) in patients with chronic, disabling conditions, in the rehabilitation settings. SGA (137) assesses nutritional status based on features of the history and physical examination. PAR-Q questionnaire (129) a 7-step questionnaire which screens for evidence of risk factors during moderate physical activity and reviews family history and disease severity. IPAQ Short Form (138) consists of 4 long and 4 short forms of IPAQ instruments administered by telephone interview. 6 MWT, 6 minute walk test; BMI, body mass index; DGE, delayed gastric emptying; FACT-Hep, Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire; HR-QOL, health related quality of life; IPAQ-SF, International Physical Activity Questionnaire Short Form; LoS, length of Stay; NR, not reported; P, prospective; PAR-Q, Physical Activity Readiness Questionnaire; PD, pancreato-duodenectomy; PNI, prognostic nutritional index; QOL, quality of life; R, retrospective; RCT, randomized controlled trial; SGA, Subjective Global Assessment.

addition to clinical benefits would provide an additional (though not the main) incentive for implementation of ERAS®. The universal adoption of ERAS® carried with it the promise of bringing us closer to the "*Quadruple Aim*" of care, health, cost and meaning in work with overarching aims of improving the individual patient's experience of care, improving the health of populations, reducing the *per capita* healthcare costs, and improving healthcare worker's experience of providing care (146).

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