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Review

# Pancreatic Cancer: Risk Factors, Diagnosis and Minimally Invasive Surgical Approach-A Comprehensive Review

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## Abstract

Pancreatic cancer represents a major health issue with poor prognosis. There are several risk factors related to this important disease and their control may influence its burden. The radical treatment for pancreatic cancer remains the surgery and the use of minimally invasive approach is nowadays considered optimal. The aim of the study was to analyze the pancreatic cancer characteristics and the safety and feasibility of the minimally invasive approach in treating this type of cancer. We conducted a literature review in Pub-Med database using mesh-terms for pancreatic cancer and minimally invasive surgery focusing on the short-term outcomes of and long-term outcomes of MIS. We also reviewed the most relevant literature studying the epidemiology of the pancreatic cancer, risk factors, histopathology, resectability and surgical options, the use of preoperative biliary drainage, neoadjuvant and adjuvant treatment. The most relevant risk factors associated with pancreatic cancer are represented by age, sex, area of living, blood group, genetic factors and the presence of diabetes, human microflora, alcohol consumption, smoking, chronic pancreatitis, obesity. Minimally invasive approach for pancreatic cancer is associated with improved intraoperative and short-term postoperative outcomes such as: reduced intraoperative blood loss, faster functional recovery, lower postoperative pain, shorter hospital stay, but similar postoperative morbidity and pancreatic fistula risk to the open approach. Regarding oncological results, minimally invasive approach provides optimal number of harvested lymph-nodes and R0 resection rates. Minimally invasive surgery for pancreatic cancer should be performed in high-volume, specialized centers with dedicated and experimented surgeons and for selected patients.

**Keywords:** pancreatic cancer; minimally invasive surgery; resectability

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## 1. Introduction

Pancreatic cancer is a major health-issue due to its unspecific symptoms in early-stages and poor prognosis. The lack of a standardized screening method and patient selection leads to late diagnosis. Even if there are several well-known risk factors, their control is usually not obtained and the burden of the pancreatic cancer remains substantial. Still, the progress regarding oncological treatment and surgical technique improved the prognosis of this important disease.

## 2. Objectives

The aim of our study is to review the literature regarding the pancreatic cancer characteristics and to analyze the use of minimally invasive surgery (MIS) in treating pancreatic cancer compared to open approach.

### 3. Materials and Methods

We reviewed the most relevant literature studying the epidemiology of the pancreatic cancer, risk factors, histopathology, resectability and surgical options, the use of preoperative biliary drainage, neoadjuvant and adjuvant treatment. We also conducted a systematic review in Pub-Med database using mesh-terms for pancreatic cancer and minimally-invasive surgery focusing on the short-term outcomes of MIS (intraoperative blood loss, surgery duration, postoperative pain, intensive care unit stay, total hospital stay, recovery of oral tolerance, complications) and long-term outcomes of MIS (disease free survival, relapse rate, overall survival). The inclusion criteria were represented by: year of publication 2015-2025, articles available in full text, article type-meta-analysis, review, systematic review, clinical study, clinical trial, controlled clinical trial, randomized controlled trial, observational study, comparative study, clinical conference, validation study, consensus development conference, case reports, multicentric study, practice guideline, language- English or Romanian. The exclusion criteria were represented by the lack of data regarding at least one of the following pieces of information: intraoperative blood loss, surgery duration, postoperative pain, intensive care unit stay, total hospital stay, recovery of oral tolerance, complications, disease free survival, relapse rate, overall survival.

### 4. Results

#### 4.1. Epidemiology

Pancreatic cancer represents a major burden in developed countries with the high-est incidence in North America, Europe and Australia, being the fourth cause of cancer-related mortality. In the European Union, it is the seventh most common form of cancer for both sexes with 100,005 new cases per year estimated in 2018 [1–4].

#### 4.2. Risk factors

The risk factors for developing pancreatic cancer might be divided into two categories: modifiable and non-modifiable factors. Modifiable risk factors are represented by: human microflora, alcohol consumption, smoking, chronic pancreatitis and obesity. Non-modifiable risk factors are represented by: age, sex, area of living, blood group, genetic factors and the presence of diabetes [5].

Pancreatic cancer occurs most common in males aged between 40 and 85 years old and extremely rare under 30 years old. It is believed that women are protected against this type of malignancy when menopausal hormone therapy is administered [5,6].

The highest incidence of pancreatic cancer is reported in African Americans and the lowest in Asian Americans and Pacific Islanders. Also, it is more prevalent in urban areas compared to rural ones probably due to socioeconomic and lifestyle changes [5,7].

Regarding the blood group, it is reported that the presence of blood group antigen increases the risk of pancreatic cancer, patients with group A, B or AB having a higher risk compared to those with 0 blood type. Some studies suggest that the association of A blood type with diabetes mellitus promotes pancreatic cancer development. The theory is supported by the host inflammatory process regulated by the ABO group antigens which might be involved in tumorigenesis [5,7–9].

Family history of pancreatic cancer significantly increases the risk of the disease in first-degree relatives, even though 80% of new cases are related to sporadic genetic mutations. Over 90% cases of pancreatic ductal adenocarcinoma are associated with activating mutations in the oncogenic hotspots in exons 2 and 3 of KRAS. Other common mutations may occur in tumor suppressor genes: mutational inactivation of CDKN2A which affects the function of p16 protein, a cell cycle regulator, mutations in TP53 which encodes proteins involved in DNA damage response and loss of Smad4 function which interferes with transforming growth factor- $\beta$  (TGF $\beta$ ) signaling [5,10–15].

Diabetes mellitus is also considered an important risk factor for pancreatic cancer development in long-standing disease with a duration over 10 years. On the other hand, new onset diabetes mellitus in elderly may hide an underlying pancreatic cancer. Moreover, it is believed that some antidiabetic medications may increase the risk for pancreatic cancer, such as Metformin. It is a two-way relationship taking into consideration that the presence of diabetes may interfere with the treatment of pancreatic cancer [5,16–22]. Roy A. et al. elaborated 5 potential explanations of the mechanisms responsible for the development of pancreatic cancer in long-standing diabetes mellitus [16].

(1) High-insulin resistance is a risk factor for pancreatic cancer even in patients without diabetes mellitus.

(2) Insulin-like growth factors (IGFs) seem to be involved in cancer development.

(3) The presence of hyperglycaemia alters specific biochemical pathways which play important roles in cancer development.

(4) The combination of obesity and inflammation which is the common ground for both of the diseases.

(5) The genetic predisposition for both diabetes mellitus and pancreatic cancer [16,23–29].

Several studies also report that the presence of diabetes mellitus is associated with worse outcomes after pancreatic resection for pancreatic cancer: higher risk of post-operative complications, higher 30-days mortality, poor median overall survival. Therefore, the achievement of a better metabolic control before surgery may improve the outcomes [16,30–36].

Human microflora has an important role in regulating the immune system and its dysregulation may contribute to carcinogenesis by several mechanisms: immunomodulatory activity- triggering immune responses involved in tumor formation and progression, microbial metabolites from the intestines such as lipo-teichoic acid (LTA) and short-chain fatty acids (SCFAs) implicated in cancer development, dysbiosis associated with gene mutations which may lead to high susceptibility of cancer, certain bacterial toxins promoting chronic inflammation and DNA alterations and damage stimulating the cancer cells growth. Specific microorganisms are believed to be more frequently found in the pancreas of the patients with pancreatic cancer such as *H. pylori*, *Clostridium*, *Bifidobacteria* and *gamma-Proteus*, even if it was considered that the pancreatic microenvironment was too aggressive for microorganism survival [5,37–46].

Smoking represents an important modifiable risk factor for pancreatic cancer, smokers having a 70% greater risk than non-smokers. The mechanisms involved might be represented by: DNA methylation, formation of DNA adducts that may activate KRAS mutations and other more complex genetic alterations that may promote pancreatic cancer development [5,47,48].

Alcohol consumption increases the risk for pancreatic cancer in a dose-dependent manner. While heavy drinking defined as over 80g of alcohol per day significantly raises the risk, low or moderate consumption seems to have no effect on pancreatic cancer risk [5,49–52].

Chronic pancreatitis is also an important risk factor for pancreatic cancer. It involves fibro-inflammatory mechanisms activating the digestive pancreatic enzymes that damage the pancreatic cells. These altered cells may present DNA damage, metaplasia, oncogenic KRAS mutations, loss of tumor suppressor barriers p16/INK4A/CDKN2A, TP53 and SMAD4/DPC4 leading to pancreatic cancer development [5,53–57].

Obesity is a relevant risk factor for pancreatic cancer since it is believed that fat cells provide an environment that makes cancer cells more viable. It is associated with KRAS mutations, high insulin resistance and diabetes mellitus, inflammation and modifications in human microflora, all being a part of pancreatic cancer development [5,58,59].

#### 4.3. Histopathology

Among primary pancreatic malignant tumors, pancreatic ductal adenocarcinoma is the most common histological type (more 90% of pancreatic cancers), but other less encountered types of pancreatic malignant tumors may occur such as acinar cell carcinoma, pancreatoblastoma, solid

pseudo-papillary neoplasm or malignant neuro-endocrine tumors which are rarer. We will predominantly refer to pancreatic ductal adenocarcinoma as being the most prevalent type of pancreatic cancer [20,60–62].

Pancreatic ductal adenocarcinoma usually develops due to mucosal lining mutations which lead to premalignant lesions and eventually to malignant transformation. The main malignant precursors are represented by: intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) [63–65].

#### 4.4. Diagnosis

Early symptoms of pancreatic cancer, that may arise 6 months before the severe ones occur are represented by early satiety with important weight loss, anorexia, sudden onset asthenia. The most common symptoms of pancreatic cancer are abdominal pain and jaundice which usually appear in more advanced tumors. New onset diabetes mellitus in elderly, pruritus, thrombophlebitis are other signs and symptoms of underlying pancreatic cancer [60,62,63,66,67].

Screening for pancreatic cancer in unselected populations is not recommended because of the low lifetime risk. Instead, it is recommended in patients with criteria of familial pancreatic cancer-inherited cancer syndromes that are involved in the development of pancreatic cancer such as: hereditary breast and ovarian cancer carriers of the BRCA1 or BRCA2 germline mutations, familial atypical multiple mole melanoma syndrome (FAMMM), Peutz-Jeghers syndrome, hereditary pancreatitis, hereditary nonpolyposis colorectal cancer (Lynch Syndrome) [63,68–70].

Surveillance for pancreatic cancer should also be implemented in patients with non-suspicious cystic lesions (every 6 to 12 months), solid lesions which do not meet the criteria for immediate resection or main pancreatic duct strictures (evaluation every 3 months) [63,71].

Even if several biomarkers are studied for screening or diagnosis of pancreatic cancer (CA, CA125, MUC5A, CEA), only CA 19-9 has been approved to evaluate the treatment response and to detect recurrent disease. It is a modified blood group antigen that is secreted in exocrine epithelial cells and found on the surface of erythrocytes. In the preoperative state, high values of CA 19-9 (over 300 UI/ml) usually correlate with an advanced disease stages and indicates a non-resectable tumor. After the resection or during the oncological treatment, elevated levels of CA 19-9 are associated with disease progression and recurrence [60,63,72–75].

The imagistic methods used in pancreatic cancer diagnosis are represented by: computed tomography scan with pancreas protocol (CT), magnetic resonance imaging (MRI), positron emission tomography (PET-CT) and ecoendoscopy with fine needle aspiration (EUS with FNA). Their benefits and limitations are illustrated in Table 1.

CT scan with pancreas protocol represents the gold-standard in pancreatic cancer imaging. It provides information regarding local tumor development and distant metastases, vascular involvement or vascular anatomic variations. It is important in determining the tumor's relationship to the superior mesenteric artery (SMA), superior mesenteric vein (SMV) and coeliac axis which further determines the resectability. Highly suspicious pancreatic tumors appear on CT scan as poorly enhanced lesions which might associate ductal dilatation or interruption, hypo-attenuation, distal pancreatic atrophy, pancreatic contour anomalies, common bile duct dilation [68,76–79].

MRI evaluation in suspected pancreatic cancer is usually useful for diagnosis in early stages as it provides a more comprehensive and detailed analysis of the pancreatic parenchyma modifications or pancreatic duct changes associated with a tumoral mass. Still, it has similar sensitivity and specificity with CT scan, so it is not considered the primary imagistic method in diagnosing pancreatic cancer as it is more expensive and less available. There are specific situations when MRI evaluation is superior and more useful than CT scan: to differentiate suspicious pancreatic lesions present on CT scan, without certain malignant characteristics pancreatic tumoral masses versus mass-forming pancreatitis, detect tumors under 2 cm, evaluation of suspected liver metastases, patients with kidney failure or severe iodine allergy not suitable for CT scan [68,80,81].

EUS involves endoscopic examination using an echoendoscope positioned in the stomach and evaluation of the pancreas through the posterior gastric wall. It allows high-quality assessment of the pancreatic parenchyma, surrounding blood vessels, lymph-nodes and left liver lobe. It is an ideal evaluation method for lesions smaller than 2 cm and suspicious for malignancy. Using FNA technique, it provides biopsy tissue useful in differentiating solid pancreatic masses with unclear characteristics or borderline resectable pancreatic masses which benefit of neoadjuvant treatment. EUS with FNA complications such as tumor spread or perforation rarely occurred [68,82–89].

PET-CT is not used alone in order to diagnose pancreatic cancer, but as a complementary method in detecting distant metastases when their presence is uncertain. Also, it is believed to be useful in assessing the tumor response during chemotherapy or radiation therapy based on the changes in SUV (standardized uptake value), but this is insufficiently studied so far [68,90–94].

In order to complete the diagnostic work-up, KRAS and BRCA testing are recommended and also genetic counselling for patients with history of familial pancreatic cancer [95].

**Table 1.** Imagistic methods-benefits and limitations (adapted after Zhang L. et al.).

Imagistic Method	Benefits	Limitations
CT	-Accessible	-Kidney injury
	-Cheapest	-Involves radiation exposure
	-Best validated	
MRI	-Offers superior evaluation of the local pancreatic disease	-More expensive
	-Does not involve radiation exposure	-Less available
	-Suitable for patients with iodine allergy	-Contraindicated in patients with metal implants
EUS+- FNA	-High sensitivity even for small lesions	-Operator dependent
	-Provides histological sample	-Less available
	-Metastatic disease evaluation	-Not suitable for metastatic disease evaluation
PET-CT	-Metastatic disease evaluation	-Expensive
	-Follow-up for recurrence or response after adjuvant therapy	-Less available
		-Involves radiation exposure

CT- computed-tomography, MRI- magnetic resonance imaging, EUS- ecoendoscopy, FNA- fine needle aspiration, PET-CT- positron emission computed tomography.

#### 4.5. Resectability and surgery

Pancreatic malignant tumors are classified as resectable and borderline resectable. Borderline resectable tumors are described using a definition based on 3 characteristics: anatomical, biological and conditional. The anatomical criteria means that, if surgery is used as primary treatment modality, there is a high risk of R1/R2 resection. The neoadjuvant treatment is used in order to increase the chances of a R0 resection. The biological criteria involve high-risk of extrapancreatic disease based on elevated CA 19-9 >500 IU/ml. The conditional criteria refer to Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or more [95,96].

The anatomical criteria detailed refers to the relationship between the tumor and surrounding blood vessels: superior mesenteric vein (SMV), portal vein (PV), superior mesenteric artery (SMA),

common hepatic artery (CHA), celiac artery (CA). According to Japanese classification of pancreatic carcinoma by the Japan Pancreas Society: Eight Edition, borderline resectable with PV/SMV invasion alone means tumor contact or invasion of the SMV/PV of 180 degrees or more, or occlusion of the SMV/PV, not exceeding the inferior border of the duodenum, with no findings of contact or invasion of the SMA, CA, or CHA. Borderline resectable with arterial invasion means tumor contact or invasion of the SMA and/or CA of less than 180 degrees without stenosis or deformity or Tumor contact or invasion of the CHA without tumor contact or invasion of the proper hepatic artery (PHA) and/or CA [77,96–100].

Unresectable pancreatic cancer because of locally-advanced tumor is described as: tumor contact or invasion of the SMV/PV of 180 or more, or occlusion of the SMV/PV extending beyond the inferior border of the duodenum or tumor contact or invasion of the SMA and/or CA of 180 degrees or more or tumor contact or invasion of the CHA, showing tumor contact or invasion of the PHA and/or CA or tumor contact or invasion of the aorta. Unresectable pancreatic cancer is also considered when there are distant metastasis including nonregional lymph-node metastasis. Patients with advanced disease associate a poor prognosis and there were described some features which predict an impaired survival such as: ECOG performance status of 2 or more, age >65 years, albumin levels <35 g/l, presence of synchronous metastases, liver metastases, number of metastatic sites and high serum levels of CA 19-9 [95,100].

Resection for pancreatic cancer located in the pancreatic head or uncinate process matching the criteria for resectability involves pancreaticoduodenectomy by open or MIS. Lymph-node dissection includes the stations: 6 (infrapyloric lymph nodes), 8a (lymph nodes in the anterosuperior group along the common hepatic artery), 8p (lymph nodes in the posterior group along the common hepatic artery), 12a (lymph nodes along the hepatic artery), 12b (lymph nodes along the bile duct), 12p (lymph nodes along the portal vein), 13 (lymph nodes on the posterior aspect of the head of the pancreas), 14t (lymph nodes along the superior mesenteric artery (tumor side), 17 (lymph nodes on the anterior surface of the head of the pancreas). The minimum number of harvested lymph-nodes should be 16. Pancreatic cancer of the body or pancreatic tail requires radical antegrade modular pancreatosplenectomy by open or MIS. Lymph-node dissection for pancreatic body cancer covers the stations: 8a (lymph nodes in the anterosuperior group along the common hepatic artery), 8p (lymph nodes in the posterior group along the common hepatic artery), 9 (lymph nodes around the celiac artery), 10 (lymph nodes at the splenic hilum), 11p (lymph nodes along the proximal splenic artery), 11d (lymph nodes along the distal splenic artery), 14t (lymph nodes along the superior mesenteric artery (tumor side), 18 (lymph nodes along the inferior margin of the pancreas) while lymph-node dissection for pancreatic tail cancer comprises the stations: 8a (lymph nodes in the anterosuperior group along the common hepatic artery), 9 (lymph nodes around the celiac artery), 10 (lymph nodes at the splenic hilum), 11p (lymph nodes along the proximal splenic artery), 11d (lymph nodes along the distal splenic artery), 18 (lymph nodes along the inferior margin of the pancreas) [95,100]. Table 2 illustrates the regional lymph nodes that should be resected depending on the location of the tumor according to Japanese Classification of Pancreatic Carcinoma, eight edition, 2024 [100].

**Table 2.** Regional lymph nodes in pancreatic carcinoma.

Pancreatic Region	Head	Body	Tail
Station number	6- infrapyloric lymph nodes	8a- lymph nodes in the anterosuperior group along the common hepatic artery	8a- lymph nodes in the anterosuperior group along the common hepatic artery
	8a- lymph nodes in the anterosuperior group along the common hepatic artery	8p- lymph nodes in the posterior group along the common hepatic artery	9- lymph nodes around the celiac artery

8p- lymph nodes in the posterior group along the common hepatic artery	9- lymph nodes around the celiac artery	10- lymph nodes at the splenic hilum
12a- lymph nodes along the hepatic artery	10- lymph nodes at the splenic hilum	11p- lymph nodes along the proximal splenic artery
12b- lymph nodes along the bile duct	11p- lymph nodes along the proximal splenic artery	11d- lymph nodes along the distal splenic artery
12p- lymph nodes along the portal vein	11d- lymph nodes along the distal splenic artery	18- lymph nodes along the inferior margin of the pancreas
13- lymph nodes on the posterior aspect of the head of the pancreas	14t- lymph nodes along the superior mesenteric artery (tumor side)	
14t- lymph nodes along the superior mesenteric artery (tumor side)	18- lymph nodes along the inferior margin of the pancreas)	
17- lymph nodes on the anterior surface of the head of the pancreas		

#### 4.6. Preoperative biliary drainage

Routine preoperative biliary drainage is not recommended being associated with a high complication rate in patients with bilirubin level < 250 mmol/l (146 mg/l). It is recommended when the bilirubin level is > bilirubin level 250 mmol/l (146 mg/l) and the patient will receive neoadjuvant therapy or the surgical procedure will be delayed for longer than 2 weeks. The endoscopic biliary drainage is the preferred approach [95,101].

#### 4.7. Neoadjuvant treatment

Neoadjuvant treatment or induction therapy as named in recent guidelines is used for patients with borderline resectable pancreatic cancer. The preferred chemotherapy regimen is represented by FOLFIRINOX (folinic acid, fluorouracil (5-FU), irinotecan, and oxaliplatin). The alternative is gemcitabine combined with oxaliplatin or capecitabine. Chemoradiation strategies failed to prove any benefit compared with FOLFIRINOX regimen alone [95,102,103].

Resectability assessment after neoadjuvant therapy should be performed in a multidisciplinary team and should be based not only on the imagistic findings as they may overestimate the tumor size or vascular invasion due to post-therapy changes, but also on CA 19-9 serum levels, patient's performance status and clinical response. PV or SMV involvement requires venous resection followed by reconstruction to achieve R0 resection and is usually performed depending on the surgeon's expertise. Unlike venous resection, arterial resection and reconstruction when CA or CHA are involved, even technically feasible associates significantly increased morbidity and mortality. Current guidelines do not recommend arterial resection after induction therapy, but "can be considered as a possibility in experienced centers on a case-by-case basis in selected patients" [95,104–106].

#### 4.8. Adjuvant treatment

Adjuvant chemotherapy after surgical resection proved survival benefit and FOLFIRINOX is reference standard adjuvant therapy for fit patients with ECOG performance status 0-1. Alternative, gemcitabine-capecitabine regimen may be used for patients aged over 75, with ECOG performance status 2 or over or with any contraindication for FOLFIRINOX. Gemcitabine alone or 5-FU-LV (5-fluorouracil-leucovorin) is indicated only in frail patients [95,107–111].

#### 4.9. MIS versus open approach

Laparoscopic pancreaticoduodenectomy was firstly reported in 1994 and, after this year, based on the results obtained by Gagner and Pomp on a series of 10 patients treated in 1997 obtaining a conversion rate of 40% and duration of surgery of 8.5 hours, the method was not considered beneficial over the open approach [112,113].

In 2009 were reported the results obtained in a cohort of 75 laparoscopic pancreaticoduodenectomies. The conversion rate was 0% with mean blood loss of 74 ml, mean operating time 357 minutes and mean hospital stay of 8,2 days. The postoperative morbidity was 26,7% and postoperative mortality rate 1,33%. The resections margins were positive in 2,6% of cases and number of retrieved lymph nodes was 14. These results were considered appropriate at that moment and led to the conclusion that laparoscopic pancreaticoduodenectomy can be safely performed by experimented surgeons with optimal oncological outcomes. The question that remained was not if the laparoscopic approach is equal to the open one, but if it may become superior to the open approach [112,114].

After these encouraging results were published, larger cohorts of laparoscopic pancreaticoduodenectomies were reported comparing their outcomes to those of the open approach.

In 2015, Sharpe S. et al. analyzed the data from the National Cancer Data Base recorded between 2010-2011 and identified 4037 (91%) patients treated by open pancreaticoduodenectomy for pancreatic adenocarcinoma and 384 (9%) patients treated by laparoscopic pancreaticoduodenectomy. The characteristics of the patients and the tumors included in the two groups were not statistically different. In this context, the laparoscopic approach was associated with shorter length of stay (8 days versus 10 days in the open approach), lower postoperative morbidity, but no difference in 30-day postoperative mortality rates when the comparison was unadjusted. When adjusting the comparison for age, tumor size, lymph-node status, type of hospital facility and Charlson comorbidity index, resulted that 30-day mortality rate is higher in laparoscopic pancreaticoduodenectomy in unexperimented centers and the risk was lowered in high-volume hospital where more than 10 laparoscopic pancreaticoduodenectomies were performed every year. The lymph-node count and positive margins rate were similar between the two groups. The study emphasized the safety of the laparoscopic approach in treating pancreatic adenocarcinoma in high-volume, experimented centers, where the learning curve has been completed [112,115].

Another cohort of 137 laparoscopic pylorus-preserving pancreaticoduodenectomies was also reported in 2015 by Song K. et al. This cohort was compared to 2055 patients treated by open pylorus-preserving pancreaticoduodenectomy for periampullary tumors. The laparoscopic approach was associated with longer operation duration (482,5 minutes versus 347,9 minutes in the open approach), but shorter postoperative hospital stay (14,3 days versus 19,2 days). Also, the need for postoperative analgesia was lower in the laparoscopic group. Still, no significant differences were found regarding intraoperative blood loss, overall and major complications, the rates of postoperative pancreatic fistula or delayed gastric emptying. The conclusion was that the minimally invasive pancreaticoduodenectomy preserves the usual short-term benefits of a abdominal minimally invasive procedure such as quicker recovery, lower postoperative pain and shorter hospitalization [112,116].

Chen S. prospectively analyzed, between January 2010 and December 2013, 180 patients treated by robotic pancreaticoduodenectomy (n=60) or open pancreaticoduodenectomy (n=120). As the experience of the surgical team increased over time, the robotic approach was associated with better operative time, even if it was still longer than in the open approach (410 minutes versus 323 minutes), less blood loss, shorter postoperative recovery and hospital stay.

The postoperative morbidity, mortality, R0 resection rate and lymph-node count were similar between the robotic and open approach. Moreover, the study reported similar disease-free survival and overall survival between the two groups which supported the surgical and oncological safety of the robotic approach in treating pancreatic cancer [112,117].

An interesting statement was found in the article title of Dokmak S. published in 2015 "Laparoscopic pancreaticoduodenectomy should not be routine for resection of periampullary tumors". This affirmation was made after comparing 46 patients treated by laparoscopic pancreaticoduodenectomy compared with 46 patients treated by open pancreaticoduodenectomy for periampullary tumors. The patients included in the laparoscopic group had a lower body mass index (BMI) and more frequently associated a soft pancreas (57% versus 47%). The duration of surgery was longer in the laparoscopic approach (342 minutes versus 264 minutes), but without significant differences regarding the length of the hospital stay (25 days versus 23 days), lymph-node count (20 versus 23) or R0 resection rate (80% in both groups). The most important finding was that the laparoscopic approach associated higher severe morbidity due to more frequent grade C pancreatic fistula (28% versus 20% in the open group), so this approach should be chosen for patients with lower risk of postoperative pancreatic fistula [112,118].

The costs and outcomes of the laparoscopic pancreaticoduodenectomy in the United States were analyzed on a sample from The Nationwide Inpatient database between 2000 and 2010 and the results were published in 2016. A total of 15,574 pancreaticoduodenectomies were performed during this period and 681 were laparoscopic pancreaticoduodenectomies. The postoperative morbidity was lower in the laparoscopic approach, but the postoperative mortality rates were comparable between the two approaches. The hospitalization charges seemed to be similar, even if the open approach associated slightly longer hospital stay. In high-volume centers, the hospitalization charges were significantly reduced by the shorter hospital stay in the laparoscopic approach group (9 days versus 13 days) [112,119].

The costs associated with robotic pancreaticoduodenectomy were compared to the open approach in the study published by Baker E. et al. in 2016 on a cohort of 71 patients: 22 robotic approach, 49 open approach. Even if the robotic approach was associated with longer operation time and higher operative charges, these seemed to be compensated by the quicker recovery and shorter hospitalization [112,120].

A captivating comparison between the total laparoscopic pancreaticoduodenectomy during the initial learning curve and open pancreaticoduodenectomy was published by Tan C-L. et al. The initial learning curve for each surgeon was represented by the first 15 cases of total laparoscopic pancreaticoduodenectomies. 30 laparoscopic cases were compared to 30 open cases and resulted that the laparoscopic approach required significantly longer operation time (513,17 minutes versus 371,67 minutes) but was associated with faster recovery and shorter hospital stay (9,97 days versus 11,87 days). Postoperative morbidity and mortality rates were similar for both approaches. The surgery and anesthesia costs were higher for laparoscopic approach compared to open approach, even if the hospitalization ones were lower [112,121].

Adam M. et al. extracted data from the National Cancer Database between 2010-2011 on patients undergoing pancreaticoduodenectomy for pancreatic cancer and identified a total of 7061 patients: 6078 treated by open approach and 983 treated by minimally invasive approach. The minimally invasive approach seemed to be more frequently used for patients with fewer comorbidities which were treated in university hospitals. Even if the oncological results were similar between the minimally invasive and open approach (number of retrieved lymph-nodes, rates of positive margins), the first one was associated with higher 30-days postoperative mortality in this study. The explanation suggested was that most cases were operated in low volume hospitals, where less than 10 minimally invasive pancreaticoduodenectomies were performed every 2 years, so the importance of an experimented, trained center for such a complex procedure was underlined [112,122].

Robot-assisted pancreaticoduodenectomy (hybrid laparoscopic and robotic) was evaluated in the study published by Kim H. S. in 2020. This study included 150 patients treated between 2015 and 2018 who underwent robot-assisted pancreaticoduodenectomy compared to 710 patients who underwent open pancreaticoduodenectomy during the same period. Robot-assisted pancreaticoduodenectomy was associated with longer operating time (361,2 versus 305,7 minutes), but without significant differences regarding the intraoperative blood loss. Also, the overall

postoperative complication rates were similar between the two approaches (24,7% in robot-assisted surgery and 30,9% in open surgery). The rates of clinically relevant postoperative pancreatic fistula were also similar (6,7% versus 6,9%). The advantages of the minimally invasive approach were represented by the lower postoperative pain and the shorter hospital stay. No differences resulted in R0 resection rates or number of harvested lymph-nodes. The 2-year survival rates were comparable (84,4% in robot-assisted pancreaticoduodenectomy and 77,8% in open pancreaticoduodenectomy). The study concluded that robot-assisted pancreaticoduodenectomy has similar early postoperative and oncological mid-term outcomes to the open approach and associates faster recovery, being considered an important tool in treating pancreatic cancer [123].

Khalid A. studied a large cohort of patients treated for pancreatic cancer (19812 patients) by minimally invasive approach (1293-6,53%) and open approach (18116-91,44%). The open approach was chosen for patients with poor biological and conditional status, ASA score over 3 and who underwent previous radiation therapy and in cases requiring venous resection. Postoperative morbidity and 30-days mortality rates were similar between the two approaches. Even if minimally invasive approach associated faster recovery and shorter hospital stay, it seemed to be linked with higher risk of pulmonary embolism. So, the minimally invasive approach was considered beneficial in terms of early results in selected patients [124].

Regarding the role of minimally invasive approach in distal pancreatectomies, a multicenter patient-blinded randomized controlled trial (LEOPARD) was conducted focusing on functional recovery and the results were published in 2019. Patients treated by minimally invasive approach benefited of faster functional recovery: 4 days versus 6 days in the group treated by open approach. Minimally invasive approach was associated with reduced operative blood loss (150 ml) compared to the open approach (400 ml) and a lower rate of severe postoperative complications (25% versus 38%), but with longer operative time (217 minutes versus 170 minutes). The risk for postoperative grade B or C pancreatic fistula was higher after minimally invasive approach (39% versus 23%) but allowing percutaneous drainage. Minimally invasive approach improved patient's quality of life and led to no postoperative 90-day mortality compared to the open approach (2%). The study concluded that minimally invasive approach is suitable for left-sided pancreatic tumors confined to the pancreas and without vascular involvement leading to improved postoperative quality of life, faster functional recovery with no significant influence on the medical expenses [125].

Another important analysis on the role of minimally invasive distal pancreatectomy involving a pan-European registry was published in 2024. It was focused on patient's characteristics, intraoperative outcomes, short-term postoperative and histopathological outcomes. Patients selected for the minimally invasive approach had a diagnosis of pancreatic cancer in 28,4% of the cases. The median age was 54-74 years old, 55% female, with a median body mass index between 23,1% and 29,4%, with and ASA (American Society of Anesthesiologists) score of 3 or over 3 in only 30,9% of the cases. 30,4% of the patients had previous abdominal surgery. Vascular involvement was encountered in only 3% of the patients treated by minimally invasive approach associating a median tumor size between 17 mm and 44 mm, only 16,2% of the tumors having a diameter over 50 mm. Minimally invasive approach associated a mean operative time of 213 minutes and intraoperative blood loss of 100 ml. The postoperative hospital stay was approximately 7 days with a readmission rate of 15,7% and 0,6% 30-day mortality rate. The rate of postoperative pancreatic fistula was 19,1%. In terms of histopathological results, the overall R0 resection rate was 83,1% (66,1% for pancreatic cancer) and the range of retrieved lymph-nodes was between 9 and 22. The results were carefully interpreted taking into account that the participating centers included also low-volume ones which might have contributed to the increased postoperative morbidity, pancreatic fistula rates and decreased R0 resection rates. Still, it draws attention to the center volume and the surgeon expertise which were not analyzed in the present study [126].

A propensity score-matched analysis conducted by Shin S. on 150 patients between December 2006 and August 2013 compared the postoperative short-term outcomes and oncological outcomes between open and laparoscopic distal pancreatectomy for left-sided pancreatic cancer. The patients

included in the open group had a median age of 65 years old compared to those included in the laparoscopic group with a median age of 61 years old. There were no significant differences regarding comorbidities between the two groups, but the body mass index was higher in the laparoscopic group. The tumors approach by open surgery were larger than those treated by laparoscopy (median diameter of 3,5 cm versus 3 cm). The tumors associating another organ invasion or vascular invasion were referred directly to open approach if diagnosed preoperatively. The operative time, number of harvested lymph nodes and R0 resection rates were similar between the two groups, but the laparoscopic group benefited of a significantly faster recovery and shorter hospitalization. The rates of postoperative pancreatic fistula were and postoperative morbidity were similar. During the follow-up period, median survival registered was 29,1 months for the open group and 33,4 months for the laparoscopic one. The study's results suggested that the laparoscopic approach is at least equal to the open approach in terms of oncological adequacy and associating improved short-term postoperative outcomes [127].

Another important national observational study conducted by Sulpice L. on the role of the laparoscopic approach in left-sided pancreatic cancer concluded that it is not widely adopted yet, even if the early and long-term outcomes obtained are similar to the open approach, raising the need for a randomized controlled trial [128].

## 5. Discussion

Another important national observational study conducted by Sulpice L. on the role of The safety and feasibility of the minimally invasive pancreatic resections (both pancreaticoduodenectomy and distal pancreatectomy) is supported by the current evidence, but there is not sufficient data on long-term outcomes after minimally invasive approach for pancreatic cancer.

The available literature states that minimally invasive surgery for pancreatic cancer should be practiced in high-volume centers with experimented surgical teams. It is because the resections performed in low-volume centers led to suboptimal oncological results with high postoperative morbidity and mortality. The indications for minimally invasive resection for pancreatic cancer are not clearly established, but general criteria extracted from multiple studies were represented by tumors with diameter under 50 mm and without vascular or regional invasion. It is clear that minimally invasive pancreatic resections are associated with short-term postoperative outcomes such as faster functional recovery, lower postoperative pain, improved quality of life, shorter hospital stay and lower 30-day readmission rates. Also, in high-volume centers, it was associated with similar histopathological outcomes to open approach: similar R0 resection rates and number of harvested lymph-nodes. Additionally, the minimally invasive approach may facilitate the faster start of the adjuvant oncological treatment by rapid recovery after surgery. Future studies are still needed in order to establish the long-term outcomes after minimally invasive resection for pancreatic cancer: recurrence rates, disease-free survival, overall survival [115–118,120–124,126,129,130].

## 6. Conclusions

1. Minimally invasive approach for pancreatic cancer is associated with improved intraoperative and short-term postoperative outcomes such as: reduced intraoperative blood loss, faster functional recovery, lower postoperative pain, shorter hospital stay, but similar postoperative morbidity and pancreatic fistula risk to the open approach.

2. Minimally invasive approach for pancreatic cancer provides optimal number of harvested lymph-nodes and R0 resection rates.

3. Minimally invasive surgery for pancreatic cancer should be performed in high-volume, specialized centers with dedicated and experimented surgeons.

4. Randomized controlled studies are needed to confirm the long-term outcomes after minimally invasive surgery for pancreatic cancer.

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## Abbreviations

The following abbreviations are used in this manuscript:

MIS	minimally invasive surgery
TGFb	transforming growth factor-b
IGFs	insulin-like growth factors
LTA	lipo-teichoic acid
SCFAs	short-chain fatty acids
PanIN	intraepithelial neoplasia
IPMN	intraductal papillary mucinous neoplasms
MCN	mucinous cystic neoplasms
FAMMM	familial atypical multiple mole melanoma syndrome
CT	computed-tomography
MRI	magnetic resonance imaging
EUS	magnetic resonance imaging
FNA	fine needle aspiration
PET-CT	positron emission computed tomography
SMV	superior mesenteric vein
PV	portal vein
SMA	superior mesenteric artery
CHA	common hepatic artery
CA	celiac artery
FOLFIRINOX	folinic acid, fluorouracil (5-FU), irinotecan, and oxaliplatin
5-FU-LV	5-fluorouracil-leucovorin

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