

Perioperative Management of Patients with Pancreatic Cancer – the ERAS Protocols

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Rezumat

Managementul perioperator al pacienților cu adenocarcinom pancreatic bazat pe protocoalele ERAS

Introducere: Cancerul pancreatic reprezintă a cincea cauză de deces de natură neoplazică în țările industrializate. Este o boală fatală, cu prognostic rezervat, rezecția chirurgicală rămâne sigurul tratament cu viză curativă, dar complicațiile asociate având impact semnificativ asupra supraviețuirii, prognosticului și calității vieții. Protocoalele ERAS au fost dezvoltate pentru a compensa aceste neajunsuri și pentru ameliorarea recuperării după rezecțiile pancreatice majore.

Material și metodă: A fost realizat un review sistematic urmărind ghidurile PRISMA. Articolele originale publicate în bazele de date disponibile online, Pubmed (Medline), Embase și Cochrane în perioada 2017 – 2022 au fost scanate pe baza cuvintelor specificate și au fost evaluate după aplicarea criteriilor de includere.

Rezultate: S-a obținut un număr total de 252 de studii, după cercetarea bazelor de date. Cele care nu s-au validat au fost excluse din studiu, rămânând a fi incluse în review 7 cercetări originale.

Concluzii: Protocoalele ERAS sunt sigure pentru aplicarea în practica clinică. Acestea s-au dovedit eficiente în managementul perioperator al pacienților supuși rezecțiilor pancreatice. Pe baza evidențelor, protocoalele reduc durata spitalizării, îmbunătățesc funcția gastro-intestinală și grăbesc vindecarea postoperatorie.

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Cuvinte cheie: recuperare îmbunătățită, ghiduri, duodenopancreatectomie, management post-operator, prognostic

Abstract

Background: Pancreatic cancer represents the fifth leading cause of death in industrialized countries. The prognosis is reserved, surgical resection being the only curative treatment, but the complications associated bear important impact on the patients' survival, prognosis, and quality of life. The ERAS protocols come to meet these shortcomings for enhanced recovery after major pancreatic resections.

Material and method: A systematic review was performed following the guidelines outlined by The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Original articles published in the online databases Pubmed (Medline), Embase and Cochrane since 2017 until 2022 were screened after using specific keywords.

Results: A total of 252 studies was obtained by searching through online databases. Following the exclusion criteria, we included 7 studies in the systematic review.

Conclusions: The ERAS protocols are safe to be applied in the common practice. They are efficient in the perioperative management of patients undergoing pancreatic resections. They can further decrease hospitalization stay, promote better recovery of gastrointestinal function, and speed up postoperative recovery.

Key words: enhanced recovery, guidelines, pancreatoduodenectomy, perioperative management, prognosis

Introduction

Pancreatic cancer is represented by malignant tumors originating from the exocrine pancreas. Adenocarcinoma is the most common pancreatic neoplasia (95% of cases) and the fifth leading cause of death in industrialized countries. The prognosis is reserved, surgical resection still being the only curative treatment, despite this a concerning percentage of them are unresectable at the time of diagnosis (1).

The incidence of pancreatic cancer is between 6-10 cases/ 100,000 inhabitants and increases with age (80% of the cases are diagnosed between 60-80 years of age). In Romania, the incidence of pancreatic neoplasm is considered high (11.7/ 100,000 in men and 7.9/ 100,000 in women) (2).

Surgical resection is the only therapeutic method with curative potential. Unfortunately, only 15-20% of patients are candidates for pancreatectomies. Moreover, the prognosis is

reserved even after complete resection. Survival at 5 years after pancreatoduodenectomy is 25-30% for patients without lymph node metastasis and only 10% for those with advanced N stage (3). The average lifespan for patients with locally advanced, non resectable tumors without treatment is 8-12 months and 3-6 months for those with distant metastases on presentation. For patients with metastatic disease, chemotherapy prolongs survival, but generally no more than 12 months (4).

Complications are caused by local extension of the tumor: obstruction of the common bile duct, duodenal stenosis, and upper digestive hemorrhage (5). Absolute surgical contraindications are related to the patient's condition and the presence of metastases. Neoplastic invasion of the superior mesenteric artery, celiac trunk and the presence of liver metastases are criteria of non resectability (6). Borderline tumors are considered those with portal vein or superior mesenteric vein invasion. Depending

on the location, cephalic pancreatoduodenectomy, distal pancreatectomy or, on a smaller scale, total pancreatectomy is performed (7).

Palliative treatment is reserved for unresectable tumors and consists of: jaundice relief – biliary decompression, bypassing of duodenal stenosis, pain treatment, and systemic treatment, radiochemotherapy (8).

Taking into account the aggressiveness of tumor, difficulties and complications implied, which often may result from surgery, it is important to develop a care guide for these patients able to standardize the therapeutic management in order to reduce complications, hospitalization stay, and the death rate of these patient. The aim of this article is to provide practical and evidence-based recommendation for the management of the patients with pancreatic cancer undergoing major resections.

Material and Method

The methodological algorithm for this systematic review consists of the definition of search strategies, selection criteria, and data extraction. This study followed the guidelines outlined by The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

The original articles published in the online databases Pubmed (Medline), Embase, and Cochrane since January 2017 until February 2022 were screened. Specific keywords were used to find eligible studies: (pancreatic cancer) AND (pancreatoduodenectomy) AND (complications) AND (surgery) AND (prognosis) AND (management) AND (enhanced recovery) AND (guidelines). Screening was performed by two independent reviewers in order to further diminish bias.

The selection criteria were: eligible studies that included data of current management of the patients with pancreatic cancer and how the perioperative attitude could influence the general prognosis of the patients undergoing pancreatic resections.

The exclusion criteria were: case series, letter to editors and brief reports, meta-

analyses, non-English articles, non-surgical patients, no pancreatic resection, only palliative treatment.

Data extraction pathway: following a full review of the eligible studies, two independent reviewers performed data extraction and crosschecked all results. During the process of selection and the extraction of data any disagreement between the two reviewers was discussed with a third and fourth reviewer.

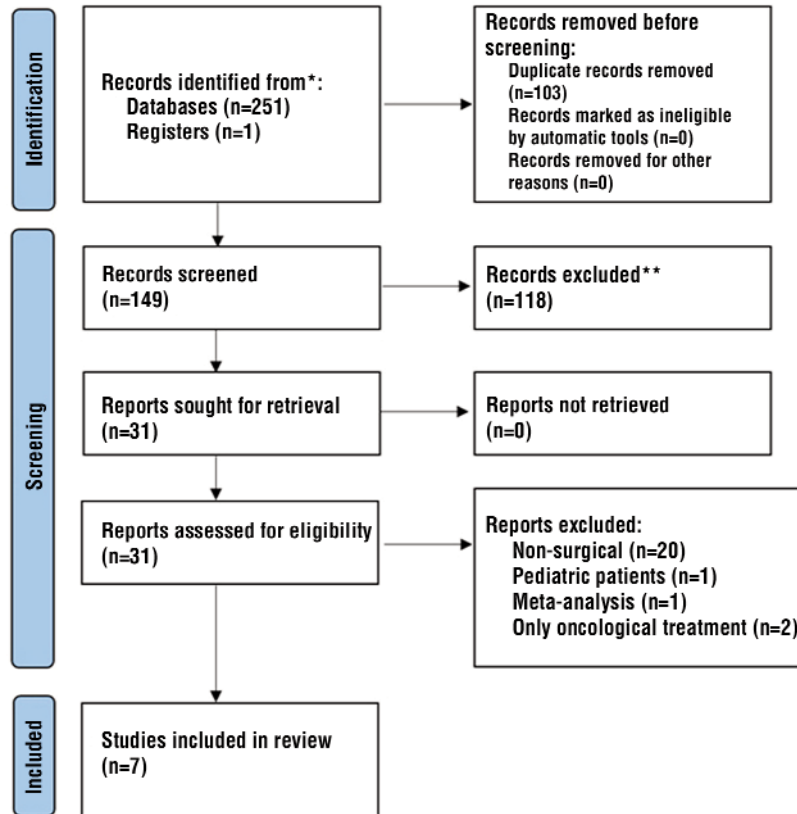
Results

A total of 252 studies was obtained by searching through Pubmed/Medline, Embase, and Cochrane databases. After exclusion of duplications, 149 were screened for titles and abstracts. We excluded 118 studies after screening, resulting in 31 articles, which were further fully reviewed. Following the exclusion criteria, we included 7 studies in the review (see *Fig. 1*).

The included studies investigated factors related to postoperative recovery, hospitalization costs, administration of vasopressors, mortality, morbidity, complication rate, socioeconomic status of patients diagnosed with pancreatic cancer. Their objectives include the feasibility of ERAS protocols and recovery after surgery. Data related to the treatment performed, survival rate, and the effect of immuno-nutrition were analyzed (see *Table 1*).

Deng X et al. (9) showed in their research that patients in the ERAS group had a shorter ICU stay than those in the traditional group (4.01 days vs. 4.22 days; $p=0.733$). In addition, the nasogastric suction tube placed before surgery was removed substantially earlier in the ERAS group compared with the traditional group ($p=0.012$). Patients in the ERAS group resumed transit earlier than those in the control group ($p=0.041$). Consequently, drainage tubes were removed the first days after surgery in the ERAS group, statistically significant compared with the traditional group $p=0.038$. Only 15 individuals in the ERAS group experienced delayed gastric evacuation (DGE) in contrast with 32 patients from the traditional group ($p=0.02$). Moreover, two patients in the ERAS group developed pulmonary infectious

Figure 1. PRISMA flow chart for the selected studies included in the systematic review



complications, in comparison with four individuals in the traditional group. One patient in the ERAS group developed incisional site infection and six in the traditional group ($p=0.012$).

In his study, Kagedan (10) found that patients undergoing surgery after the implementation of clinical pathways had a significantly shorter postoperative hospitalization stay compared with the control patients ($p=0.005$), a finding that was maintained

when comparing total postoperative length of stay including re-admissions within 30 days ($p=0.003$). Mean total inpatient costs for the hospitalization were \$25,732.85 in the control group and \$15,678.45 in the clinical pathways group ($p=0.024$). Laboratory expenses ($p=0.001$), medical imaging ($p=0.021$), patient meals ($p=0.023$), and pharmacy costs ($p=0.043$) decreased in correlation with the use of clinical pathways. There was a net decrease in the combined total 30-day postoperative

Table 1. General overview of the included studies

Author	Year	Investigated variable	Number of patients	Objectives
Deng X et al. (9)	2017	Post-operative recovery factors	159	Feasibility of ERAS protocols
Kagedan DJ et al. (10)	2017	Hospitalization cost and re-admission costs	121	Effect of clinical pathways on direct hospitalization costs
Gaignard E et al. (11)	2018	Absence of nasogastric decompression	139	Enhanced recovery
Laks S et al. (12)	2018	Administration of vasopressor	132	Feasibility of the ERAS protocols
Aoyama T et al. (13)	2018	Mortality, morbidity, hospitalization, re-admission rate	44	Recovery after surgery
Tumas J et al. (14)	2020	Rate of infectious complications	70	Effect of immuno-nutrition
Hoehn RS et al. (15)	2021	Socioeconomic status	281	Disparities in the treatment and survival

hospitalization cost of \$13,245.57 among patients managed according to the clinical pathways ($p=0.016$), with the majority of the savings attributable to ICU, nursing, and pharmacy expenses. The median index of postoperative length of stay was considerably shorter ($p=0.001$) in the ERAS group. The mean total cost of the postoperative hospitalization was \$10,562.28 for patients who met the clinical pathways goals and \$20,392.8 for those who did not, yielding a significant difference of \$9,830.53 ($p=0.002$). Those who completed the clinical pathway targets in ward nursing care ($p=0.003$), medical imaging ($p=0.003$), allied healthcare ($p=0.014$), laboratory testing ($p=0.041$), and patient feeding ($p=0.001$) incurred considerable cost savings. Similarly, a comparison of the total hospital expenditures for 30 days revealed a substantial net reduction of \$9,418.58 ($p=0.001$).

Gaignard et al. (11) reported that the length of hospitalization and incidence of postoperative grade 2 or higher complications according to the Clavien-Dindo grading system were significantly higher in the “nasogastric tube group”, maintaining the tube at least 3 days after surgical procedure. The incidence and severity of the delayed gastric emptying, implying grade B or C were similarly higher in the “nasogastric tube group” (45.5% vs 7.5%, $p=0.001$). On the other hand, there was no difference in the 90-day postoperative mortality rate between the two groups ($p=0.18$).

After stratifying the groups based on the pancreatic resection type, Laks's (12) analysis revealed that a high necessity of vasopressor infusion was only detected in Whipple procedures (74% vs. 49%, $p=0.03$). Among all patients who had a vasopressor infusion, the median proportion of operating time spent on vasopressors was 62%. Significantly more patients using vasopressors were diagnosed with adenocarcinoma ($p = 0.0001$). There were no other significant changes in the intraoperative variables. There was no indication that the use of vasopressor infusions substantially enhanced the risk of leaks ($p=0.51$) or clinically significant leakage ($p=0.68$).

Aoyama et al. (13) emphasized in their study that several preoperative elements (preoperative counseling, use of oral bowel preparation, preoperative fasting and preoperative treatment with carbohydrates, absence of preanesthetic medication) and intraoperative elements (use of epidural analgesia, use of short-acting anesthetic agent, use of warm air body heating in the operating room) of ERAS protocols appeared feasible. Among the five postoperative elements (early mobilization, prevention of nausea and vomiting, stimulation of gut motility, early removal of catheters, perioperative oral nutrition, introduction of solid food on day 4 after surgery, nasogastric-tube removal) appeared feasible, with a 90% performance rate. However, early catheter removal did not appear to bring important impact.

Tumas et al. (14) demonstrated that males were more likely to be malnourished than females, and that variations in phase angle evaluated by bioelectrical impedance analysis were statistically significant ($p=0.044$). Similarly, significant differences in cytokine concentrations were observed between patients with pancreatic ductal adenocarcinoma and patients with other periampullary tumors prior to surgery. Patients with pancreatic ductal adenocarcinoma had higher indicators of systemic inflammation. After surgery, pancreatic ductal adenocarcinoma patients exhibited statistically significant reductions in systemic inflammatory markers.

Hoehn et al. (15) have shown that a multidisciplinary clinic may minimize socioeconomic differences in the perioperative treatment and prolong survival for patients with tumors of the head of the pancreas. They demonstrated that there are numerous discrepancies in cancer care and that further research is required to comprehend these obstacles. However, patients with complicated malignancies are best served at a high-volume facility with a specialized multidisciplinary team, which strives to expedite care, enhance outcomes, and reduce treatment differences based on socioeconomic considerations.

Discussions

The primary or possibly the only potentially curative treatment for malignant tumors of the head of the pancreas is pancreatoduodenectomy or the Whipple procedure. Pancreatoduodenectomy procedure is challenging and frequently results in postoperative complications. The mortality rate for pancreatoduodenectomy is now considered to be around 5% (16,17), but in high-volume centers, it has even been further lowered to 1-2% (18,19) due to advancements in medical technology, the introduction of various advanced instruments and equipment, ongoing perioperative management optimization, and the tendency toward centralization. However, the total postoperative complication rate remains substantial, ranging from 30% to 60% (20). The length of the hospital stay is specifically prolonged by complications such as pancreatic fistula, delayed stomach emptying, wound infections and intraperitoneal abscesses, which further raise the possibility of re-admission, re-operation and even death. Higher standards must therefore be proposed for more sophisticated perioperative management in the clinic. The ERAS protocols are risk-free and have been successfully used in colorectal surgery initially and then many other digestive surgical procedures. At the moment, the method is being used broadly and worldwide on patients with pancreatic adenocarcinoma, urging for major pancreatic resections (21).

ERAS is an evidence-based, multimodal, and multidisciplinary approach of the surgical patient care, striving to improve perioperative treatment and outcomes. In order to reduce postoperative complications, promote function recovery, shorten hospital stay and achieve rapid rehabilitation, the core principles of the ERAS concept include: reducing the patient's fasting time, providing preoperative oral carbohydrates, multimodal analgesia, goal-directed fluid therapy, encouraging early feeding, early extubation, and early mobilization. Surgery, anesthesia, nursing, nutrition, pain management and rehabilitation departments must work together in a multi-discipli-

nary team for ERAS to prove successful in the current practice (22).

Due to the potential for increased pulmonary complications and protracted nausea and vomiting, some studies have shown that regular nasogastric suction tube placement is unnecessary in elective abdominal surgery (20). A nasogastric tube, however, was used for gastrointestinal decompression in order to reduce anastomotic leakage, due to the challenging repair of pancreatojejunostomy. In the ERAS group, the nasogastric tube was also withdrawn early, allowing an earlier resumption of oral diet. The fact that fewer ERAS patients than those in the conventional group experienced pulmonary complications — only two vs four — also contributed to the reduction of any other systemic and local associated complication. Furthermore, early removal of the nasogastric suction tube did not prove to be a negative impact factor on the anastomotic leakage volume, nor did it occur more frequently (20).

The most frequent and difficult post-pancreatoduodenectomy complication, pancreatic fistulas can result in fatal delayed large upper digestive hemorrhage or intraperitoneal bleeding and SIRS (23,24). General variables, such as advanced age, jaundice, malnutrition, and procedure-related factors, such as intraoperative blood loss, protracted surgery, resection type, soft pancreatic parenchyma, undilated pancreatic duct, and anastomosis method were risk factors for pancreatic fistula (25). Additionally, pancreatic fistulas followed by a late secondary hemorrhage were the primary cause of the majority of fatalities. Historically, pancreatic fistula was treated by long-term drainage tube flushing. However, some surgeons conclude that prolonged drainage extends hospital stays by increasing the risk of intra-abdominal abscess, wound infections, exacerbation of abdominal discomfort, impairment of lung function, erosion of hollow viscera, and peripancreatic vasculature (26).

Importantly, patients with pancreatic ductal adenocarcinoma had preoperative and postoperative alterations in the systemic inflammatory markers. Reprogramming the

metabolism and the immune system are essential characteristics of pancreatic cancer. Neoplastic tissue is characterized by a dynamic and complex production of pro-inflammatory cytokines that co-modulate the microenvironment in order to promote carcinogenesis and distant metastasis (27,28). IL-6 is one of the most well-researched cytokines with carcinogenesis-promoting action, its release is governed, among other mechanisms, by activation of the K-ras signaling pathway and hypoxic microenvironment (29). According to these findings and other research, immunonutrition may help patients with pancreatic ductal adenocarcinoma more than those with benign pancreatic diseases or less aggressive tumors.

Also unknown is the effect of immunonutrition on people with nutritional deficits vs those who are nutritionally normal. In the research conducted by Braga et al., the greatest clinical advantages were reported in patients at high risk or with existing malnutrition (30), while Klek et al. identified immunonutrition benefits in malnourished patients over many trials (31,32). Martin et al. discovered that patients who received preoperative immunonutrition had a decreased incidence of malnutrition and a smaller decrease in serum albumin following surgery (33,34). Silvestri et al. found that immunonutrition decreased the risk of infectious complications and length of hospitalization in patients without nutritional deficiencies (35), however Hübner et al. did not find any differences between patients with malnutrition and those without (36).

Socioeconomic differences in cancer care can arise at numerous points along a continuum spanning cancer prevention, screening, and diagnosis to multidisciplinary treatment decisions, which ultimately influence postoperative results and long-term survival. Several national cohort studies have demonstrated that the incidence of pancreatic cancer is greater in patients with a poor socioeconomic status, which may be attributed to lifestyle variables such as smoking, alcohol abuse, and obesity (36,37). Other studies have shown decreased rates of stage-specific surgery for pancreatic

cancer directly proportional with a poor socioeconomic status (38). Nonetheless, big national databases do not contain specific information on tumor features, perioperative decision making, and surgical outcomes (39). Such data are required for a comprehensive examination of the cancer care continuum discrepancies.

The limitations of our study consist of the scarcity of data available for study regarding the ERAS protocols applied to pancreatic surgery. There is a need for more study to corroborate each step of the process, and a multidisciplinary team to enhance patient's outcomes in pancreatic surgery. To offer more reliable data, prospective research involving multiple centers and large samples is required. Since laparoscopic pancreaticoduodenectomy is becoming more common in hepatobiliary surgery, the ERAS guidelines furthermore start promoting the use of minimally invasive procedures, therefore, the need for outcome analysis in these cases.

Conclusions

Globally, ERAS practices are prevalent in high volume healthcare facilities. They are safe to be applied in the common practice. Although each intervention may have a small effect individually, their combined effect is known to reduce postoperative hospital stay, re-admission rates, admission costs and increase overall patient's satisfaction, by speeding up the gastrointestinal function resumption after surgery and postoperative recovery. The unexpected and complicated nature of pancreatic major surgery makes the establishment of ERAS protocols difficult, but these obstacles should be overcome in order to provide quality patient care. An ERAS team is necessary to ensure that each step is correctly taken in the common clinical practice, in order to provide precise and tailored patient's treatment, to increase patient's compliance and to support patient's recovery.

Conflicts of Interests

The authors declare no conflicts of interest

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