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SURGICAL MANAGEMENT OF PANCREATIC CANCER: SYSTEMATIC REVIEW IN LITERATURE

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Abstract

This review is aiming to review the types of surgical intervention for pancreatic cancer. A systemic search for the terms: Pancreatic Cancer, prevention, methods for surgical intervention was done up to 2018 in the period between the first of September to the 6th of December in different databases including Google Scholar, Science Direct and NCBI including PubMed, Studies has been rated as being high quality by an established evaluation process based on the DyunaMed criteria and its levels of evidence. we randomly selected one or two studies to avoid repetitive results. Based on findings and results this review found early results with the use of minimally invasive technique in pancreatic surgery are promising. Recent data on the use of the laparoscopic procedure is better than the PDP and the other hand the use of the PPW is more effective to prevent the subsequent complications.

Keywords: *Pancreatic Cancer, Surgical Management , Surgical Methods*

Abbreviation: *used in this review are: **lpd:** laparoscopic pancreaticoduodenectomy. **opd**: open pancreaticoduodenectomy. **ppw**: pylorus-preserving pancreaticoduodenectomy. **lratp**: laparoscopic robot-assisted total pancreatectomies.*

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INTRODUCTION:

Pancreatic cancer is the fourth leading cause of cancer-related death. Only about 6% of patients are alive 5 years after diagnosis. One reason for this low survival rate is that most patients are diagnosed at a late stage, when the tumor has spread to surrounding tissues or distant organs. [1] Less than 20% of cases are diagnosed at an early stage that allows them to undergo potentially curative surgery. However, even for patients with a tumor that has been surgically removed, local and systemic recurrence is common and the median survival is only 17-23 months.[1] This underscores the importance to identify factors that can predict post resection survival. With technical advances and centralization of care, pancreatic surgery has become a safe procedure. The future optimal treatment for pancreatic cancer is dependent on increased understanding of tumor biology and development of individualized and systemic treatment. Previous experimental studies have reported that mucins, especially the MUC4 mucin, may confer resistance to the chemotherapeutic agentgemcitabine and may serve as targets for the development of novel types of intervention. [1]

Treatment of pancreatic cancer remains a major therapeutic challenge for contemporary medicine. It is the most lethal neoplasm of the gastrointestinal tract, with a five-year survival rate of only 5%. [2] Estimates from the United States of America indicate that 44,030 new cases of this disease were diagnosed in 2011 and 37,660 people died from this disease. [3] Complete surgical resection of the tumor is still the only potentially curative therapeutic option for the treatment of pancreatic ductal carcinoma, which is the predominant histological type of neoplasm of this gland. Its location in the retro peritoneum, with complex anatomical relationships with the duodenum, biliary tract, inferior vena cava and aorta, and mainly, the involvement of mesenteric vessels, has hugely delayed the evolution of pancreatic surgery. [4]

Advances in surgery in the late nineteenth century were reflected in the surgical procedures of the pancreas. [4] The predominant location of tumors is in the head of the pancreas, which, due to its anatomical characteristics and to preserve surgical oncological principles, should be resected along with the duodenum. [4] This resection, called pancreaticoduodenectomy, is one of the most challenging and specialized procedures performed by gastrointestinal surgeons. Advances in operative techniques and surgical materials, the evolution of anesthesia and intensive care units, the emergence of antibiotics to control infections and great advances in diagnostic and therapeutic radiology have yielded a decrease in mortality rate from above 50% to less than 3% in specialized centers for the treatment of this disease. Unfortunately, these surgical advances are still associated with poor outcomes in long-term patient survival due to local recurrences or distant metastases. The increased regionalization of treatment for this disease in recent decades has allowed great. [4]

METHODS:

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISRM) declaration standard for systematic reviews. A systemic search for the terms: Pancreatic Cancer, management, methods for surgical management) was done up to 2018 in the period between the first of September to the 6th of December in different databases including Google Scholar, Science Direct and NCBI including PubMed. for, researches, review articles and reports, published over the past 5 years. Books published on Pancreatic Cancer management.

Our search was completed without language restrictions. Then we extracted data on study year, study design, and key outcome on Pancreatic Cancer management. The selected studies were summarized, and unreproducible studies were excluded. Selected data is shown in the Table 1.

Studies has been rated as being high quality by an established evaluation process based on the DyunaMed criteria and it's based on the level of evidence as following:

Level 1 (likely reliable) evidence: representing research results addressing clinical outcomes and meeting an extensive set of quality criteria which minimize bias. example: Randomized controlled trial/meta-analysis.

Level 2 (mid-level) evidence: representing results addressing clinical outcomes and using some methods of scientific investigation but not meeting the quality criteria to achieve level 1 evidence labeling. Example: well-designed non-randomized clinical trials.

Level 3 (lacking direct) evidence: representing reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion and conclusions extrapolated indirectly from scientific studies.

Inclusion Criteria:

Pancreatic cancer conditions under any method of surgical management of pancreatic cancer

Exclusion criteria were:
-Conditions other than pancreatic cancer.

-Non-surgical method for pancreatic cancer management as chemotherapy, radiotherapy.

Data extraction and analysis
Information's relating to the systemic review question elements was extracted from the studies and collated in quantitative tables.

RESULTS:

Operative techniques for pancreas cancer include the standard pancreaticoduodenectomy (Whipple procedure) and pylorus-preserving pancreaticoduodenectomy. Extended retroperitoneal lymphadenectomy and superior mesenteric vein and/or portal vein resection have recently been evaluated for maximal surgical clearance of disease. The type of pancreatic anastomosis has also been examined, including pancreaticojejunostomy versus pancreaticogastrostomy. Several institutions have reported their results for laparoscopic pancreatic resection with comparable results to open resection. Various post-operative strategies have been evaluated for reduction of post-operative complication rates, including the use of octreotide (somatostatin analogue) , pancreatic enzyme replacement therapy, erythromycin and nutritional support. The purpose of this article is to review the preoperative, operative, and post-operative management strategies in the treatment of pancreatic cancer.

Pancreaticoduodenectomy:
Currently, most studies in support of radical pancreaticoduodenectomy are nonrandomized retrospective studies. [5-7] which are limited by their lack of concurrent controls and lack of random allocation to standard versus radical resection. Contrary to many of these published reports, a nonrandomized comparison by Henne-Bruns et al. found no survival advantage to extended retroperitoneal lymphadenectomy. [8] However, one prospective, randomized multicenter Italian study by Pedrazzoli et al. [9] suggested a survival advantage. This study accrued 81 patients with pancreatic adenocarcinoma over 3 years and allocated patients to standard versus radical lymphadenectomy. While the two groups were similar with respect to multiple preoperative parameters, morbidity, and overall survival, a posthoc subgroup analysis suggested that patients with node-positive tumors had a significantly ($P <$ .05) better survival after radical lymphadenectomy. [10]

Distal pancreatectomy:

The LEOPARD trial is the first multicenter randomized controlled trial comparing MIDP to ODP. On the World Health Organization trial registry website, incorporating all (inter)national trial registries, there are only two single-center randomized trials reported in this field. The first trial (LAPOP) with a total sample size of 60 patients is from Sweden and is planned to be completed in 2020. [11] Patients are not blinded to the intervention in this trial. The second trial is from the USA and was never started. [12]

laparoscopic pancreaticoduodenectomy

Current literature supports the use of laparoscopic pancreaticoduodenectomy (LPD) as an alternative to open pancreaticoduodenectomy (OPD) for pancreatobiliary malignancies. Studies done so far are case series and matched comparisons; a randomized trial analysing two has not been reported. RCT included 64 patients with resectable peri-ampullary or pancreatic head cancer, randomized by computer generated random numbers into either LPD or OPD group during September 2013 to August 2015. Sample size was 32 in each arm, assuming power of study 80% & type I error of 0.05. Primary outcome measure was hospital stay, secondary outcome measures were blood loss, operation time, pathological radicality and complication rate. Mean operative time 260.2 min (±11.10) in OPD, 359.4 min (±13.84) in LPD ($p = 0.0308$). Mean blood loss 300.6 ml (±46.56) in OPD, 249.8 ml (±22.33) in LPD ($p < 0.001$). Conversion rate of 3.1%. The median length of stay in OPD was 12 days (6–30), LPD of 8 days (5–52) ($p = 0.0001$). Pancreatic fistula 18.75% in OPD; 15.60% in LPD ($p = 0.314$), overall complications (Clavien Dindo) 31.25% in OPD; 25% in LPD ($p = 0.755$) and 3.1% mortality in each arm. Mean nodes retrieved in OPD 17.00 (±1.47), LPD 18.97 (±1.0) with 0.95 CI, $p = 0.059$. [14]

pylorus-preserving pancreaticoduodenectomy (PPW):
Pancreatic cancer is a leading cause of cancer death. Two surgical procedures can lead to a cure: the classic Whipple operation, in which part of the pancreas, the gallbladder, the duodenum, the pylorus (outlet of the stomach), and the distal (lower) part of the stomach are removed, and the so-called pylorus-preserving pancreaticoduodenectomy, or pylorus-preserving Whipple operation, in which the stomach

and the pylorus are not removed. [15]

laparoscopic robot-assisted total pancreatectomies (LRATP):

The da Vinci surgical system_ (dVss) (Intuitive Surgical, Sunnyvale, California, USA) enhances surgical dexterity in laparoscopic operations [16] On a priori grounds, considering also the added costs of the new technology, robotic assistances could be worth using if permitting otherwise unfeasible minimally invasive operations or improving patient outcomes. In fact, robotic assistance has minimally expanded the range of feasibility of laparoscopic operations, and improvement in patient outcomes, proposed for many operations, has not been unambiguously demonstrated yet. [17-22]

Palliative biliary stents for obstructing pancreatic cancer

The majority of patients with cancer of the pancreas are diagnosed only after blockage of the bile ducts has occurred. Surgical bypass (SBP) or endoscopic stenting (ES) of the blockage are the treatment options available for these patients. 29 randomised controlled trials that used surgical by-pass, endoscopic metal stents or endoscopic plastic stents in patients with malignant bile duct obstruction. All included studies contained groups where cancer of the pancreas was the most common cause of bile duct obstruction. This review shows that endoscopic stents are preferable to surgery in palliation of malignant distal bile duct obstruction due to pancreatic cancer. The choice of metal or plastic stents depends on the expected survival of the patient; metal stents only differ from plastic stents in the risk of recurrent bile duct obstruction. Polyethylene stents and stainless-steel alloy stents (Wallstent) are the
most studied stents. [23]

Table (1) Results from Sequencing Studies:

Intervention	Author	sample	Outcomes measurement	Main Results	Level of evidence
Pancreaticoduodenectomy	Yeo CJ, et al. 2002. [10]	299	postoperative morbidity, mortality, and survival data pathological radicality	Radical (extended) pancreaticoduodenectomy can be performed with similar mortality but some increased morbidity compared to standard pancreaticoduodenectomy. The data to date fail to indicate that a survival benefit is derived from the addition of a distal gastrectomy and retroperitoneal lymphadenectomy to a pylorus-preserving pancreaticoduodenectomy.	**Level 2**

Distal pancreatectomy	Thijs D, et al. 2017.[13]	102	primary outcome is time to functional recovery (days) secondary outcomes of this trial include operative outcomes (type of approach, vascular tumor involvement, hospital stay, secondary outcome measures were blood loss, operation time, pathological radicality and complication rate.		**Level 2**
laparoscopic pancreaticoduodenectomy	S. Palanisamy, et al. 2016.[14]	64	Primary outcome measure was hospital stay, secondary outcome measures were blood loss, operation time, pathological radicality and complication rate.	study establishes safety of LPD in terms of short term outcomes, complications, mortality and oncological radicality to that of OPD, has benefits of shorter hospital stay, reduced blood loss and lesser wound complications. Comparisons in terms of disease free survival and long term survival remains to be seen	**Level 2**
pylorus-preserving pancreaticoduodenectomy (PPW).	Hüttner FJ, et al. 2016.[15]	512	RCTs comparing CW versus PPW	Current evidence suggests no relevant differences in mortality, morbidity, and survival between the two operations. However, some perioperative outcome measures significantly favour the PPW procedure.	**Level 2**
laparoscopic robot-assisted total pancreatectomies (LRATP)	Ugo B, et al. 2014.[24]	LRATP = 12 were compared to 11 case-matched open total pancreatectomies.	Age, sex, American Society of Anesthesiologists score, body mass index, estimated blood loss, need for blood transfusions, operative time, tumor type, tumor size, number of examined lymph nodes, margin status, post-operative complications, 90 day or in-hospital mortality, length of hospital stay, and readmission rate.	LRATP is feasible in selected patients, but further experience is needed to draw final conclusions.	**Level 2**

Palliative biliary stents	Moss AC, et al. 2006.[23]	1,700	Different types of endoscopic plastic and metal stents	Endoscopic metal stents are the intervention of choice at present in patients with malignant distal obstructive jaundice due to pancreatic carcinoma. In patients with short predicted survival, their patency benefits over plastic stents may not be realised. Further RCTs are needed to determine the optimal stent type for these patients.	**Level 2**

DISCUSSION:

The biology of pancreatic cancer is particularly challenging, not only because of the late presentation of the disease but especially because of the somewhat atypical pathways of spread through the peritoneal cavity, perineural channels, and bloodstream dissemination. [10]

Pancreatic cancer is a leading cause of cancer death. Two surgical procedures can lead to a cure: the classic Whipple operation, in which part of the pancreas, the gallbladder, the duodenum, the pylorus (outlet of the stomach), and the distal (lower) part of the stomach are removed, and the so-called pylorus-preserving pancreaticoduodenectomy, or pylorus-preserving Whipple operation, in which the stomach and the pylorus are not removed.

Observational cohort studies have suggested that minimally invasive distal pancreatectomy (MIDP) is associated with better short-term outcomes compared with open distal pancreatectomy (ODP), such as less intraoperative blood loss, lower morbidity, shorter length of hospital stay, and reduced total costs. Confounding by indication has probably influenced these findings, given that case-matched studies failed to confirm the superiority of MIDP. This accentuates the need for multicenter randomized controlled trials, which are currently lacking. We hypothesize that time to functional recovery is shorter after MIDP compared with ODP even in an enhanced recovery setting.

The LEOPARD trial is a multicenter randomized controlled trial designed to assess whether MIDP reduces the time to functional recovery compared with ODP, in an enhanced recovery setting. LEOPARD was initiated by the Dutch Pancreatic Cancer Group, a national collaboration of surgeons, gastroenterologists, medical oncologists, pathologists, (interventional) radiologists, dietitians and nurses, which aims to improve the treatment of benign, premalignant and malignant pancreatic disease. [13]
Current literature supports the use of laparoscopic pancreaticoduodenectomy (LPD) as an alternative to open pancreaticoduodenectomy (OPD) for pancreatobiliary malignancies. Studies done so far are case series and matched comparisons; a randomized trial analysing two has not been reported. No LRATP was converted to conventional laparoscopy, hand-assisted laparoscopy or open surgery despite, two patients (18.1 %) required vein resection and reconstruction. LRATP was associated with longer mean operative time (600 vs. 469 min; p = 0.014) but decreased mean blood loss (220 vs. 705; p = 0.004) than open surgery. Post-operative complications occurred in similar percentages after LRATP and open surgery. Complications occurring in most patients (5/7) after LRATP were of mild severity (Clavien-Dindo grade I and II). One patient required repeat laparoscopic surgery after LRATP, to drain a fluid collection not amenable to percutaneous catheter drainage. One further patient from the open group required repeat surgery because of bleeding. No patient had margin positive resection, and the mean number of examined lymph nodes was 45 after LRATP and 36 after open surgery. [24].

CONCLUSIONS:

Pancreatic resection for the treatment of tumors can now be considered safe. However, the ultimate achievement of good results still seems distant. Effective screening measures that enable earlier diagnosis, identification of patients at risk, and the search for better results from complementary treatments, would appear to be the most important steps for improving the cure rate for this disease. On the other hand, with the advances in perioperative care, radical resection with inclusion of adjacent vascular structure to achieve negative margin status

can be performed with comparable mortality and morbidity in high-volume centers. Early results with the use of minimally invasive technique in pancreatic surgery are promising. Recent data on perioperative care to decrease morbidity with pancreatic surgery will also be discussed.

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