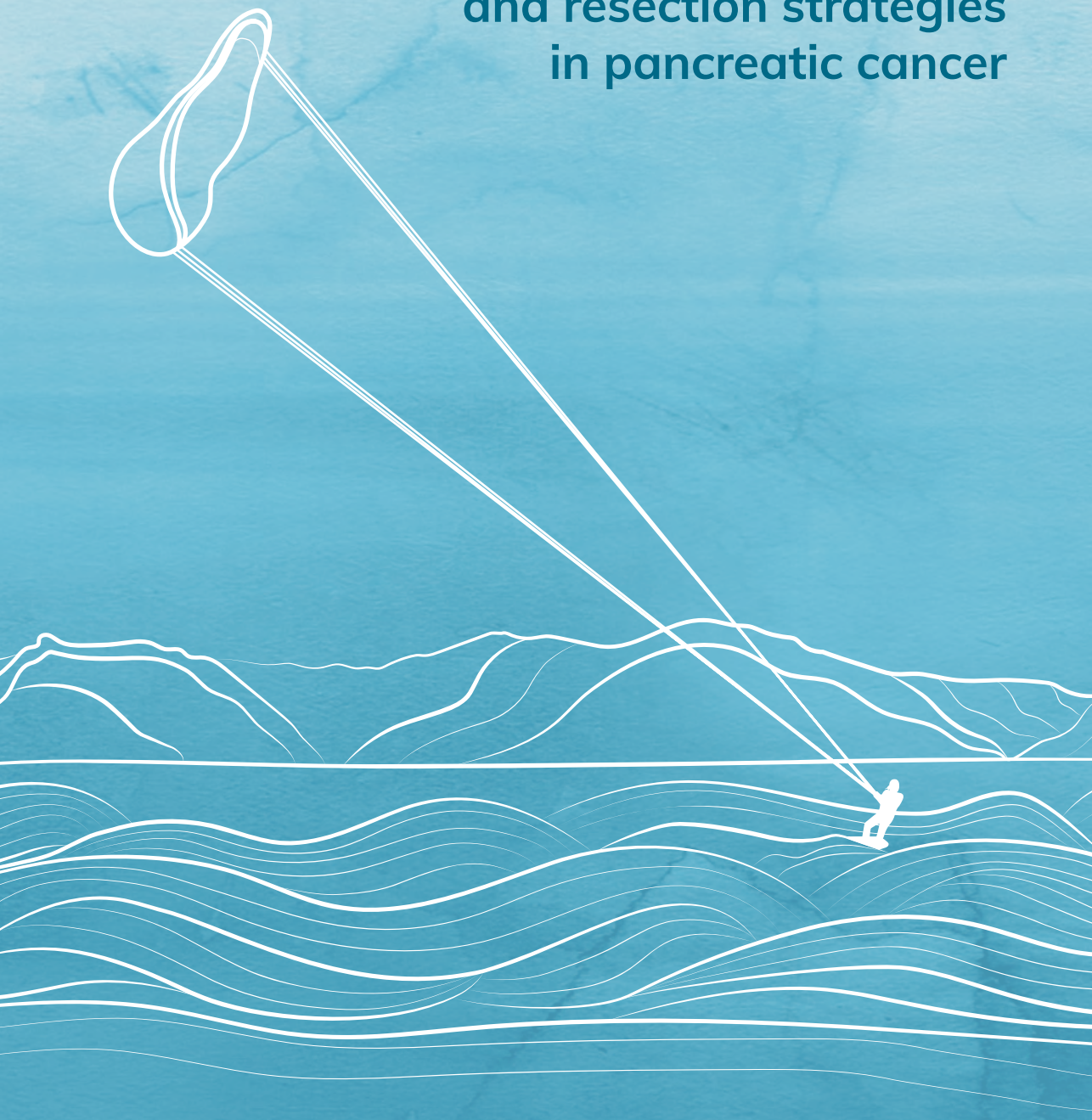
Novel imaging biomarkers and resection strategies in pancreatic cancer



Deniece Rivière

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Deniece Rivière

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Chapter 1

General introduction and outline of the thesis

Pancreatic cancer

The pancreas is a retroperitoneal organ. It is an elongated, flat, lobulated gland that lies transversely on the posterior abdominal wall. The pancreas contains exocrine and endocrine glands that secrete digestive enzymes and insulin. The pancreas is anatomically divided into the head, neck, body, and tail (Figure 1). The head, the widest part; lies within the inner curve created by duodenum. The inferior extension of the head is the uncinate process, a hook shaped continuation of the inferomedial part of the head.

In the Netherlands more than 2800 patients are diagnosed with pancreatic cancer annually (1). Worldwide incidence continues to increase and pancreatic cancer is predicted to become the second most common cause of cancer-related mortality (2, 3). Approximately 95% of pancreatic cancers occur within the exocrine pancreas and may originate from ductal epithelium, acinar cells, or connective tissue. Ductal adenocarcinoma is the most prevalent type, accounting for 90% of pancreatic tumors. The majority arises at the head of the pancreas (approximately 70%) and often presents with biliary obstruction leading to dark urine and pale colored stools, painless jaundice, and cachexia-related symptoms (appetite loss, weight loss, fatigue) (4). In contrast, body and tail pancreatic cancers present with more nonspecific symptoms, including abdominal pain, back pain, and cachexia-related symptoms.

While survival rates for many cancers have improved dramatically over the last 20 years, pancreatic cancer has persistently poor outcomes and disproportionally high mortality. Despite advancements in surgical and systemic treatment strategies, 5-years survival rates improved from less than 5% to 12% for all stages combined over the last two decades (5). Of all patients, 50% present with metastatic disease, 30% with locally advanced disease and 20% with localized resectable disease (6).

Risk factors

Certain risk factors have been identified, such as smoking, chronic pancreatitis, diabetes, obesity, and genetic mutations, including breast and ovarian cancers (BRCA1/2, PALB2), familial atypical nevus and melanoma syndrome (CDKN2A, P16 Leiden variant), hereditary chronic

pancreatitis syndrome (germline mutation PRSS1), Li/Fraumeni syndrome (mutation in TP53), Lynch syndrome (i.e. hereditary non-polyposis colon cancer) and Peutz-Jeghers syndrome (mutation in STK11 gene) (7). While sporadic pancreatic cancer is predominantly a disease of the elderly, with a median age at diagnosis of 71 years (4), approximately 10% of pancreatic cancers have a familial origin, indicating a hereditary cancer syndrome. In these high-risk groups, the International Cancer of the Pancreas Consortium (CAPS) recommends starting screening at age 50, with yearly surveillance if no pancreatic lesions are detected at baseline assessment (8). Currently, in high-risk individuals, annual endoscopic ultrasound (EUS) and/or pancreatic magnetic resonance imaging (MRI) are the procedures of choice for surveillance, usually in investigational screening registries. EUS detected more solid lesions than MRI, however MRI might be preferred as a noninvasive procedure. The diagnostic yield for significant precursor lesions and pancreatic cancer seems to vary between hereditary cancer syndromes. It remains unclear whether imaging-based surveillance for pancreatic cancer indeed improves survival (9-11).

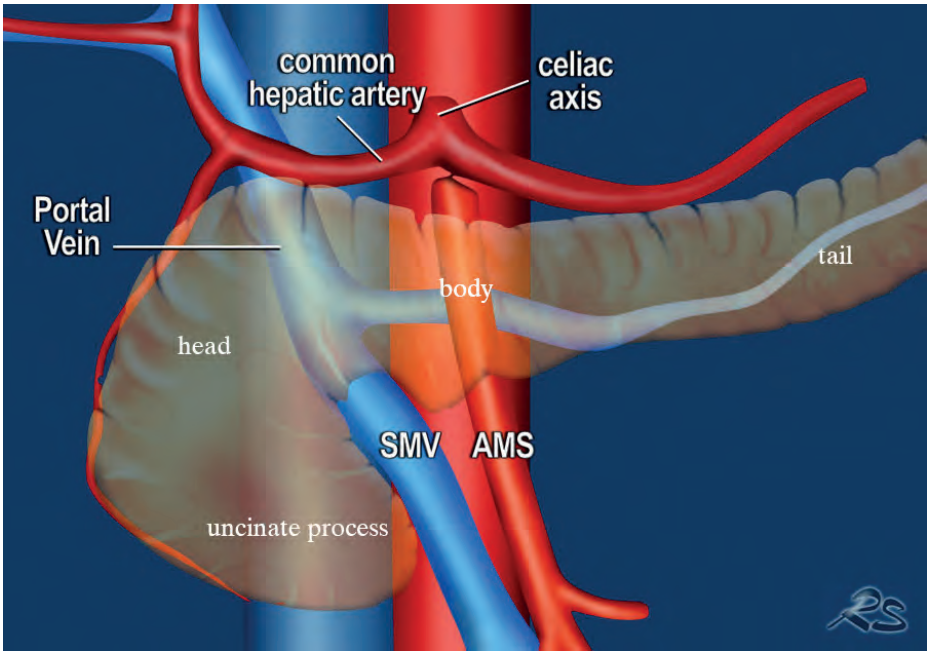

Figure 1. Pancreas anatomy
(image adapted with permission from Robin Smithuis www.radiologyassistent.nl)

Clinical work up

Clinical work up includes a complete history, physical examination, and laboratory evaluation, including a complete blood count, electrolyte panel, tumor markers, and liver function tests, to assess potential obstructive biliary issues. The most extensively studied tumor marker for pancreatic cancer is CA 19–9. Increased levels of CA 19–9 indicate a high tumor burden and is usually related to tumor size, presence of metastasis, and patient prognosis. Serial monitoring of CA 19–9 is useful after surgery or to track response to systemic therapy in patients who present with elevated levels. However, increased CA 19-9 levels may also be present in benign pancreatic and hepatobiliary diseases, and various gastrointestinal, urological, pulmonary, and gynecological diseases (12). Furthermore, 5-10% of the population are low or non-secretors of CA 19-9 (13). The relationship between the tumor marker CEA and pancreatic cancer remains unclear. Recent studies showed elevated CEA is an unfavorable prognostic indicator (14, 15).

Imaging plays a critical role in the diagnosis, staging, and therapeutic decision-making process. Although transabdominal ultrasound is commonly used in the initial workup of abdominal pain or jaundice, its usefulness in pancreatic cancer diagnosis and staging is limited by difficulties in visualizing the pancreas, particularly the tail, due to body habitus and/or commonly interposed bowel gas. The liver is usually well visualized, and ultrasound may be the first imaging modality used for the evaluation of liver metastases.

Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS) are invasive modalities that allow for visualization of the pancreas and surrounding structures. ERCP is the preferred drainage strategy to relieve symptoms of jaundice with biliary stents. ERCP with intraductal biopsies can be useful in patients with undetermined biliary strictures. It is associated with a significant complication rate, such as post-procedural pancreatitis, duodenal perforation, cholangitis, and liver abscesses, which potentially leads to a postponement of cancer treatment. EUS can be used for lesion detection and local tumor staging. Additionally, EUS guided fine-needle aspiration/ biopsy (FNA/B) is the gold standard for tissue sampling of suspected pancreatic lesions or suspected metastases (i.e., atypical portocaval lymph nodes). EUS is a safe procedure with a high diagnostic yield; FNA sensitivity 92%, 100% specificity, 100% positive

predictive value, 43% negative predictive value, and 93% accuracy. EUS and ERCP can be combined in a single session, as this strategy offers advantages such as reducing the number of hospital visits, procedure time, anesthetic requirement, and costs. The overall complication rate is significantly higher after same session EUS/ERCP (20% vs. 36%), but the incidence of post-procedural pancreatitis is not significantly different between same session (19%) and separate EUS and ERCP group (12%) (16, 17). Preoperative biliary drainage is associated with a delay in surgery, but no differences in surgical complications or survival (18, 19). The current standard for diagnosis and staging of pancreatic cancer is contrast-enhanced computed tomography (CECT), due to its availability, superb spatial resolution, and speed. The pancreas protocol is a multiphasic acquisition, with a late arterial (pancreatic) phase timed to optimize peak enhancement of the pancreas and peripancreatic arterial structures, and a portal venous phase for optimal enhancement of venous structures and to maximize detectability of typically hypodense liver metastases. On CECT pancreatic cancer typically appears as an ill-defined, hypoenhancing mass compared to adjacent normal pancreatic parenchyma on pancreatic and portal venous phase in 75-90% of cases, with delayed enhancement on later phase images because of decreased vascularity and desmoplastic stroma (Figure 2B)(20). Diagnosis of pancreatic cancer on CECT is not always straightforward, as they frequently show atypical imaging features, such as isoattenuation, a cystic mass, a mass without dilatation of the upstream duct, multiple masses or a lesion diffusively infiltrating the pancreas without distorting its configuration. Mimics of pancreatic cancer are (chronic) mass forming pancreatitis or (focal) autoimmune pancreatitis (21). CT has a sensitivity, specificity, and diagnostic accuracy of 90% (95% CI = 87–93), 87% (95% CI = 79–93) and 89% (95% CI = 85–93) respectively for the detection of pancreatic cancer (22). Early-stage pancreatic cancer detection on CECT remains challenging, as small (< 2 cm) lesions can be easily missed with a reported sensitivity as low as 45% (23). In these cases, diagnosis is dependent on the presence of secondary findings, such as ductal dilatation, ductal interruption, distal pancreatic atrophy, pancreatic contour anomalies, diffuse hypoattenuation and common bile duct dilatation (24).

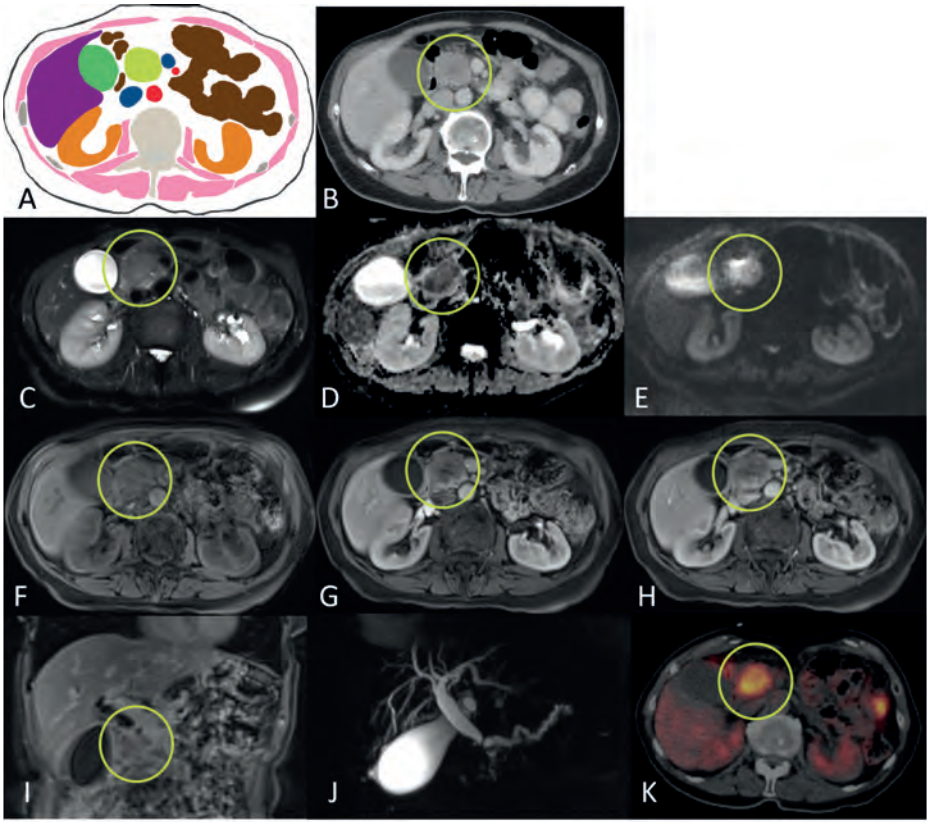

Figure 2. Diagnostic imaging of a typical pancreatic ductal adenocarcinoma in a 78-year-old patient who underwent pancreatoduodenectomy for a poorly differentiated pT3N1 tumor in the pancreatic head.

A *drawing anatomy: yellow = tumor; purple = liver; green = gall bladder; brown = bowel; orange = kidney; red = arteries (aorta and SMA); blue = veins (VCI and VMS); pink = muscle; grey = bone.* **B** *CT abdomen venous phase: hypoattenuating tumor. C-J MRI MRCP pancreas iv contrast: T2w Haste mild-moderately hyperintense tumor(C), diffusion restriction with low values on ADC(D) with high intensity on b800(E), T1w VIBE pre-contrast (F) hypointense tumor, hypovascular with rim enhancement in arterial phase (G) and venous phase (H) with progressive enhancement in the delayed phase (I). Dilated common bile duct and pancreatic duct (double duct sign) and dilated gallbladder on MRCP(J).* **K** *^{18}F-FDG-PET: intense FDG-uptake in the tumor.*

Multi-planar reconstruction allows for precise visualization of the relationship of the primary tumor to the important arterial and venous structures, thereby providing an assessment of vascular invasion and resectability. However, the accuracy of CECT in assessment of vascular invasion shows a sensitivity of only 60% with a specificity of 94% (25). The

reason for favoring specificity over sensitivity for vascular invasion is to avoid denying surgery to patients with potentially resectable tumors (26). Current anatomical and morphology-based evaluation with CECT results in inaccurate tumor delineation and poorly reproducible measurements of tumor size. The shortcomings of CECT are not limited to the T status. Inadequate lymph node staging, in addition to the poor local tumor staging, is a concern. The increased prevalence of lymph node metastasis at time of diagnosis and the impact of lymph node status on the prognosis underscores the importance of thorough evaluation. The established criterion for lymph node involvement in pancreatic cancer is lymph node enlargement. Using the usual cut-off of 10 mm short-axis diameter yields a sensitivity of 44% and a specificity of 82% (27). Furthermore, 10-20% of patients do have unexpected liver metastases, peritoneal carcinomatosis or locally advanced disease at the time of surgery (28-30). CECT has a poor sensitivity (38-76%) for the detection and characterization of liver metastases, especially in subcentimeter lesions, which are often present in pancreatic cancer (31-35). More than 50% of all liver metastases develop in the first six months postoperatively, even in patients with early tumor stage (31). These findings suggest that these liver metastases are already -synchronously- present at the time of surgery, but too small to be detected by routine preoperative ultrasound and CECT (36).

Recent advancements in MRI technology have significantly enhanced its usefulness in the diagnosis and staging of pancreatic cancer. Although MRI is not routinely implemented due to issues of its cost and availability, it is valuable in patients with impaired renal function or patients with severe hypersensitivity reaction to iodinated contrast agent. Due to its superior soft tissue contrast, MRI seems to have an advantage over CT alone in differentiating pancreatic tumors from mass-forming pancreatitis, detecting small (< 2 cm) and inconspicuous tumors, and differentiating hypertrophic pancreatic head or focal fatty infiltration of the parenchyma from true masses, through visualization of morphological changes of the pancreas parenchyma and the pancreatic duct (20). Pancreatic cancer typically shows variable intensity on T2-weighted images, is hypointense compared to normal pancreatic parenchyma on T1-weighted pre-contrast images with slower enhancement compared to normal pancreas parenchyma on pancreatic and portal venous phases, and isointense compared to normal pancreas parenchyma in delayed phases, and usually shows restricted diffusion on diffusion weighted images (Figure 2C-J). The

sensitivity, specificity, and diagnostic accuracy of MRI for the detection of pancreatic cancer is 93% (95% CI = 88–96), 89% (95% CI = 82–94) and 90% (95% CI = 86–94) respectively (22). The integration of diffusion-weighted imaging (DWI) into the standard multiphase post-contrast imaging protocol for oncological assessments is becoming more prevalent, particularly in cases where CECT results yield ambiguous findings, such as indeterminate liver lesions. DWI utilizes the constant random motion of water molecules, called Brownian motion, to depict the movement or diffusion of water in tissue structures. The degree of restriction of water diffusion can be quantitatively analyzed with the calculation of the apparent diffusion coefficient (ADC), which describes tissue signal attenuation with increasing b-values. This quantitative measurement can help differentiate between benign and malignant lesions based on their diffusion properties. Persistent high signal intensity at high b-values in combination with low signal intensity on ADC map reflects diffusion restriction. DWI is a valuable tool for detection and characterization of focal liver lesions, especially subcentimeter lesions. The pooled per-patient sensitivity and specificity of MRI combined with DWI for the detection of liver metastases of pancreatic cancer was 92.4% (95% CI = 87.4–95.6) and 97.3% (95% CI = 96.0–98.1) (37).

Positron Emission Tomography (PET) plays a crucial role in evaluating tumor behavior, utilizing functional imaging characteristics, including metabolism. Fluorine-18-2-fluoro-2-deoxyD-glucose positron emission tomography (^{18}F-FDG-PET) uses a radiotracer to detect glucose metabolism in cells, which is increased in most cancers compared to the healthy tissue. In general, the maximum standardized uptake value (SUVmax) of malignant lesions is markedly increased (Figure 2K), regardless of size, which allows PET/CT to detect small lesions. Metabolic rewiring, i.e., an individual cell's ability to use different metabolic pathways, allows cells to adapt and thrive on particularly scarce conditions of hypoxia and nutrient limitations, which are typical for pancreatic cancer. However, a low ^{18}F-FDG-uptake does not exclude pancreatic cancer. ^{18}F-FDG-PET can be useful to determine the stage of the disease, detect local recurrence and distant metastases, assess therapeutic effects, and predict prognosis in pancreatic cancer patients (38). PET/CT had a sensitivity, specificity, and diagnostic accuracy of 89% (95% CI = 85–93), 70% (95% CI = 54–84) and 84% (95% CI = 79–89) respectively for detection of pancreatic cancer (22). The SUVmax is significantly related to the survival at each stage, and patients with a low SUV tumor have a longer survival time (39, 40). Gene expression data show enrichment of

glycolytic genes in the more aggressive and therapy-resistant molecular quasi-mesenchymal subtype. Whether the glycolytic transcripts could be translated into functional glycolysis, thereby non-invasively discriminating between molecular subtypes could be the subject for further analysis (41). Despite the promising results for ^{18}F-FDG-PET, especially in the detection of occult distant metastases and altering the staging of pancreatic cancer in 10% of cases, as well as influencing decision-making in about 50% of cases and preventing unnecessary surgery in 20% of cases (38), it does not play a role in the routine staging of pancreatic cancer in the Netherlands. Certain challenges for PET/CT remain in detection of subcentimeter lesions, lymph node metastases and small liver metastases or peritoneal implants. Additionally, inflammation, especially focal pancreatitis, leads to false positive findings. Hyperglycemia is known to decrease FDG uptake, which yields false negative findings, as glucose intolerance is often seen in patients with pancreatic disease.

Staging

The staging of pancreatic carcinoma is based on the TNM classification, which considers the primary tumor (T), regional lymph nodes (N), and distant metastases (M). In the 8th edition of the American Joint Committee on Cancer (AJCC) TNM classification, introduced in 2018, adjustments were made to T and N stages (42, 43), visualized in Table 1. Distinction is made between resectable, borderline resectable, locally advanced, and metastatic cancer. The primary goal of preoperative staging is to identify all resectable tumors and rule out metastases to avoid surgical exploration in patients with unresectable tumors.

Table 1. Staging protocol for pancreatic ductal adenocarcinoma

TNM	7th edition	8th edition
Primary Tumor (T)		
pT1	Tumor limited to the pancreas, ≤ 2 cm in greatest dimension	Tumor ≤ 2 cm in greatest dimension
pT1a	-	≤ 0.5 cm
pT1b	-	> 0.5 - 1 cm
pT1c	-	> 1 – 2 cm
pT2	Tumor limited to the pancreas > 2 in greatest dimension	Tumor > 2 - 4 cm in greatest dimension
pT3	Tumor extends beyond the pancreas, without involvement of the coeliac axis or superior mesenteric artery	Tumor > 4 cm in greatest dimension
pT4	Tumor involves the coeliac axis or superior mesenteric artery	Tumor invoves coeliac axis, superior mesenteric artery and/ or common hepatic artery
Regional Lymph Nodes (N)		
pN0	No regional lymph node metastasis	No regional lymph node metastasis
pN1	Regional lymph node metastases	Regional lymph node metastases in 1-3 lymph nodes
pN2	-	Regional lymph node metastases in ≥ 4 lymph nodes
Distant Metastases (M)		
pM0	No distant metastasis	No distant metastasis
pM1	Distant metastases	Distant metastases
UICC-stage		
Ia	T1, N0, M0	T1, N0, M0
Ib	T2, N0, M0	T2, N0, M0
IIa	T3, N0, M0	T3, N0, M0
IIb	T1-3, N1, M0	T1-3, N1, M0
III	T4, any N, M0	T4, any N, M0
		Any T, N2, M0
IV	any T, any N, M1	any T, any N, M1

Due to the posterior location of the pancreas in the upper abdomen, tumors have the potential to extend via multiple peritoneal and retroperitoneal anatomic planes and invade the adjacent structures (including the stomach and duodenum, spleen, colon), important vascular structures and the celiac plexus. To determinate the resectability of the tumor, the degree of tumor-vessel contact with the celiac axis (CA), superior mesenteric artery (SMA), hepatic artery, portal vein and the superior mesenteric vein (SMV) is critical.

Additionally, tumor contact with the aorta, the first jejunal SMA and SMV branch is regarded irresectable disease. Arterial resection and reconstruction are performed in only in highly selected cases (44), as arterial resection results in increased postoperative mortality, complications, and impaired survival (45). In the Netherlands, the resectability-criteria developed by the Dutch Pancreatic Cancer Group (DPCG) are applied, which uses slightly different definitions that define pancreatic cancer resectability compared to other international guidelines, see Table 2 (7, 46, 47).

Lymph node metastasis is a significant risk factor affecting survival, with around 65% incidence in resected patients (48). Nodal involvement in the peripancreatic area does not impact surgical planning, however, it may guide therapeutic strategies, especially for systemic adjuvant treatment. Lymph node metastasis is one of the most important predictors for recurrence in resected pancreatic cancer, in addition to margin status and the microscopic assessment of perivascular, lymphatic and perineural invasion (49-51). Hepatic artery and particularly para-aortic lymph node metastasis, not included in standard lymphadenectomy, is associated with decreased survival (Figure 3) (52). The identification of distant metastases, including extra regional lymph node metastases, is essential as it precludes surgical resection. Common sites of distant metastases are liver (76-90%), lymph nodes (10-25%), lung (20-25%), peritoneum (20%), and bones (7-15%) (53, 54). Synchronous metastases are limited to a single organ in 65-80% of patients. Isolated pulmonary metastatic disease is not common, though these patients have better outcomes compared to patients with isolated liver metastases (resp. 6 months versus 4 months) (53, 55).

Management

Resectable tumors are usually treated with an upfront surgical resection. The optimal neoadjuvant regimen for resectable tumors is still under investigation. Depending on the anatomical location of the tumor available options for the resection of pancreatic cancer are pancreatoduodenectomy, distal pancreatectomy or total pancreatectomy. Pancreatoduodenectomy involves the en-bloc removal of the pancreatic head, duodenum, gallbladder, distal common bile duct, proximal jejunum, and regional lymph nodes. This procedure includes the creation of a hepaticojejunostomy and a pancreatojejunostomy. In the Whipple procedure (Figure 4), the gastric

antrum is removed, and a gastrojejunostomy is created. The pylorus-preserving variant retains the gastric antrum and the first portion of the duodenum with a duodenojejunostomy. Distal pancreatectomy resects the distal portion of the pancreas at or to the left of the superior mesenteric vein, with or without splenectomy. Unlike pancreatoduodenectomy, no anastomoses are created in this procedure, resulting in almost normal postsurgical anatomy.

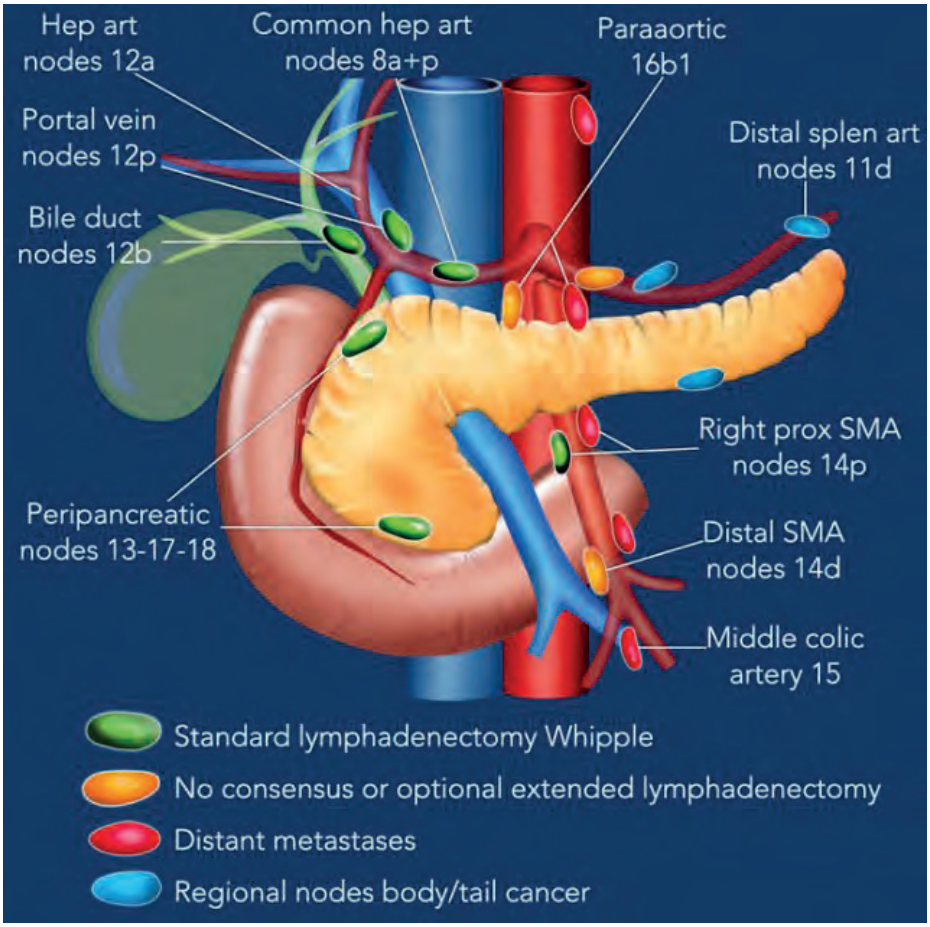

Figure 3. *Lymph node stations pancreas*
(with permission from Robin Smithuis www.radiologyassistent.nl)

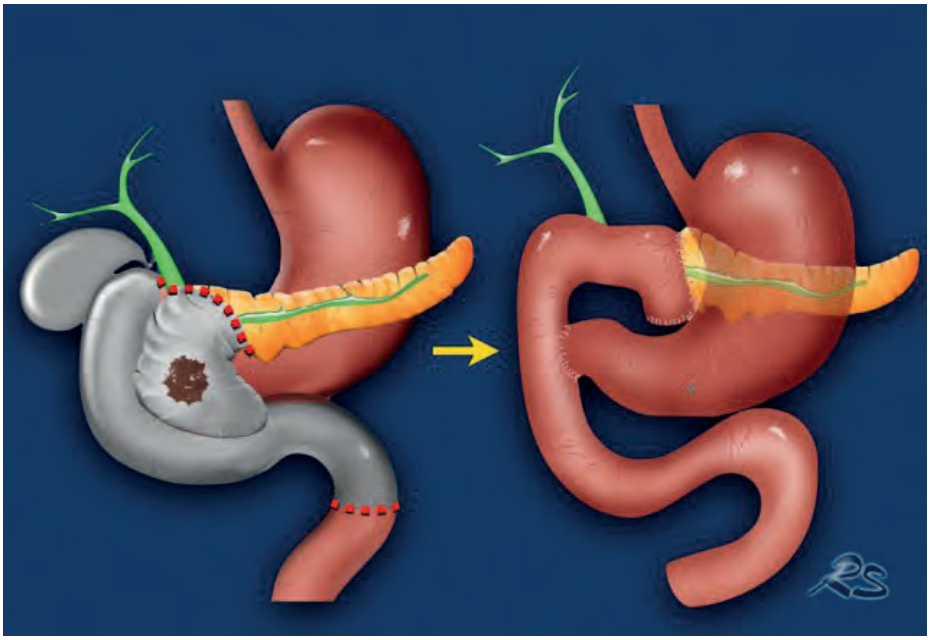

Figure 4. Whipple procedure before and after
(with permission from Robin Smithuis www.radiologyassistent.nl)

Less extensive pancreas-sparing techniques, such as pancreatic sparing partial or total duodenectomy, surgical ampullectomy, tumor enucleation or middle segment resection, are sometimes used for certain types of low-grade or benign tumors that can be removed with a minimal margin of the pancreatic tissue. Pancreatic surgery is a high-risk procedure. Especially, the reconstruction of the pancreatoenteric anastomosis is associated with postoperative complications including pancreatic fistulas, anastomotic leaks, bleeding, and infection (56, 57). The presence of anatomic arterial variants increases the risk for intraoperative vascular injuries related postoperative complications, such as hepatic ischemia and pseudoaneurysms, and necessitates clear and detailed radiological reporting to guide surgical planning. Even in expert hands, surgical morbidity rates of pancreatic resections are substantial, around 50-60%, with in hospital mortality rate of 4% (58, 59). Laparoscopic surgery has become the standard for many procedures, progressively extending their influence in the pancreatic surgery field. Robotic surgery is a promising minimal invasive technique that overcomes many of the key shortcomings of traditional laparoscopy, which include monocular vision, limited degrees of freedom and the effects of pivot and fulcrum, especially in the context

of mastering intricate suturing techniques (60). General implementation of robotic surgery in pancreatic procedures is still investigated due to the complexity and lack of data on long-term safety and oncological clearance.

Borderline resectable tumors present a challenge due to their potential for involvement of adjacent vessels. In recent years, neoadjuvant chemotherapy (NAT) is the current standard practice in high-volume centers for resectable and borderline resectable pancreatic cancer, NAT aims to reduce tumor size, thereby improving the complete resection rate, while avoiding unnecessary surgery in patients who exhibit progressive disease or develop metastases during treatment. This ultimately contributes to an improvement in overall survival (61). In resectable and borderline resectable pancreatic cancer, the overall resection rate was lower in the neoadjuvant group compared to those who had surgery first, however, there was an improved overall survival, a higher R0 resection rate and an increased time until recurrence (62). Preferred first-line regimens in the neoadjuvant setting include modified 5-fluorouracil + leucovorin + irinotecan + oxaliplatin (mFOLFIRINOX) and albumin-bound paclitaxel (nab-Paclitaxel) + gemcitabine; the former is limited to patients with preserved performance status (63). Locally advanced tumors, in the absence of distant metastases, are usually treated with induction systemic chemotherapy. In intention-to-treat analysis 24% of patients with borderline resectable tumors and 9% of patients with locally advanced tumors underwent curative pancreatic resection after neoadjuvant chemotherapy, with R0 resection rate of almost 60% (64). Favorable results of surgical resection for locally advanced tumors after undergoing successful chemotherapy therapy or chemoradiation, so-called “conversion surgery” have been reported with a significantly better prognosis than in the non-resected group (65, 66). In some cases, surgical or laparoscopic exploration may be required to confirm the presence of metastatic disease, resectability or to evaluate the response to chemotherapy.

Post-operative chemotherapy (adjuvant chemotherapy) significantly improves outcomes and is therefore the current standard care in patients recovered from pancreatic surgery. mFOLFIRINOX led to a significantly longer disease-free survival, overall survival, metastasis-free survival, and cancer-specific survival than treatment with gemcitabine, however, at the expense of greater treatment toxicity, and is therefore reserved for patients in a good physical condition. Gemcitabine/capecitabine is the preferred regimen among patients with reduced performance status (67, 68). In the

end, one out of two patients can receive adjuvant chemotherapy, and less than 10% completes the recommended regimen (69). The role of adjuvant radiotherapy for resected pancreatic cancer is controversial (70, 71).

Palliative chemotherapy or supportive care is given to patients with metastatic disease, intended to improve patient survival and suppress disease-related symptoms (pain and cholestasis) with acceptable quality of life. Bypass surgery is a palliative option to relieve (obstructive) digestive symptoms. EUS-guided gastro-jejunostomy is an alternative and is currently compared with surgical bypass techniques in a nation-wide RCT (72).

Histopathology

The histological classification is based on the WHO typing of tumors of the exocrine pancreas, ampulla of Vater and extrahepatic bile duct. Recognition of the variants of pancreatic cancer is important because they can differ in post-operative adjuvant treatment and clinical behavior, e.g., colloid carcinoma has a significantly better prognosis than conventional pancreatic ductal adenocarcinoma (PDAC). Most pancreatic cancers originate from noninvasive microscopic pancreatic intraepithelial neoplasia (PanIN) and macroscopic precursor lesions, such as intraductal papillary mucinous neoplasms (IPMN) (73). Ductal adenocarcinomas are infiltrative tumors composed of atypical cells arranged in irregular, incomplete tubular, or glandular structures, embedded in abundant desmoplastic tumor stroma. This desmoplastic reaction may surpass the growth of neoplastic glands such that neoplastic cells in the pancreatic mass are outnumbered by non-neoplastic cells. The desmoplastic reaction is composed of a mixture of dense collagen, fibroblasts, delicate vessels, and inflammatory cells. Chronic pancreatitis frequently coexists due to pancreatic duct infiltration and activation of the pancreatic cancer stroma. The findings of luminal necrosis and incomplete lumina support the diagnosis of invasive ductal adenocarcinoma over reactive glands. Perineural and vascular invasion is very common (74). Pancreatic cancer is well known to be very heterogenous in its morphological phenotype, appearing as a wide spectrum of patterns involving cancer gland formation and tumor stroma composition (75).

After resection, histopathology analysis of the resected specimen is performed to confirm the diagnosis of pancreatic ductal adenocarcinoma

and to map the extent of disease. This includes pathological TNM stage, tumor size, tumor grade, the assessment of lymph node metastases, tumor permeation along lymphatics, blood vessels and neurons, and the resection margin status. Ductal adenocarcinomas are graded based on the extent of glandular differentiation: well differentiated more than 95% of the tumor is composed of glands, moderately differentiated if 50-95% consists of glands, and poorly differentiated if less than 50% exhibits glandular features (76).

Tumor resection completeness should be assessed macroscopically and confirmed by microscopic examination. Pancreatic cancer exhibits an infiltrative and discontinuous growth pattern, with cancer cells frequently identified well beyond the grossly identified border of the lesion. To ensure a comprehensive evaluation, extensive sampling is necessary to accurately assess the extent of viable tumor and its relationship to the margins. Although there is still controversy over the definition of microscopic margin involvement, carcinomas located less than 1 mm from the resection margin are typically considered incompletely excised. Involvement of the anterior margin is from an anatomical point-of-view not considered R1. Notably, microscopic margin involvement is a common finding in pancreatic cancer, affecting over 75% of cases , and it strongly correlates with survival (77). Sampling of the entire pancreas specimen is recommended for a reliable diagnosis of complete response after neoadjuvant therapy. Accurate evaluation of tumor regression requires extensive sampling. The entire tumor bed and any adjacent abnormal-looking tissues should be processed for histological examination (78). Ideally, histological evaluation of the tumor response and outcome prognostication, guides decisions on adjuvant regimens, and is a valuable tool in comparative trials of NAT. However, identification of the effect of NAT in resected pancreatic cancer proved unreliable, and interobserver agreement for the most commonly used tumor response scoring systems (TRS) by the College of American Pathologists (CAP) and the MD Anderson Cancer Center (MDACC) was suboptimal (79). Most TRS systems are based on an evaluation of either the proportion of the cancer cells that remain viable following treatment or the proportion of tumor cells that have been destroyed by therapy, although the tumor burden before therapy is unknown and it is unclear how the residual viable cancer cells should be assessed after therapy. Anatomical based comparison with the original tumor size is inadequate because tumor size measurements based on imaging and histopathology specimen often yield divergent results, even in treatment naïve patients. Determination of the

amount of residual viable cancer cells in relation to the treatment-induced fibrosis is unreliable too, as fibrosis for reasons other than neoadjuvant treatment, i.e., concurrent (chronic obstructive) pancreatitis and/or extensive stromal reaction inherent to pancreatic cancer, is likely to be histologically indistinguishable from fibrosis secondary to tumor regression. There is a need for consensus on how to assess the tumor response to preoperative therapy (80).

Table 2. Resectability criteria pancreatic cancer

	DPCG 2012	**JPS 2019**	**NCCN 2022**
Resectable			
	CA, SMA, CHA: no contact SMV/PV: ≤90°	CA, SMA, CHA: no contact SMV/PV: <180° without vein occlusion	CA, SMA, CHA: no contact SMV/PV: <180° without vein contour irregularity
Borderline resectable			
	CA, SMA, CHA: ≤90° SMV/PV: 90-270°	CA, SMA: <180° without stenosis or deformity CHA: tumor contact without contact or invasion of the PHA and/or CA SMV/PV: >180° or occlusion vein, not exceeding the inferior border of the duodenum	CA, SMA: <180° CHA: solid tumor contact without extension to CA or HA bifurcation or contact with variant arterial anatomy SMV/PV: >180° or tumor contact ≤ 180° with contour irregularity or thrombosis IVC: solid tumor contact
Irresectable/ Locally advanced			
	CA, SMA, CHA: >90° SMV/PV: >270° or occlusion vein	CA, SMA: >180° CHA: tumor contact or invasion of the PHA and/or CA AO: tumor contact or invasion SMV/PV: >180° or occlusion vein, exceeding the inferior border of the duodenum	CA, SMA: >180° AO: tumor contact or invasion SMV/PV: Unreconstructible due to extensive tumor involvement or venous occlusion

Abbreviations: AO = aorta, CA = celiac axis, CHA = common hepatic artery, DPCG = Dutch Pancreatic Cancer Group, IVC = inferior vena cava, JPS = Japan Pancreas Society, NCCN = National Comprehensive Cancer Network, PHA = proper hepatic artery, PV = portal vein, SMA = superior mesenteric artery, SMV = superior mesenteric vein.

Follow-up and recurrence

Despite the poor long-term survival and extremely high risk of recurrence, no evidence-based guidelines for surveillance after resection exist. Follow up schemes are individualized to the patient in order to minimize emotional stress and costs (81). More than 80% of recurrences occur within 2 years after resection and can be locoregional and/or to distant sites. High rates of recurrence after curative resection inevitably lead to dismal rates of long-term survival (82). The most common distant site of recurrence is the liver, occurring in the first six months after resection with poor post recurrence survival (83). Advancements in systemic treatment, radiotherapy and ablation techniques may significantly impact post-recurrence survival, thus necessitating the identification of the optimal surveillance strategy (84).

Aim and outline of this thesis

As the understanding of periampullary and pancreatic cancer continues to develop, there is a growing need for more detailed diagnostic workup, evaluation and prediction of therapy response and subsequent planning of surgical approach, particularly with the development of resectable and borderline resectable disease criteria and increasing use of neoadjuvant therapies, different systemic therapy options and minimally invasive surgery. Identifying novel biomarkers is necessary to move forwards in a precision medicine era. CECT serves as a cornerstone in the diagnostic staging of pancreatic cancer. Nonetheless, challenges remain in discerning tumor resectability, detecting small or isovascular tumors, assessing lymph node involvement, identifying subcentimeter liver metastases and peritoneal metastases. There is a pressing need for advancements in imaging technology to optimize staging and enhance treatment stratification, ultimately leading to improved outcomes. This thesis hopes to improve outcomes in periampullary and pancreatic cancer through focus on the development of new diagnostic techniques and evaluating new treatment options.

Surgical resection is currently the only potential cure for periampullary and pancreatic cancer. Modifications of the conventional procedures have been developed in an attempt to improve outcomes or to minimize the associated morbidity, for example through minimally invasive surgery.

Therefore, the aim of **Chapter 2** is to compare laparoscopic versus open distal pancreatectomy for pancreatic cancer in a systematic review and meta-analysis. The cost effectiveness comparison of laparoscopic versus open distal pancreatectomy is described in **Chapter 3**. **Chapter 4** describes the study protocol for the systematic review and meta-analysis to compare laparoscopic versus robotic versus open pancreaticoduodenectomy for periampullary malignant and benign tumors.

A considerable proportion of patients undergo unnecessary surgery because of underestimation of the extent of the cancer on CT. **Chapter 5** evaluates the diagnostic accuracy of EUS following CT for assessing the resectability in pancreatic cancer. Adequate preoperative diagnosis, staging and patient selection are crucial to prevent unnecessary surgery. New biomarkers are needed to improve patient selection preoperatively and to personalize treatment. In **Chapter 6** the value of MRI and ADC is studied in relation to overall survival and tumor grade in whole mount specimen of resected PDAC. **Chapter 7** investigates another possible biomarker combining perfusion and metabolism of the tumor using contrast-enhanced CT and ^{18}F-FDG-PET in relation to the overall survival.

Intraoperative detection of small liver or peritoneal metastasis is the most frequent cause of aborted surgery in candidates with a preoperative CT diagnosis of a resectable tumor. In **Chapter 8** a retrospective comparison between preoperative CT and MRI for the detection of synchronous liver metastases is presented, to investigate the possible improvement of liver metastases detection with MRI. **Chapter 9** is a presentation of the study protocol of the prospective study investigating the diagnostic accuracy of contrast-enhanced and diffusion-weighted MRI for liver metastases.

Finally, this thesis is completed by a general discussion in **Chapter 10**, summarizing the results and conclusions of the presented studies and discussing future perspectives.

Chapter	Clinical problem	Aim
2. Laparoscopic versus open distal pancreatectomy for pancreatic cancer	Surgical resection is currently the only potential curative treatment of pancreatic cancer. In other organs, laparoscopic surgery reduces complications and length of hospital stay compared with open surgery. Concerns remain about the safety of laparoscopic distal pancreatectomy.	To assess the benefits and harms of laparoscopic distal pancreatectomy versus open distal pancreatectomy for people undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma of the body or tail of the pancreas, or both.
3. Cost-effectiveness of laparoscopic versus open distal pancreatectomy for pancreatic cancer	It is unknown if laparoscopic distal pancreatectomy for pancreatic cancer is cost-effective.	To perform a model-based cost-utility analysis of laparoscopic versus open distal pancreatectomy for pancreatic cancer.
4. Laparoscopic versus robotic versus open pancreaticoduodenectomy for periampullary malignant and benign tumors.	For many surgical procedures, minimally invasive surgery is currently preferred over open surgery. Concerns remain about the safety of minimally invasive versus open pancreatoduodenectomy.	To assess the benefits and harms of laparoscopic versus robot-assisted versus open pancreatoduodenectomy for people with benign, premalignant, and malignant disease.
5. Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer	A considerable proportion of patients undergo unnecessary laparotomy because of underestimation of the extent of pancreatic cancer on CT. Other imaging methods have been used to detect local invasion or distant metastases not visualized on CT, which could prevent unnecessary laparotomy.	To determine the diagnostic accuracy of MRI, PET scan, and EUS performed as an add-on test or PET-CT as a replacement test to CT scanning in detecting curative resectability in pancreatic and periampullary cancer.
6. No predictive value of tumor volume ADC-value for tumor grade and overall survival in resectable pancreatic ductal adenocarcinoma	Poor tumor differentiation is a statistically significant independent prognosticator of overall survival after resection, disease specific survival, early recurrence, and post recurrence survival. The histopathological grade is typically unknown when treatment decisions are made, and therefore not useful for determining whether neoadjuvant therapy should be considered.	To determine if the ADC-value of pancreatic ductal adenocarcinoma could be a predictor of tumor aggressiveness, and to assess its association with tumor grades according to WHO classification, Adsay classification, and Kalimuthu classification, using whole-mount pancreatectomy specimens.

Chapter	Clinical problem	Aim
7. Flow metabolic phenotype of pancreatic cancer. A new prognostic biomarker?	Accurate patient stratification prior to treatment is crucial to benefit from treatment. Non-invasive imaging biomarkers that correlate better with tumor biology, as opposed to conventional anatomic-morphologic approaches, are needed.	To investigate the relationship between the qualitative flow-metabolic phenotype and overall survival of PDAC and its potential clinical utility, using tumor attenuation on routine contrast-enhanced CT as a surrogate for the vascularity and [18F]-FDG uptake as a surrogate for metabolic activity on [18F]-FDG-PET.
8. Improving preoperative detection of synchronous liver metastases in pancreatic cancer with combined contrast-enhanced and diffusion-weighted MRI	Synchronous liver metastases are not identified pre-operatively, as they are too small to be detected by routine preoperative ultrasound and CECT.	To explore the value of gadolinium-enhanced MRI combined with diffusion-weighted MRI in addition to contrast-enhanced CT for detection of synchronous liver metastases for potentially resectable pancreatic cancer.
9. Diagnostic accuracy of contrast-enhanced diffusion-weighted MRI for liver metastases of pancreatic cancer: towards adequate staging and follow-up of pancreatic cancer – DIA-PANC study	Without high-quality evidence of the benefit of MRI in the routine staging of pancreatic cancer, it is not implemented in clinical practice.	To analyze the accuracy of diffusion-weighted, contrast-enhanced MRI to detect liver metastases in patients with pancreatic cancer.

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Chapter 2

Laparoscopic versus open distal pancreatectomy for pancreatic cancer

Deniece Riviere, Kurinchi Selvan Gurusamy, David A Kooby, Charles M Vollmer, Marc GH Besselink, Brian R Davidson, Cornelis JHM van Laarhoven, and Cochrane Upper GI and Pancreatic Diseases Group

Abstract

Background

Surgical resection is currently the only treatment with the potential for long-term survival and cure of pancreatic cancer. Surgical resection is provided as distal pancreatectomy for cancers of the body and tail of the pancreas. It can be performed by laparoscopic or open surgery. In operations on other organs, laparoscopic surgery has been shown to reduce complications and length of hospital stay as compared with open surgery. However, concerns remain about the safety of laparoscopic distal pancreatectomy compared with open distal pancreatectomy in terms of postoperative complications and oncological clearance.

Objectives

To assess the benefits and harms of laparoscopic distal pancreatectomy versus open distal pancreatectomy for people undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma of the body or tail of the pancreas, or both.

Search methods

We used search strategies to search the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index Expanded and trials registers until June 2015 to identify randomised controlled trials (RCTs) and non-randomised studies. We also searched the reference lists of included trials to identify additional studies.

Selection criteria

We considered for inclusion in the review RCTs and non-randomised studies comparing laparoscopic versus open distal pancreatectomy in patients with resectable pancreatic cancer, irrespective of language, blinding or publication status.

Data collection and analysis

Two review authors independently identified trials and independently extracted data. We calculated odds ratios (ORs), mean differences (MDs) or hazard ratios (HRs) along with 95% confidence intervals (CIs) using both fixed-effect and random-effects models with RevMan 5 on the basis of intention-to-treat analysis when possible.

Main results

We found no RCTs on this topic. We included in this review 12 non-randomised studies that compared laparoscopic versus open distal pancreatectomy (1576 participants: 394 underwent laparoscopic distal pancreatectomy and 1182 underwent open distal pancreatectomy); 11 studies (1506 participants: 353 undergoing laparoscopic distal pancreatectomy and 1153 undergoing open distal pancreatectomy) provided information for one or more outcomes. All of these studies were retrospective cohort-like studies or case-control studies. Most were at unclear or high risk of bias, and the overall quality of evidence was very low for all reported outcomes.

Differences in short-term mortality (laparoscopic group: 1/329 (adjusted proportion based on meta-analysis estimate: 0.5%) vs open group: 11/1122 (1%); OR 0.48, 95% CI 0.11 to 2.17; 1451 participants; nine studies; I2 = 0%), long-term mortality (HR 0.96, 95% CI 0.82 to 1.12; 277 participants; three studies; I2 = 0%), proportion of people with serious adverse events (laparoscopic group: 7/89 (adjusted proportion: 8.8%) vs open group: 6/117 (5.1%); OR 1.79, 95% CI 0.53 to 6.06; 206 participants; three studies; I2 = 0%), proportion of people with a clinically significant pancreatic fistula (laparoscopic group: 9/109 (adjusted proportion: 7.7%) vs open group: 9/137 (6.6%); OR 1.19, 95% CI 0.47 to 3.02; 246 participants; four studies; I2 = 61%) were imprecise. Differences in recurrence at maximal follow-up (laparoscopic group: 37/81 (adjusted proportion based on meta-analysis estimate: 36.3%) vs open group: 59/103 (49.5%); OR 0.58, 95% CI 0.32 to 1.05; 184 participants; two studies; I2 = 13%), adverse events of any severity (laparoscopic group: 33/109 (adjusted proportion: 31.7%) vs open group: 45/137 (32.8%); OR 0.95, 95% CI 0.54 to 1.66; 246 participants; four studies; I2 = 18%) and proportion of participants with positive resection margins (laparoscopic group: 49/333 (adjusted proportion based on meta-analysis estimate: 14.3%) vs open group: 208/1133 (18.4%); OR 0.74, 95% CI 0.49 to 1.10; 1466 participants; 10 studies; I2 = 6%) were also imprecise. Mean length of hospital stay was shorter by 2.43 days in the laparoscopic group than in the open group (MD -2.43 days, 95% CI -3.13 to -1.73; 1068 participants; five studies; I2 = 0%). None of the included studies reported quality of life at any point in time, recurrence within six months, time to return to normal activity and time to return to work or blood transfusion requirements.

Authors' conclusions

Currently, no randomised controlled trials have compared laparoscopic distal pancreatectomy versus open distal pancreatectomy for patients with pancreatic cancers. In observational studies, laparoscopic distal pancreatectomy has been associated with shorter hospital stay as compared with open distal pancreatectomy. Currently, no information is available to determine a causal association in the differences between laparoscopic versus open distal pancreatectomy. Observed differences may be a result of confounding due to laparoscopic operation on less extensive cancer and open surgery on more extensive cancer. In addition, differences in length of hospital stay are relevant only if laparoscopic and open surgery procedures are equivalent oncologically. This information is not available currently. Thus, randomised controlled trials are needed to compare laparoscopic distal pancreatectomy versus open distal pancreatectomy with at least two to three years of follow-up. Such studies should include patient-oriented outcomes such as short-term mortality and long-term mortality (at least two to three years); health-related quality of life; complications and the sequelae of complications; resection margins; measures of earlier postoperative recovery such as length of hospital stay, time to return to normal activity and time to return to work (in those who are employed); and recurrence of cancer.

Background

Description of the condition

Adenocarcinoma of the pancreas is the most common malignancy of the exocrine pancreas. It is the tenth most common cancer in the United States, the fifth most common cause of cancer-related mortality in the East and the fourth most common cause of cancer-related mortality in the West (Parkin 2001; Parkin 2005; Yamamoto 1998). In 2012, 338,000 people were newly diagnosed with pancreatic cancer, and 330,000 deaths were the result of pancreatic cancer globally (IARC 2014). Global variation has been noted in the incidence of pancreatic cancer, with an age-standardised annual incidence rate of 7.2 per 100,000 in more developed regions and an age-standardised annual incidence rate of 2.8 per 100,000 in less developed regions (IARC 2014). A similar trend has been noted in an age-standardised annual mortality rate of 6.8 per 100,000 population in more developed regions and 2.7 per 100,000 population in less developed regions due to pancreatic cancer (IARC 2014). Mortality rates due to pancreatic cancer are increasing in the United States (Ma 2013). Pancreatic adenocarcinoma has a poor prognosis for many reasons. It is a biologically aggressive cancer that is relatively resistant to chemotherapy and radiotherapy and has a high rate of local and systemic recurrence (Abrams 2009; Ghaneh 2007; Orr 2010). Surgical resection remains the only treatment with the potential for long-term survival and cure. However, about half the people have metastatic disease at presentation, and one-third have locally advanced unresectable disease, leaving only about 10% to 20% of people suitable for resection (Tucker 2008). Overall five-year survival after radical resection ranges from 7% to 25% (Cameron 1993; Livingston 1991; Niederhuber 1995; Nitecki 1995; Orr 2010; Trede 1990), with median survival of 11 to 15 months (British Society of Gastroenterology 2005). With adjuvant chemotherapy, median survival after radical resection ranges between 14 and 24 months (Liao 2013).

Pancreatic cancer can occur in the head of the pancreas or in the body and tail of the pancreas. In early pancreatic cancer (with no invasion of adjacent structures such as the superior mesenteric vein, portal vein or superior mesenteric artery), surgical resection remains the primary treatment of choice for people likely to withstand major surgery.

Description of the intervention

Surgical resection is provided as pancreaticoduodenectomy for cancers of the head of the pancreas and as distal pancreatectomy for cancers of the body and tail of the pancreas (Park 2013). In open distal pancreatectomy, surgical access to the abdominal cavity (and hence the pancreas) is attained by upper midline incision, bilateral subcostal incision (roof-top or Chevron incision) or transverse abdominal incision (Fernandez-Cruz 2006). In laparoscopic distal pancreatectomy, surgical access to the abdominal cavity (and hence the pancreas) is typically attained by four small ports (holes) of about 1 cm each through which laparoscopic instruments can be inserted after the abdomen is distended using carbon dioxide pneumoperitoneum. For people with pancreatic cancer, the pancreas and the spleen are removed together (en bloc) after isolation and mobilisation of the distal pancreas, spleen, and surrounding lymph nodes from surrounding structures such as the stomach, colon, diaphragm, and kidneys by dividing attachments and blood vessels (Fernandez-Cruz 2006). Although splenic preservation is possible in open or laparoscopic distal pancreatectomy (Fernandez-Cruz 2006), the spleen is usually removed during distal pancreatectomy for cancers because of concern about cancer clearance in spleen preservation surgeries (Fernandez-Cruz 2005). However, no evidence suggests that splenectomy improves cancer clearance.

After resection of the body and tail of the pancreas, the cut surface of the pancreatic remnant (pancreatic stump) is usually closed with staples or sutures (Diener 2011). Despite this, a high incidence of clinically significant pancreatic fistula (11%) has been reported (Diener 2011; Montorsi 2012), and various interventions including somatostatin analogues may be used to decrease pancreatic fluid secretion (Gurusamy 2013), and fibrin sealants (in the form of glue (Suzuki 1995) or patches (Montorsi 2012)) to seal the pancreatic stump.

Distal pancreatectomy can also be performed with the assistance of a robot (robot-assisted distal pancreatectomy). In robot-assisted distal pancreatectomy, laparoscopic instruments are controlled by a robot. This is generally considered distinct from laparoscopic distal pancreatectomy (Daouadi 2013). The term 'minimally invasive distal pancreatectomy' is usually used to describe both laparoscopic distal pancreatectomy and robot-assisted distal pancreatectomy.

How the intervention might work

For many surgical procedures, laparoscopic surgery is currently preferred over open surgery. Laparoscopic surgery includes surgical procedures such as cholecystectomy (removal of gallbladder), colon cancer treatment and hysterectomy (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009). Laparoscopic surgery is preferred over open surgery because it is associated with decreased pain, decreased blood loss, shorter hospital stay, earlier postoperative recovery, better cosmesis (physical appearance) and decreased costs (Bijen 2009; Keus 2006; Kooby 2008; Reza 2006; Rutz 2014; Talseth 2014; Walsh 2009).

Why it is important to do this review

A smaller incision and earlier postoperative recovery appear to be potential advantages of laparoscopic distal pancreatectomy; however, the safety of this approach for a procedure that has a high complication rate and cancer clearance after laparoscopic distal pancreatectomy must be ensured before the method can be widely recommended. Healthcare providers have expressed concerns about cancer clearance because port-site metastases (recurrence of cancer at the laparoscopic port site) have been reported after laparoscopic surgery for many different cancers (Kais 2014; Palomba 2014; Song 2014). Animal research has shown that increased intra-abdominal pressure during laparoscopy (pneumoperitoneum) may drive malignant cells into ports, resulting in seeding of the port site and port-site metastases (Hopkins 1999). Also, malignant cells may be adherent to laparoscopic instruments that are introduced and removed through the ports, resulting in seeding of the port site and port-site metastases (Hopkins 1999). Other issues include the adequacy of cancer clearance in terms of resection margins and the extent of lymph nodes removed through laparoscopy. Therefore, oncological efficacy (cancer clearance) is an important issue with laparoscopic distal pancreatectomy. No Cochrane review has examined this topic.

Objectives

To assess the benefits and harms of laparoscopic distal pancreatectomy versus open distal pancreatectomy for people undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma of the body or tail of the pancreas, or both.

Methods

Criteria for considering studies for this review

Types of studies We planned to include only randomised controlled trials (RCTs) in this review. However, we found no RCTs on the topic, so we performed a meta-analysis of observational studies clearly highlighting the bias involved in interpretation of results. We included studies reported as full text, studies published as abstract only and unpublished data.

Types of participants We included adults undergoing distal pancreatectomy for pancreatic ductal adenocarcinoma. Although we excluded people undergoing distal pancreatectomy for neuroendocrine cancers (cancers that arise from neural and endocrine cells; Rindi 2011), when possible we included trials in which no separate outcome data were available for people undergoing distal pancreatectomy for pancreatic adenocarcinoma, provided that distal pancreatectomy for other causes including neuroendocrine cancer was performed in less than 10% of participants included in the trial.

Types of interventions We included trials comparing laparoscopic distal pancreatectomy versus open distal pancreatectomy provided that the only difference between groups was the use of the laparoscopic or open method of access to the pancreas. We excluded studies that compared different methods of laparoscopic distal pancreatectomy, robotic distal pancreatectomy, or open distal pancreatectomy.

Types of outcome measures

Primary outcomes

1. Mortality
    a. Short-term mortality (in-hospital mortality or mortality within three months)
    b. Long-term mortality

2. Serious adverse events (within three months). We will accept the following definitions of serious adverse events:
    a. Clavien-Dindo classification (Clavien 2009; Dindo 2004): grade III or greater
    b. International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guideline (ICH-GCP 1996): serious adverse

events defined as any untoward medical occurrences that result in death, are life-threatening, require hospitalisation or prolongation of existing hospitalisation or result in persistent or significant disability/incapacity

c. Individual complications that can clearly be classified as grade III or greater with the Clavien-Dindo classification (Clavien 2009; Dindo 2004), or as a serious adverse event with the ICH-GCP classification
d. Clinically significant pancreatic fistulas (type B or type C International Study Group on Pancreatic Fistula (ISGPF) definition) (Bassi 2005)

3. Health-related quality of life (using any validated scale)
   a. Short-term (four weeks to three months).
   b. Medium-term (longer than three months to one year)

Secondary outcomes

1. Recurrence (local recurrence, surgical wound recurrence (also called port-site metastasis in the laparoscopic group) or distal metastasis)
   a Short-term recurrence (within six months)
   b. Long-term recurrence (recurrence at maximal follow-up)

2. Adverse events (within three months). We will accept all adverse events reported by the study author irrespective of their severity

3. Perioperative blood transfusion requirements (during surgery or within one week after surgery) (whole blood or red cell transfusion)
   a. Proportion of people requiring blood transfusion
   b. Quantity of blood transfusion

4. Measures of earlier postoperative recovery
   a. Length of hospital stay (including the index admission for distal pancreatectomy and any surgical complication-related re-admissions)
   b. Time to return to normal activity (return to preoperative mobility with no additional carer support)
   c. Time to return to work (for people who were employed previously)

5. Positive resection margins (presence of macroscopic or microscopic cancer tissue at the plane of resection) at histopathological examination after surgery

We based our choice of clinical outcomes (above) on the necessity to assess whether laparoscopic surgery results in adequate cancer clearance, is safe and is beneficial in terms of decreased blood transfusion requirements; earlier postoperative recovery, allowing earlier discharge from hospital, return to normal activity and return to work; and improvement in health-related quality of life. We highlighted that positive resection margins at histopathological examination after surgery represent a surrogate outcome, and we have included this to explore whether positive resection margins after surgery are responsible for any differences in survival or mortality.

We included studies that met the inclusion criteria irrespective of whether they reported our secondary outcomes.

Search methods for identification of studies

Electronic searches We conducted a literature search to identify all published and unpublished RCTs and non-randomised studies and to identify potential studies in all languages. We translated non-English language papers and assessed them for potential inclusion in the review as necessary.

We searched the following electronic databases to identify potential studies.

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 6) (Appendix 1*).
2. MEDLINE (1966 to June 2015) (Appendix 2*).
3. EMBASE (1988 to June 2015) (Appendix 3*).
4. Science Citation Index (1982 to June 2015) (Appendix 4*).
5. We also conducted a search of ClinicalTrials.gov (ClinicalTrials.gov; Appendix 5*) and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en/; Appendix 6*) on 20 June 2015.

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* Appendices were not printed here due to space limitations and may be accessed at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011515.pub2/full)

Searching other resources We checked the reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and asked them to identify other published and unpublished studies.

We searched PubMed for errata or retractions from eligible trials (www.ncbi.nlm.nih.gov/pubmed) on 14 December 2015.

Data collection and analysis

Selection of studies Two review authors (D Riviere and K Gurusamy) independently screened titles and abstracts for inclusion of all potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved full-text study reports, and two review authors (D Riviere and K Gurusamy) independently screened these reports, identified studies for inclusion and identified and recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion and identified and excluded duplicates and collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and Characteristics of excluded studies table.

Data extraction and management We used a standard data collection form that had been piloted on at least one study in the review to record study characteristics and outcome data. Two review authors (D Riviere and K Gurusamy) extracted study characteristics from included studies and detailed them in a Characteristics of included studies table. We extracted the following study characteristics:

1. Methods: study design, total study duration and run-in, number of study centres and locations, study settings, withdrawals, date of study.
2. Participants: number, mean age, age range, gender, American Society of Anesthesiologists (ASA) status (ASA 2014), inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, concomitant interventions.
4. Outcomes: primary and secondary outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

Two review authors (D Riviere and K Gurusamy) independently extracted outcome data from included studies. If outcomes were reported multiple times for the same time frame, for example, if short-term health-related quality of life was reported at six weeks and at three months, we chose the later time point (i.e. three months) for data extraction. For time-to-event outcomes for which data were censored, we extracted data to calculate the natural logarithm of the hazard ratio (HR) and its standard error using the methods suggested by Parmar et al. (Parmar 1998).

We included all randomised participants for medium-term and long-term outcomes (e.g. mortality, quality of life), and this will not be conditional upon short-term outcomes (e.g. being alive at three months, having a low or high quality-of-life index at three months).

We noted in the Characteristics of included studies table whether outcome data ware reported in an unuseable way. We resolved disagreements by consensus. One review author (D Riviere) copied data from the data collection form into Review Manager 5 (RevMan 2014). We double-checked that the data were entered correctly by comparing study reports versus how the data were presented in the systematic review.

Assessment of risk of bias in included studies Two review authors (D Riviere and K Gurusamy) independently assessed risk of bias for each study. We planned to use the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). However, because randomised controlled trials on the topic were insufficient, we used relevant risk of bias domains from 'A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions' (ACROBAT-NRSI) (Sterne 2014).

We assessed risk of bias according to the following domains:

1. Bias due to confounding.
2. Bias due to selection of participants.
3. Bias due to departure from intended intervention.
4. Bias in measurement of outcomes.
5. Bias due to missing data.
6. Bias in selection of reported findings.
7. We resolved disagreements by discussion.

We graded each potential source of bias as critical, serious, moderate, low or no information and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes when necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from a participant-reported pain scale). When information on risk of bias relates to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for studies that contributed to each outcome.

Assessment of bias in conducting the systematic review We conducted the review according to the published protocol and reported deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect We analysed dichotomous data as odds ratio (OR) and continuous data as mean difference (MD) when the outcome was reported or was converted to the same units in all trials (e.g. hospital stay). We planned to calculate standardised mean difference (SMD) when different scales were used for measuring the outcome (e.g. quality of life) and planned to ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader and report when the directions were reversed, if this was necessary. We planned to calculate the rate ratio (RaR) for outcomes such as adverse events and serious adverse events when it was possible for the same person to develop more than one adverse event (or serious adverse event). If study authors had calculated the RaR of adverse events (or serious adverse events) in the intervention versus control based on Poisson regression, we planned to obtain the RaR by the Poisson regression method in preference to RaR calculated on the basis of the number of adverse events (or serious adverse events) that occurred during a certain period. We calculated the HR for time-to-event outcomes such as long-term mortality.

We undertook meta-analyses only when this was meaningful (i.e. when treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

Trialists commonly indicate when they have skewed data by reporting medians and interquartile ranges. When we encountered this, we planned to note that the data were skewed by following the rough guide for identifying skewed distribution available in the Cochrane Handbook for Systematic Reviews of Interventions and considered the implication of this.

When multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (e.g. laparoscopic distal pancreatectomy method 1 vs open pancreatectomy, laparoscopic distal pancreatectomy method 2 vs open pancreatectomy) must be entered into the same meta-analysis, we planned to half the control group to avoid double-counting. The alternative way of including such trials with multiple arms is to pool the results of laparoscopic distal pancreatectomy method 1 and laparoscopic distal pancreatectomy method 2 and compare these with open pancreatectomy. We planned to perform a sensitivity analysis to determine whether results of the two methods of dealing with multi-arm trials led to different conclusions. However, we found no study with more than two arms that could be included in this review.

Unit of analysis issues The unit of analysis was the individual participant undergoing distal pancreatectomy. As expected, we found no cluster-randomised trials for this comparison.

Dealing with missing data We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data when possible (e.g. when a study was identified as abstract only). If we were not able to obtain the information from investigators or study sponsors, we imputed mean from median (i.e. considered median as the mean) and calculated standard deviation from standard error, interquartile range or P value according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), but we assessed the impact of including such studies as indicated in a sensitivity analysis. Standard deviation could be calculated from P values; therefore, we did not impute standard deviation as the highest standard deviation in remaining trials included in the outcome.

Assessment of heterogeneity We used the I2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity as per the Cochrane Handbook for Systematic Reviews of

Interventions (> 50% to 60%; Higgins 2011), we planned to explore this through prespecified subgroup analysis).

Assessment of reporting biases We attempted to contact study authors to ask them to provide missing outcome data. When this was not possible, and when missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by using a sensitivity analysis.

If we were able to pool more than 10 trials, we created and examined a funnel plot to explore possible publication biases. We used Egger's test to determine the statistical significance of the reporting bias (Egger 1997). We considered a P value less than 0.05 as statistically significant reporting bias.

Data synthesis We performed analyses using Review Manager 5 (RevMan 2014). We calculated 95% confidence intervals for the treatment effect and used the Mantel-Haenszel method for dichotomous data, the inverse variance method for continuous data and generic inverse variance for time-to-event data. We planned to use the inverse variance method for count data. We used both fixed-effect (Demets 1987) and random-effects models (DerSimonian 1986) for the analysis. In case of discrepancy between the two models, we reported both results; otherwise, we reported only results from the fixed-effect model.

'Summary of findings' table We created a 'Summary of findings' table by using all selected outcomes. We used the five GRADE (Grades of Recommendation, Assessment, Development and Evaluation Working Group) considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data to the meta-analyses for prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) and GRADEpro software. We justified all decisions to downgrade or upgrade the quality of studies by using footnotes, and we made comments to aid the reader's understanding of the review when necessary. We considered whether any additional outcome information was provided that we were unable to incorporate into meta-analyses, and we planned to note this in the

comments and state whether it supports or contradicts information derived from the meta-analyses.

Subgroup analysis and investigation of heterogeneity We planned to carry out the following subgroup analyses:

1. People with different anaesthetic risk (ASA I (a healthy person) or II (a person with mild systemic disease) vs ASA III or greater (a person with severe systemic disease or worse)).
2. Different body mass index (BMI) (healthy weight (BMI 18.5 to 25) vs overweight or obese (BMI ≥ 25)).
3. Use of fibrin sealants versus no use of fibrin sealants.
4. Stapler closure versus suture closure of pancreatic stump.
5. We used all primary outcomes in the subgroup analyses.

We planned to use the formal Chi2 test for subgroup differences to test for subgroup interactions.

Sensitivity analysis We planned to perform sensitivity analysis defined a priori to assess the robustness of our conclusions by:

1. excluding trials at unclear or high risk of bias (≥ 1 risk of bias domain (other than blinding of surgeon) classified as unclear or high);
2. excluding trials in which either mean or standard deviation or both are imputed;
3. excluding cluster RCTs in which adjusted effect estimates are not reported; and
4. using different methods of dealing with multi-arm trials (see Measures of treatment effect).

Reaching conclusions We based our conclusions only on findings from the quantitative or narrative synthesis of studies included in this review. We avoided making recommendations for practice and believe that our implications for research will give the reader a clear sense of where the focus of any future research in the area should be and will reveal remaining uncertainties.

Results

Description of studies

Results of the search We identified 2340 references through electronic searches of The Cochrane Library (Wiley) (n = 1), MEDLINE (OvidSP) (n = 650), EMBASE (OvidSP) (n = 1382), Science Citation Index Expanded (n = 488), ClinicalTrials.gov (n = 2) and the World Health Organization (WHO) Trials Register (n = 7). After duplicate references were removed, 1596 references remained. We excluded 1505 clearly irrelevant references by reading the abstracts. We retrieved from the full publication a total of 91 references for further detailed assessment. We excluded 76 references (62 studies) for the reasons listed in the Characteristics of excluded studies table[**]. Fifteen references reporting 12 non-randomised studies fulfilled the inclusion criteria (Characteristics of included studies). The reference flow is shown in Figure 1.

Included studies We included a total of 12 non-randomised studies (Braga 2015; Ceppa 2013; Dancea 2012; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Stauffer 2015; Vijan 2010; Zhang 2014). All 12 were retrospective studies (Braga 2015; Ceppa 2013; Dancea 2012; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Stauffer 2015; Vijan 2010; Zhang 2014). Nine studies were single institutional studies (Ceppa 2013; Dancea 2012; Hu 2014; Lee 2015; Rehman 2014; Shin 2015; Stauffer 2015; Vijan 2010; Zhang 2014). Two were multi-centre studies (Kooby 2010; Sharpe 2015). It was not clear whether one study was a single-centre or a multi-centre study (Braga 2015). Nine were cohort studies (Ceppa 2013; Dancea 2012; Hu 2014; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Stauffer 2015; Zhang 2014), and the remaining three were case-control studies (Braga 2015; Kooby 2010; Vijan 2010).

Only one study reported ASA status (Shin 2015). Most participants in this study belonged to ASA I and II. Only one participant with ASA IV was included in this study (Shin 2015). This study did not report outcome data separately by ASA status. None of the studies reported individuals with healthy weight versus overweight or obese participants. Fibrin sealant was

[**] Characteristics of excluded studies were not printed here due to space limitations and may be accessed at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011515.pub2/full)

not used routinely, or its use was not reported in any of the studies. Two studies routinely used stapler closure (Shin 2015; Zhang 2014). Information on stapler use was not available for the remaining studies.

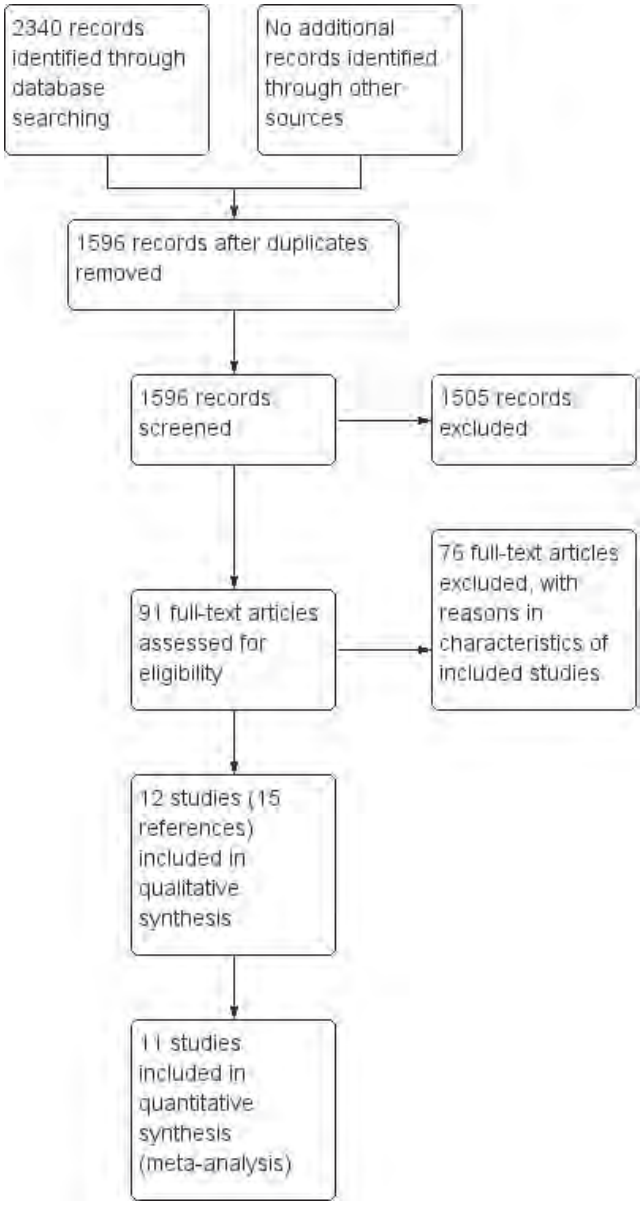


Figure 1. Study flow diagram.

Investigators in four studies used four ports to perform laparoscopic distal pancreatectomy (Hu 2014; Rehman 2014; Vijan 2010; Zhang 2014). Information on the number of ports was not available for the remaining studies. Four studies included participants who underwent distal pancreatectomy with or without splenectomy (Braga 2015; Hu 2014; Vijan 2010; Zhang 2014). The remaining studies did not state whether they included participants who underwent distal pancreatectomy with splenectomy. Two studies routinely placed one or more drains (Braga 2015; Hu 2014). One study reported selective drain use (Vijan 2010). Information on drain use was not available for the remaining studies.

The 12 studies included a total of 1593 participants. One study excluded 17 patients (metastatic disease (n = 12) and conversion to open procedure (n = 5)) (Shin 2015). After these 17 patients were excluded, a total of 1576 participants underwent laparoscopic distal pancreatectomy (n = 394) or open distal pancreatectomy (n = 1182). One study did not report any outcomes of interest for this review (Stauffer 2015). Upon exclusion of this study, a total of 1506 participants undergoing laparoscopic distal pancreatectomy (353 participants) or open distal pancreatectomy (1153 participants) contributed to one or more outcomes in this review. Mean or median age ranged from 50 years to 66 years in the five studies that reported this information (Hu 2014; Kooby 2010; Rehman 2014; Sharpe 2015; Shin 2015). The average proportion of females ranged from 36.7% to 72.7% in the four studies that reported this outcome (Hu 2014; Kooby 2010; Rehman 2014; Shin 2015). The average follow-up period was one month in one study (Braga 2015). In another study, the follow-up period was 12 to 72 months (range) (Hu 2014). Information on the follow-up period was not available for the remaining studies. Outcomes reported in these studies are summarised in Characteristics of included studies[***].

Data were available for the entire cohort of participants who underwent laparoscopic and open distal pancreatectomy and for those who underwent laparoscopic distal pancreatectomy versus matched controls of open distal pancreatectomy in one study (Kooby 2010). We used data from the matched control analysis because long-term mortality was available for this analysis only.

[***] Characteristics of included studies were not printed here due to space limitations and may be accessed at the Cochrane Library https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011391.pub2/full

Excluded studies We excluded 38 studies because separate data on patients with pancreatic cancer were not provided Abu Hilal 2012; Baker 2011; Baker 2013; Barrie 2014; Belli 2012; Cao 2014; Cheek 2014; Cho 2011; de Rooij 2015; DiNorcia 2010; Duran 2014; Durlik 2013; Ejaz 2014; Eom 2008; Ferrara 2014; Finan 2009; Fox 2012; Jayaraman 2010; Jeon 2014; Kang 2010; Kooby 2008; Lee 2014; Limongelli 2012; Magge 2013; Malde 2012; Matejak-Gorska 2013; Mehta 2012; Nakamura 2009; Pieretti-Vanmarcke 2014; Rooij 2014; Rosales-Velderrain 2012; Sherwinter 2012; Soh 2012; Stauffer 2013; Tseng 2011; Velanovich 2006; Zhao 2010; Zibari 2014). We excluded nine studies because they excluded patients with benign or premalignant disease (Butturini 2011; Casadei 2010; Chen 2012; Chung 2014; Gumbs 2008; Matsumoto 2008; Morikawa 2012; Sahay 2011; Slepavicius 2014). We excluded seven studies because the indication for surgery was not stated (Kausar 2010; Liao 2014; Newman 2010; Parikh 2015; Stauffer 2012; Vicente 2013; Yoon 2012). Two studies did not include open distal pancreatectomy as control (Daouadi 2011; Tang 2007). One study did not include distal pancreatectomy (Langan 2014). We excluded five studies because they were reviews or provided comments (Ahmed 2015; Limongelli 2014; Mehrabi 2015; Nigri 2011; Ricci 2015).

Table 1. Summary of findings for the main comparison

Patient or population: patients with pancreatic cancer
Settings: secondary or tertiary care centre
Intervention: laparoscopic distal pancreatectomy
Comparison: open distal pancreatectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Open distal pancreatectomy	Laparoscopic distal pancreatectomy			
Short-term mortality	**10 per 1000**	**5 per 1000** (1 to 22)	**OR 0.48** (0.11 to 2.17)	1451 (9 studies)	⊕⊖⊖⊖ **Very low**[a,b]
Long-term mortality Follow-up: 2 to 3 years	**549 per 1000**	**535 per 1000** (480 to 590)	**HR 0.96** (0.82 to 1.12)	277 (3 studies)	⊕⊖⊖⊖ **Very low**[a,c]
Serious adverse events (proportion)	**51 per 1000**	**88 per 1000** (28 to 247)	**OR 1.79** (0.53 to 6.06)	206 (3 studies)	⊕⊖⊖⊖ **Very low**[a,b,c]
Pancreatic fistula (grade B or C)	**66 per 1000**	**77 per 1000** (32 to 175)	**OR 1.19** (0.47 to 3.02)	246 (4 studies)	⊕⊖⊖⊖ **Very low**[a,b,c,d]

None of the studies reported quality of life at any time point.

*The basis for the **assumed risk** is the mean control group proportion. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a] *We found no randomised controlled trials. The non-randomised studies included in this review were at unclear or high risk of bias for most domains*
[b] *Confidence intervals were wide*
[c] *Sample size was small*
[d] *I^2 was high and little overlap of confidence intervals was evident.*

Table 2. Summary of findings 2

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Open distal pancreatectomy	Laparoscopic distal pancreatectomy			
Recurrence at maximal follow-up	**495 per 1000**	**363 per 1000** (239 to 507)	**OR 0.58** (0.32 to 1.05)	184 (2 studies)	⊕⊖⊖⊖ **Very low**[a,b,c]
Adverse events (proportion)	**328 per 1000**	**317 per 1000** (209 to 448)	**OR 0.95** (0.54 to 1.66)	246 (4 studies)	⊕⊖⊖⊖ **Very low**[a,b,c]
Length of hospital stay	Mean length of hospital stay in the control groups was **9.4 days**	Mean length of hospital stay in the intervention groups was **2.43 lower** (3.13 to 1.73 lower)		1068 (5 studies)	⊕⊖⊖⊖ **Very low**[a]
Positive resection margins	**184 per 1000**	**143 per 1000** (99 to 198)	**OR 0.74** (0.49 to 1.10)	1466 (10 studies)	⊕⊖⊖⊖ **Very low**[a,b]

None of the studies reported perioperative transfusion requirements, time to return to normal activity or time to return to work

**The basis for the assumed risk is the mean control group proportion. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)*

CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

[a]*We found no randomised controlled trials. The non-randomised studies included in this review were at unclear or high risk of bias for most domains*

[b]*Confidence intervals were wide*

[c]*Sample size was small*

Risk of bias in included studies

Bias due to confounding Risk of bias due to confounding was critical in five studies (Ceppa 2013; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015) because the open distal pancreatectomy group had more extensive cancer. Risk of bias due to confounding was 'no information' for the seven remaining studies (Braga 2015; Dancea 2012; Hu 2014; Kooby 2010; Stauffer 2015; Vijan 2010; Zhang 2014). Although some studies reported no baseline differences between groups, these studies were not powered to measure baseline differences.

Bias due to selection of participants In three studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on surgeon preference (Ceppa 2013; Lee 2015; Rehman 2014). In two studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on participant preference (Hu 2014; Shin 2015). One study excluded patients who underwent conversion to open surgery despite meeting inclusion criteria (Shin 2015). This study was considered to be at critical risk of bias related to selection of participants. Risk of bias was 'no information' for the remaining four of the five studies for which decisions to perform laparoscopic distal pancreatectomy or open distal pancreatectomy were based on surgeon or participant preference (Ceppa 2013; Hu 2014; Lee 2015; Rehman 2014). The criteria used to perform laparoscopic or open distal pancreatectomy were not stated in the remaining studies (Braga 2015; Dancea 2012; Kooby 2010; Sharpe 2015; Stauffer 2015; Vijan 2010; Zhang 2014), so risk of bias remains 'no information' in these studies.

Bias due to departures from intended intervention Three studies were at moderate risk of bias; study authors replied that no differences were noted in postoperative management of participants (Ceppa 2013; Kooby 2010; Lee 2015). None of the remaining studies reported whether participant care other than laparoscopic or open procedure was identical in the two groups. These studies were classified as 'no information'.

Bias in measurement of outcomes Three study authors replied that outcome assessors were not blinded (Ceppa 2013; Kooby 2010; Lee 2015). This might have introduced bias in measurement of outcomes other than mortality. So we classified these studies as 'no information'. Risk of

bias was classified as 'no information' for the remaining studies because information on outcome assessor blinding was not reported.

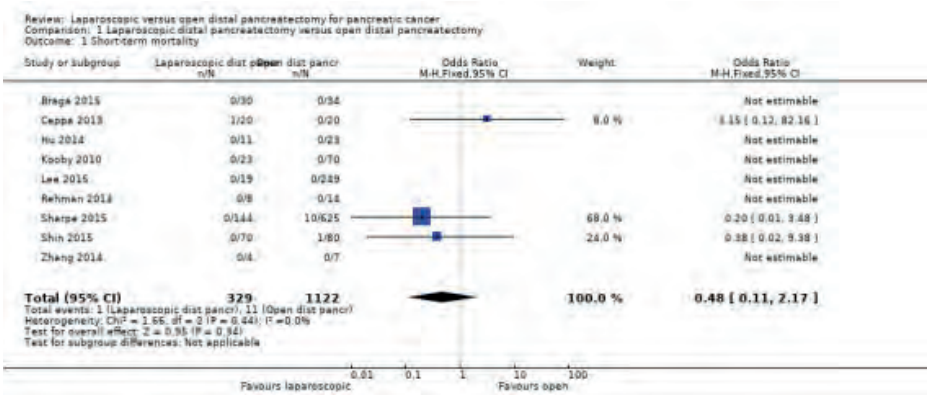
Bias due to missing data Two studies were at low risk of bias; all eligible participants were included in the study (Ceppa 2013), and a clear participant flow indicated that all participants who underwent laparoscopic or open distal pancreatectomy were included (Hu 2014). Two studies were at critical risk of bias because participants who underwent conversion to open surgery were excluded despite meeting inclusion criteria (Shin 2015), or because some participants in the open group were not matched for the laparoscopic group (Kooby 2010). It was not clear whether any participants were excluded from analysis in the remaining studies. Therefore, we classified these studies as 'no information'.

Bias in selection of reported findings Four studies reported mortality and morbidity adequately and can be considered at low risk of bias for selective outcome reporting (Ceppa 2013; Hu 2014; Rehman 2014; Shin 2015). The remaining studies were considered to be at serious or critical risk of bias depending upon whether they did not report morbidity alone, or whether they did not report both mortality and morbidity, because one would expect that studies comparing laparoscopic distal pancreatectomy versus open distal pancreatectomy would report data on mortality and morbidity in a detailed manner.

Effects of interventions

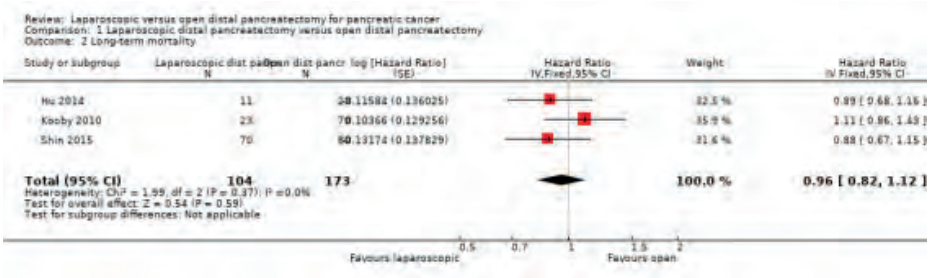
The effect of intervention is summarised in Table 1 and Table 2.

Mortality Nine studies reported short-term mortality (perioperative mortality) (Braga 2015; Ceppa 2013; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Zhang 2014). Investigators reported no statistically significant differences in short-term mortality between the two groups (laparoscopic group: 1/329 (adjusted proportion based on meta-analysis estimate: 0.5%) vs open group: 11/1122 (1%); OR 0.48, 95% CI 0.11 to 2.17; 1451 participants; nine studies; I2 = 0%) (Analysis 1.1). A random-effects meta-analysis revealed no change in results.



Analysis 1.1. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

Three studies reported long-term mortality (Hu 2014; Kooby 2010; Shin 2015). Three-year mortality was between 44% and 75% in these studies (Hu 2014;Kooby 2010; Shin 2015). Researchers noted no statistically significant differences in long-term mortality between the two groups (HR 0.96, 95% CI 0.82 to 1.12; 277 participants; three studies; I2 = 0%) (Analysis 1.2). A random-effects meta-analysis revealed no change in results.



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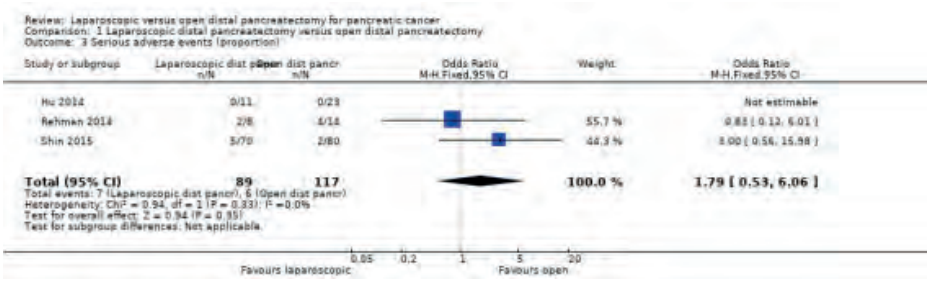
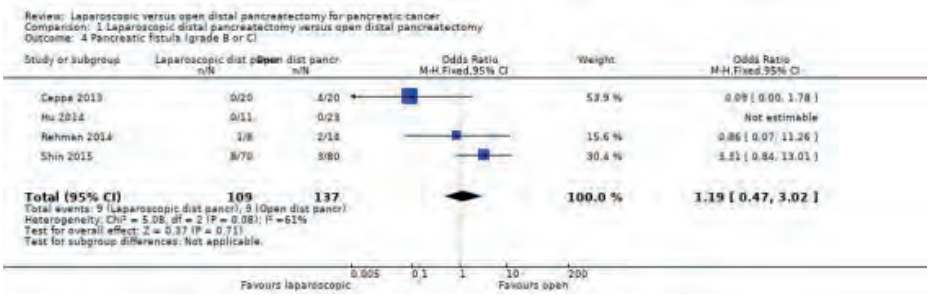
Serious adverse events Three studies reported the proportions of participants with serious adverse events (Hu 2014; Rehman 2014; Shin 2015). One study reported no serious adverse events (Hu 2014). Serious adverse events in the other studies included complications that required radiological or surgical re-intervention and grade III pancreatic fistula (Rehman 2014;Shin 2015). Investigators reported no statistically significant differences in the proportions of people with serious adverse events between the laparoscopic group (7/89: adjusted proportion: 8.8%) and the

open group (6/117: 5.1%) (OR 1.79, 95% CI 0.53 to 6.06; 206 participants; three studies; I2 = 0%) (Analysis 1.3). A random-effects meta-analysis revealed no change in results.



Analysis 1.3. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

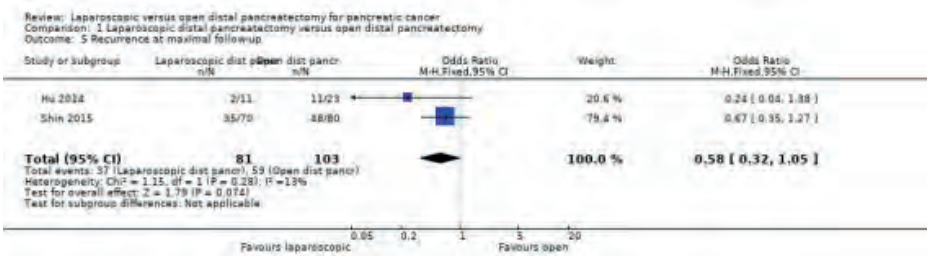
Pancreatic fistula Four studies reported the proportions of participants with clinically significant pancreatic fistula (grade B or C) (Ceppa 2013; Hu 2014; Rehman 2014; Shin 2015). Researchers noted no statistically significant differences in the proportions of people with pancreatic fistula between the laparoscopic group (9/109: adjusted proportion: 7.7%) and the open group (9/137: 6.6%) (OR 1.19, 95% CI 0.47 to 3.02; 246 participants; four studies; I2 = 61%) (Analysis 1.4). The I2 statistic and visual inspection of forest plots provided evidence of heterogeneity, i.e. lack of overlap of confidence intervals. However, the Chi2 test for heterogeneity was not statistically significant (P value = 0.08). A random-effects meta-analysis revealed no change in results.



Analysis 1.4. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

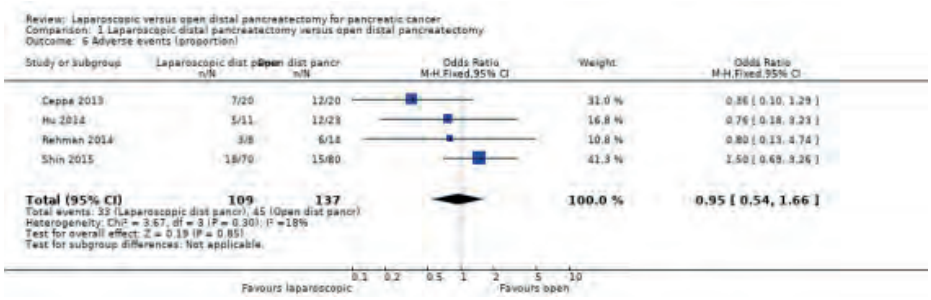
Quality of life None of the studies reported quality of life at any point in time.

Recurrence None of the studies reported recurrence within six months. Two studies reported recurrence at maximal follow-up (Hu 2014; Shin 2015). In one study, two participants (18%) in the laparoscopic group versus 11 participants (48%) in the open group had recurrence at maximal follow-up of 12 to 72 months (Hu 2014). In another study, 35 participants (49%) in the laparoscopic group versus 48 participants (60%) in the open group had recurrence at maximal follow-up (follow-up period not stated) (Shin 2015). Details were insufficient to permit calculation of the hazard ratio for recurrence. So we calculated the odds ratio of recurrence at maximal follow-up. Results showed no statistically significant differences between groups (laparoscopic group: 37/81 (adjusted proportion based on meta-analysis estimate: 36.3%) vs open group: 59/103 (49.5%); OR 0.58, 95% CI 0.32 to 1.05; 184 participants; two studies; I2 = 13%) (Analysis 1.5). A random-effects meta-analysis revealed no change in results.



Analysis 1.5. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

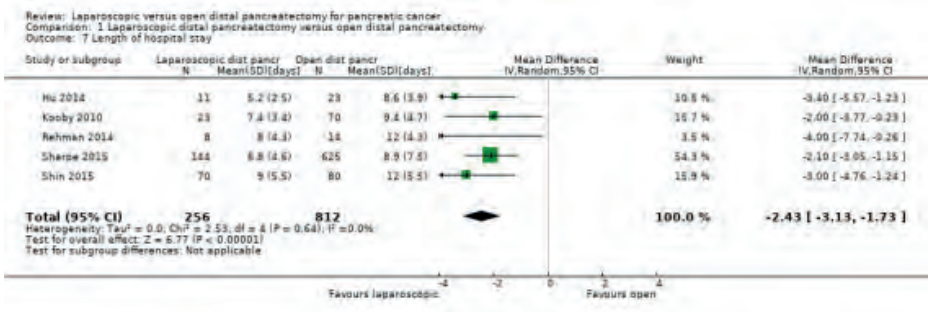
Adverse events Four studies reported the proportions of participants with adverse events of any severity (Ceppa 2013; Hu 2014; Rehman 2014; Shin 2015). Researchers reported no statistically significant differences in the proportions of people with adverse events between the laparoscopic group (33/109: adjusted proportion: 31.7%) and the open group (45/137: 32.8%) (OR 0.95, 95% CI 0.54 to 1.66; 246 participants; four studies; I2 = 18%) (Analysis 1.6). A random-effects meta-analysis revealed no change in results.



Analysis 1.6. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

Measures of earlier postoperative recovery Five studies reported length of hospital stay (Hu 2014; Kooby 2010; Rehman 2014; Sharpe 2015; Shin 2015). The median of mean lengths of hospital stay in these studies was 9.4 days in the open distal pancreatectomy group. Mean length of hospital stay was statistically significantly shorter in the laparoscopic group than in the open group (MD -2.43 days, 95% CI -3.13 to -1.73; 1068 participants; five studies; I2 = 0%) (Analysis 1.7). We imputed mean and SD from median and P value for length of hospital stay for two studies (Rehman 2014; Shin 2015). No change in results occurred when we excluded these two studies (MD -2.25 days, 95% CI -3.03 to -1.47; 896 participants; three studies; I2 = 0%) (Analysis 3.1). A random-effects meta-analysis revealed no change in results.

No studies reported any of the other measures of earlier postoperative recovery such as return to normal activity and return to work.



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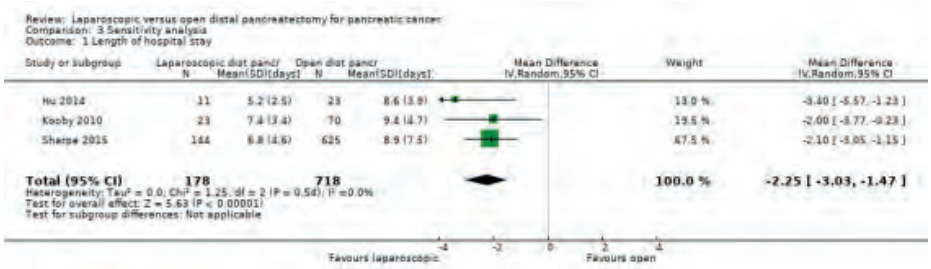
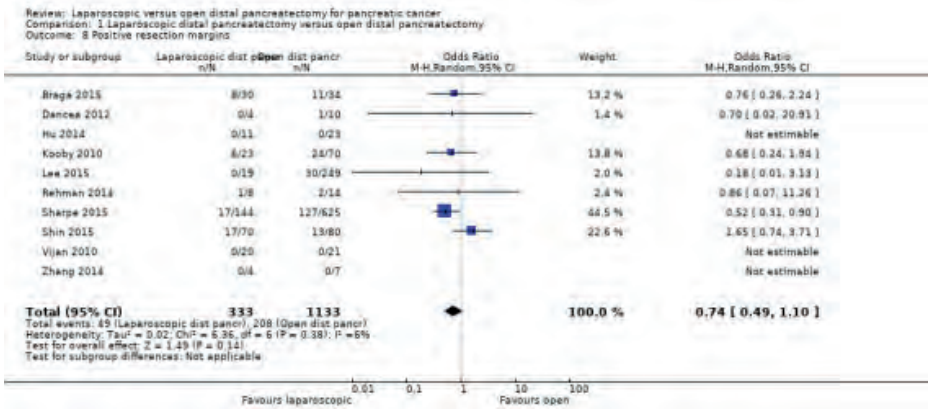


Analysis 3.1. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

Blood transfusion requirements None of the studies reported blood transfusion requirements.

Positive resection margins Ten studies reported the proportions of participants with positive resection margins (Braga 2015; Dancea 2012; Hu 2014; Kooby 2010; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Vijan 2010; Zhang 2014). The fixed-effect model revealed a statistically significantly lower proportion of people with positive resection margins between the two groups (laparoscopic group: 49/333 (adjusted proportion: 14.3%) vs open group: 208/1133 (18.4%); OR 0.69, 95% CI 0.48 to 1.00; 1466 participants; 10 studies; I2 = 6%) (Analysis 1.8). The random-effects model revealed no statistically significant differences between groups in the proportions of people with positive resection margins (OR 0.74, 95% CI 0.49 to 1.10).

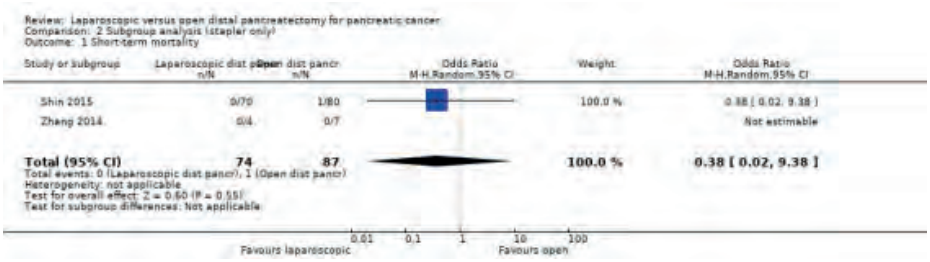


Analysis 1.8. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

Assessment of reporting biases We assessed reporting bias only for the positive resections margin because this was the only outcome included in 10 trials. We found no evidence of reporting bias upon visualisation of the funnel plot and completion of Egger's test (P value = 0.9798).

Subgroup analysis

Stapler closure Stapler closure was standard procedure in two studies (Shin 2015; Zhang 2014). The remaining studies did not report whether stapler closure was performed or did not report outcome data separately for stapler closure. We found no change in the results of short-term mortality, long-term mortality, proportions of people with serious adverse events or clinically significant pancreatic fistula in this subgroup as compared with the main analysis (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4).



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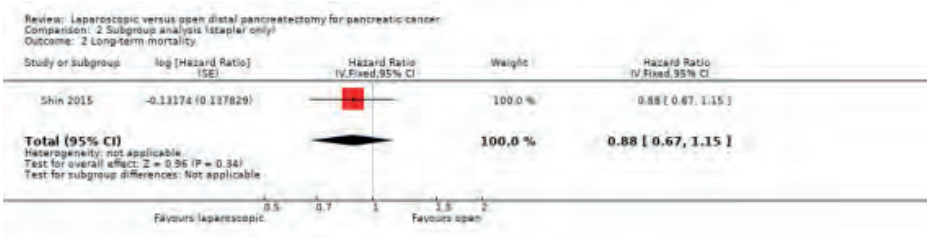

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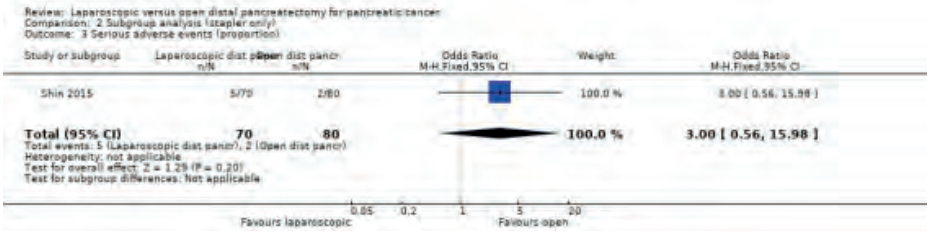

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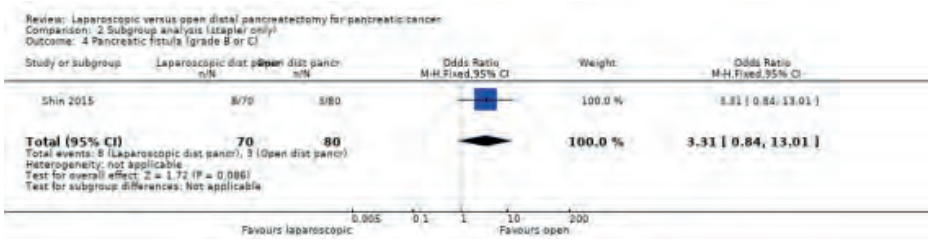

Analysis 2.4. Images available at https://doi.org/10.1002/14651858.CD011391.pub2

We examined no other subgroups. So we were not able to use the formal Chi2 test for differences in subgroup interactions.

Other subgroup analyses We were not able to perform subgroup analyses of different anaesthetic risks or weights or fibrin sealants because the studies did not report this information or did not report outcome data separately for different categories.

Sensitivity analysis We performed no other planned sensitivity analysis other than exclusion of studies in which standard deviation was calculated from the P value because no studies were at low risk of bias and we identified no cluster RCTs.

Discussion

Summary of main results

In this systematic review, we compared the benefits and harms of laparoscopic versus open distal pancreatectomy. We found no randomised controlled trials (RCTs) on this topic. We included in this review 12 observational studies that compared laparoscopic versus open distal pancreatectomy; 11 studies (1506 participants: 394 underwent laparoscopic distal pancreatectomy and 1182 open distal pancreatectomy) provided information for one or more outcomes. People with less extensive cancer underwent laparoscopic distal pancreatectomy, and those with more extensive cancer underwent open distal pancreatectomy in some studies (Ceppa 2013;Rehman 2014; Sharpe 2015). We found no statistically significant differences between laparoscopic and open distal pancreatectomy in terms of short-term mortality, long-term mortality, proportions of participants with serious adverse events, pancreatic fistula

(grade B or C), recurrence at maximal follow-up, proportions of participants with any adverse events and proportions of people with positive resection margins. None of the studies reported quality of life, short-term recurrence, proportions of participants requiring blood transfusion, time to return to normal activity (return to preoperative mobility with no additional carer support) or time to return to work. Mean length of hospital stay was 2.4 days shorter in the laparoscopic distal pancreatectomy group than in the open distal pancreatectomy group. For other surgeries, laparoscopic procedures have been shown to be advantageous over open procedures in terms of fewer complications, shorter hospital stay or both (Bijen 2009; Keus 2006; Reza 2006; Walsh 2009). So the reduction in hospital stay may be due to quicker postoperative recovery resulting from the minimally invasive nature of laparoscopic surgery. It may also be due to bias to confounding, as people with less extensive cancer received laparoscopic distal pancreatectomy and those with more extensive cancer underwent open distal pancreatectomy. Differences in length of hospital stay are important only if laparoscopic distal pancreatectomy provides equivalent cancer clearance as open distal pancreatectomy. Although the confidence intervals were relatively narrow for long-term mortality, it is not possible to conclude that laparoscopic distal pancreatectomy provides cancer clearance equivalent to that of open distal pancreatectomy because of bias due to confounding, as discussed in the Quality of the evidence section. In addition to bias, the relatively small sample size for most outcomes makes study findings unreliable on the basis of random error.

Overall completeness and applicability of evidence

The studies included in this review examined ductal adenocarcinoma of the distal pancreas and different stages (I to III) of pancreatic cancer. Hence, the findings of this review are applicable only to distal pancreatic ductal adenocarcinomas that are amenable to potentially curative surgery. One study clearly mentioned that investigators included participants classified as American Society of Anesthesiologists (ASA) stage I to IV (Shin 2015). Remaining studies did not state the ASA status of participants. In any case, all included studies examined only participants who could withstand major surgery. Hence, the findings of this review are applicable only to patients who can withstand major surgery.

Quality of the evidence

The overall quality of evidence was very low. Major reasons for this were that the studies were observational; consequently, the risk of confounding bias was unclear or high. Studies did not report baseline differences for all confounding factors, and the sample size was not sufficient to reveal differences in confounding factors. Even if the sample size was large and all confounding factors were reported, one cannot rule out the problem of residual confounding. It is not clear whether this would have introduced bias into the results.

In three studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on surgeon preference (Ceppa 2013; Lee 2015; Rehman 2014). In two studies, the decision to perform laparoscopic distal pancreatectomy or open distal pancreatectomy was based on participant preference (Hu 2014; Shin 2015). Surgeon preference could be the result of the surgeon's experience with either technique, which one study author reported in the reply (Lee 2015). Also, it is quite possible that participants with less extensive cancer were operated laparoscopically or were given the choice between laparoscopic and open distal pancreatectomy, and those with more extensive cancer were operated by open surgery. Open distal pancreatectomy was associated with greater tumour size, lymph node sampling and the presence of lymph node metastasis in one study (Ceppa 2013). In another study, participants with large tumours (> 10 cm) considered difficult to mobilise laparoscopically were reserved for open resections (Rehman 2014). In a third study, more participants in the open group received neoadjuvant chemotherapy or radiation and had larger tumours (Sharpe 2015). All of these factors are associated with more advanced disease. This suggests that participants with more advanced disease had open distal pancreatectomy and those with less advanced disease underwent laparoscopic distal pancreatectomy.

Unless RCTs ensure that the same types of participants receive laparoscopic and open distal pancreatectomy, one cannot present reliable conclusions on the safety and effectiveness of laparoscopic versus open distal pancreatectomy because of residual confounding. In terms of other types of bias, many outcomes were subjective, and the retrospective nature of most of the studies means that blinding of outcome assessors is extremely unlikely, even though we have classified this risk as unclear because such information was not provided in the study reports. This may also introduce

bias. Complications were not reported adequately in most studies, leading to selective outcome reporting bias.

Another factor that decreased the quality of evidence was the small sample size resulting in wide confidence intervals for many outcomes. Future studies should be adequately powered to measure differences in clinically important outcomes. Heterogeneity was not significant in the effect estimates for most outcomes despite differences in study design.

Potential biases in the review process

We planned to include only RCTs in this review. However, in the absence of any RCTs, we have reported the best available evidence on this topic. We removed the RCT filter to ensure that observational studies were not removed by electronic filters. Two review authors independently selected studies with no language restrictions and extracted data, decreasing potential errors in study selection and data extraction. However, this is a systematic review of non-randomised studies. Mandatory registration was not required; therefore, studies showing that laparoscopic distal pancreatectomy had poorer results than open distal pancreatectomy may not have been submitted to the journals by study authors because laparoscopic distal pancreatectomy is a new procedure compared with the established treatment of open distal pancreatectomy. So we cannot rule out publication bias.

We imputed mean and calculated standard deviation from median and P values for length of hospital stay in two studies (Rehman 2014; Shin 2015). Exclusion of these two studies did not alter effect estimates for length of hospital stay, suggesting that this imputation of mean and calculation of standard deviation are unlikely to result in bias. We calculated the hazard ratio for long-term mortality using methods suggested by Parmar et al (Parmar 1998), which assume constant proportional hazards. Kaplan-Meier curves in these studies indicated that proportional hazards appeared constant.

Agreements and disagreements with other studies or reviews

This is the first systematic review on laparoscopic distal pancreatectomy versus open distal pancreatectomy with specific reference to pancreatic cancer. Seven study authors concluded that laparoscopic distal pancreatectomy is a safe and feasible surgical modality (Ceppa 2013; Hu

2014; Lee 2015; Rehman 2014; Sharpe 2015; Shin 2015; Zhang 2014). Four study authors suggested that laparoscopic distal pancreatectomy offers equivalent oncological outcomes (Hu 2014; Lee 2015; Rehman 2014; Sharpe 2015). Despite the statement made by one of the study authors that a randomised controlled trial comparing cancer outcomes for laparoscopic and open distal pancreatectomy for pancreatic ductal adenocarcinoma is likely to fail because of the small target patient population that would satisfy the criteria for enrolment (Kooby 2010), we agree with three study authors that a randomised controlled trial is necessary to assess the role of laparoscopic surgery in the treatment of people undergoing distal pancreatectomy (Ceppa 2013; Hu 2014; Rehman 2014).

Authors' conclusions

Implications for practice

Currently, no randomised controlled trials have compared laparoscopic distal pancreatectomy versus open distal pancreatectomy for patients with pancreatic cancer. In observational studies, laparoscopic distal pancreatectomy is associated with shorter hospital stay as compared with open distal pancreatectomy. However, this association is unlikely to be causal. Currently no available information has revealed a causal association in the differences between laparoscopic versus open distal pancreatectomy.

Implications for research

Future studies should try to address as many issues mentioned below as possible. The rationale for the study design is mentioned alongside.

1. Study design: randomised controlled trial (only a randomised controlled trial can establish a causal association in this situation).
2. Participants: people with potentially resectable distal pancreatic cancer (stages I and II adenocarcinoma of the pancreas) fit to undergo major surgery. Alternatively, people undergoing distal pancreatectomy for benign or malignant pancreatic disease but stratified according to benign or malignant pancreatic lesions.
3. Intervention: laparoscopic distal pancreatectomy.
4. Control: open distal pancreatectomy.
5. Outcomes: important patient-oriented measures such as short-term mortality and long-term mortality (at least two to three years), health-

related quality of life, complications and the sequelae of complications, resection margins, measures of earlier postoperative recovery such as length of hospital stay, time to return to normal activity and time to return to work (for those who are employed) and recurrence of cancer. In addition, information on resource use can be collected if the purpose was cost-effectiveness in addition to effectiveness. Two to three years of follow-up has been suggested because three-year mortality was between 44% and 75% in these studies (Hu 2014;Kooby 2010; Shin 2015) .

Other aspects of study design:

1. observer-blinded randomised controlled trial: to control for selection bias and detection bias;
2. identical care apart from laparoscopic versus open distal pancreatectomy: to control for performance bias; and
3. inclusion of all participants in the analysis and performance of an intention-to-treat analysis: to control for attrition bias.

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We thank peer reviewers, copy editors and the Cochrane Editorial Unit for their comments.

We thank the study authors who provided further information.

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* Indicates the major publication for the study

Chapter 3

Cost-effectiveness of laparoscopic versus open distal pancreatectomy for pancreatic cancer

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Abstract

Background

A recent Cochrane review compared laparoscopic versus open distal pancreatectomy for people with for cancers of the body and tail of the pancreas and found that laparoscopic distal pancreatectomy may reduce the length of hospital stay. We compared the cost-effectiveness of laparoscopic distal pancreatectomy versus open distal pancreatectomy for pancreatic cancer.

Method

Model based cost-utility analysis estimating mean costs and quality-adjusted life years (QALYs) per patient from the perspective of the UK National Health Service. A decision tree model was constructed using probabilities, outcomes, and cost data from published sources. A time horizon of 5 years was used. One-way and probabilistic sensitivity analyses were undertaken.

Results

The probabilistic sensitivity analysis showed that the incremental net monetary benefit was positive (£3,708.58 (95% confidence intervals (CI) -£9,473.62 to £16,115.69) but the 95% CI includes zero, indicating that there is significant uncertainty about the cost-effectiveness of laparoscopic distal pancreatectomy versus open distal pancreatectomy. The probability laparoscopic distal pancreatectomy was cost-effective compared to open distal pancreatectomy for pancreatic cancer was between 70% and 80% at the willingness-to-pay thresholds generally used in England (£20,000 to £30,000 per QALY gained). Results were sensitive to the survival proportions and the operating time.

Conclusions

There is considerable uncertainty about whether laparoscopic distal pancreatectomy is cost-effective compared to open distal pancreatectomy for pancreatic cancer in the NHS setting.

Background

Pancreatic cancer is the tenth most common cancer in the United States, the fifth most common cause of cancer-related mortality in the East and the fourth most common cause of cancer-related mortality in the West [1–3]. Adenocarcinoma of the pancreas is the most common malignancy of the exocrine pancreas. In 2012, 338,000 people were newly diagnosed with pancreatic cancer globally, and 330,000 deaths were the result of pancreatic cancer [4]. Surgical resection with adjuvant chemotherapy remains the only treatment with the potential for long-term survival. However, about half the people have metastatic disease at presentation, and one-third have locally advanced unresectable disease, leaving only about 10% to 20% of people suitable for resection [5]. Surgical resection is either pancreatoduodenectomy for cancers of the head of the pancreas or distal pancreatectomy for cancers of the body and tail of the pancreas [6]. Approximately, 20% of 30% of pancreatic resections are distal pancreatectomies [7, 8]. In open distal pancreatectomy, surgical access to the abdominal cavity (and hence the pancreas) is attained by upper midline incision, bilateral subcostal incision (roof-top or Chevron incision) or transverse abdominal incision [9]. In laparoscopic distal pancreatectomy, surgical access to the abdominal cavity (and hence the pancreas) is typically attained by 4 to 6 small ports (holes) of about 5 to 12 mm each through which laparoscopic instruments can be inserted after the abdomen is distended using carbon dioxide pneumoperitoneum [9]. After resection of the body and tail of the pancreas, the cut surface of the pancreatic remnant (pancreatic stump) is usually closed with staples or sutures [10]. A recent Cochrane review compared laparoscopic distal pancreatectomy with open distal pancreatectomy for pancreatic cancer [11]. This review found that the hospital stay may be shorter with laparoscopic distal pancreatectomy compared to open distal pancreatectomy [11]. There was no evidence of differences in short-term term or long-term mortality, complications, recurrence, lymph node retrieval or cancer-free resection margins between laparoscopic and open distal pancreatectomy. The aim of this study is to perform a model-based cost-utility analysis of laparoscopic versus open distal pancreatectomy for pancreatic cancer.

Methods

A model-based cost-utility analysis estimating mean costs and quality-adjusted life years (QALYs) per patient was performed. We compared laparoscopic versus open distal pancreatectomy. The time horizon was 5 years and an NHS perspective to measure costs was used. A time horizon of 5 years was judged to be appropriate because cancer-related mortality is likely to occur during this period. Any impact on costs and health-related quality of life is likely to be captured or indicated within this period. Discounting of costs and utilities was performed at the rate of 3.5% per annum [12]. A decision tree model was constructed (Fig 1). A patient undergoing distal pancreatectomy for cancer of the body or tail of the pancreas may have the operation done by laparoscopic or open procedure. A proportion of patients undergoing laparoscopic distal pancreatectomy may require conversion to open procedure. A proportion of patients in whom laparoscopic distal pancreatectomy was completed successfully will develop complications, a proportion of whom may die within 90 days. Those who are alive at 90 days may die between 90 days and 1 year; a proportion of people who are alive at 1 year may die between 1 year and 2 years; and so on. The decision tree pathways in the people who required conversion from laparoscopic distal pancreatectomy to open procedure and those who had open surgery at the outset were identical to those in whom the procedure was completed laparoscopically.

The decision tree was populated with probabilities, outcomes, and cost data from published sources whenever possible. Literature searches were undertaken of articles published up to March 2017 that reported on utilities in patients with pancreatic cancer and patients undergoing pancreatectomy. We also reviewed the Cost-Effectiveness Analysis Registry (CEA) at Tufts University for information on quality of life [13]. Costs were obtained from the National Schedule of Reference costs (2014–2015) [14]. We assumed that the people who died in each period did so at a constant rate during the period. We assumed that patients who died received supportive care in the last 3 months prior to their death. When no data were available from published sources, a range of values were used in the model. For example, there was paucity of data on the impact of complications on health-related quality of life after distal pancreatectomy. There is no information available on the impact of complications on the quality of life after pancreatic surgery. Based on small studies not sufficiently powered to identify differences in

liver and gynaecological surgery, there was no evidence of difference in health-related quality of life between complicated and uncomplicated surgery [15, 16]. However, this is counterintuitive and therefore we used a hypothetical 20% relative decrease in short-term HRQoL because of surgical complications based on the opinion of clinical experts; this was varied in sensitivity analysis. Similarly, there was no data on the health-related quality of life in the first 90 days after laparoscopic distal pancreatectomy. We used a hypothetical 10% relative increase in short-term HRQoL in laparoscopic versus open distal pancreatectomy. We performed a scenario analysis where we assumed that there was no difference in short-term HRQoL in laparoscopic versus open distal pancreatectomy.

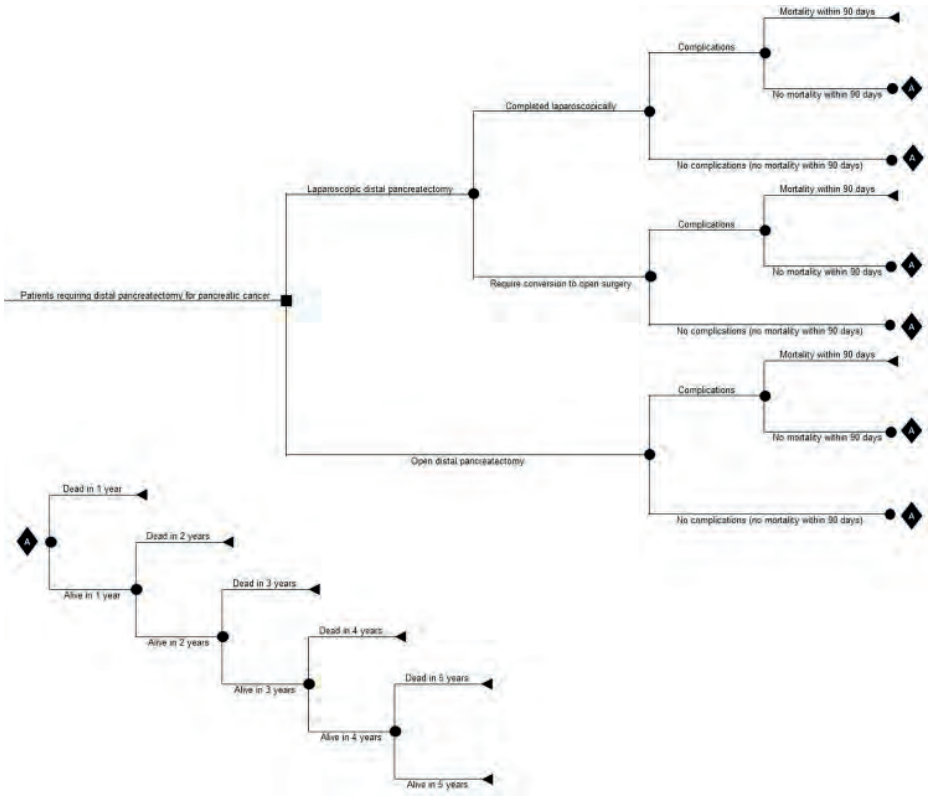

Figure 1. Decision tree showing the decision tree pathways in the people with body and tail of pancreatic cancer who underwent distal pancreatectomy.

Costs of surgery

Since the costs of laparoscopic pancreatic surgery was not available from the NHS reference costs, we estimated the costs based on the operating time and hospital stay from the studies included in the Cochrane review [11] and based on local estimates and the bed stay costs of NHS reference costs of 'Complex Open, Hepatobiliary or Pancreatic Procedures, with CC Score 0 to 2' HRG code: GA04D. For complicated surgery, we included a relative increase of 30% in costs based on the relative increase in costs between GA04C (CC score 3+) and GA04D (CC score 0 to 2) of 'Complex Open, Hepatobiliary or Pancreatic Procedures' of NHS reference costs. In addition, the costs for staplers were included for about 90% of patients in whom the procedure was started laparoscopically (i.e. those in whom the procedure was started and completed laparoscopically and in those whom the procedure was converted from laparoscopic to open procedure) and about 70% of patients in whom the procedure was started as open procedure. We performed a sensitivity analysis where we assumed that 100% of laparoscopic distal pancreatectomy was performed using staplers and all of the open distal pancreatectomy was performed using hand-sewn stump closure. We estimated that one stapler will be used in 90% of the patients and two staplers will be used in 10% of the patients for distal pancreatectomy. We did not include any capital costs for laparoscopic equipment as we anticipated that all centres performing distal pancreatectomy have laparoscopic equipment for carrying out other procedures such as laparoscopic cholecystectomy. The inputs used in the decision tree model and the source of these input is shown in Table 1.

Measuring cost-effectiveness

Cost-effectiveness was measured using net monetary benefits (NMBs). For each treatment, the NMB was calculated as the mean QALYs per patient accruing to that treatment multiplied by decision-makers' maximum willingness to pay for a QALY (also referred to as the cost-effectiveness threshold), minus the mean cost per patient for the treatment. In the UK, the lower and upper limit of the maximum willingness to pay for a QALY are £20 000 (approximately € 22 350 and 26 250 USD) and £30 000 (approximately € 33 500 and 39 400 USD) respectively [12]. NMBs were calculated using the base case parameter values shown in Table 1; these are deterministic results because they do not depend on chance. The option with the highest NMB represents best value for money. The NMB for laparoscopic surgery minus the NMB for open surgery is the incremental NMB. If the incremental NMB is positive (negative) then laparoscopic surgery (open surgery) represents better value for money.

Table 1. Parameters used in the model and their source.

Parameter	Type of distribution	Mean (gamma or continuous), lower limit (uniform), number with event (dichotomous)	Standard deviation (gamma or continuous), upper limit (uniform), number without event (dichotomous)	Point estimate	Source / Notes
Probabilities					
90-day mortality (laparoscopic distal pancreatectomy)	Beta	1	328	0.3%	Data from Cochrane review [11]
Complications (laparoscopic distal pancreatectomy)	Beta	33	76	30.3%	Data from Cochrane review [11]
Conversion (laparoscopic distal pancreatectomy)	Beta	70	278	20.1%	Data from Cochrane review [11]
1-year mortality (laparoscopic distal pancreatectomy)	Beta	21	83	20.2%	Data from Cochrane review [11]
2-year mortality (laparoscopic distal pancreatectomy)	Beta	44	60	42.3%	Data from Cochrane review [11]
3-year mortality (laparoscopic distal pancreatectomy)	Beta	64	40	61.5%	Data from Cochrane review [11]
4-year mortality (laparoscopic distal pancreatectomy)	Beta	74	19	79.6%	Data from Cochrane review [11]
5-year mortality (laparoscopic distal pancreatectomy)	Beta	76	17	81.7%	Data from Cochrane review [11]
90-day mortality (open pancreatectomy)	Beta	11	1111	1.0%	Data from Cochrane review [11]
Complications (open distal	Beta	45	92	32.8%	Data from Cochrane review [11]
1-year mortality (open distal pancreatectomy)	Beta	50	123	28.9%	Data from Cochrane review [11]
2-year mortality (open distal pancreatectomy)	Beta	84	89	48.6%	Data from Cochrane review [11]
3-year mortality (open distal pancreatectomy)	Beta	110	63	63.6%	Data from Cochrane review [11]
4-year mortality (open distal pancreatectomy)	Beta	124	26	82.7%	Data from Cochrane review [11]
5-year mortality (open distal pancreatectomy)	Beta	126	24	84.0%	Data from Cochrane review [11]
Costs					
Hospital stay (per day)	Gamma	£352.48	£195.24	£352.48	National schedule of reference costs 2015 to 2016: the main schedule GA04D (Complex Open, Hepatobiliary or Pancreatic Procedures, with CC Score 0 to 2) (median and quartiles converted to mean and standard deviation) [14]
Operating time (per minute)	Uniform	£17.00	£18.00	£17.50	Local estimate
Stapler	Uniform	£200.00	£300.00	£250.00	Local estimate
Proportion of patients in whom stapler was used in laparoscopic distal pancreatectomy	Beta	90	10	90%	Local estimate
Proportion of patients in whom stapler was used in open distal pancreatectomy	Beta	70	30	70%	Local estimate
Costs of distal pancreatectomy	-	-	-	-	There is no estimate available for laparoscopic or open distal pancreatectomy. The costs of pancreatectomy were based on the hospital stay, operating time, and the number of staplers used. In addition, we used a 30% relative increase in the costs related to complicated procedures based on the relative increase in costs of GA04C (CC score 3+) versus GA04D (CC score 0 to 2) of 'Complex Open, Hepatobiliary or Pancreatic Procedures' of NHS reference costs.
Health-related quality of life					
Complicated laparoscopic distal pancreatectomy—first 3 months	Beta	0.2	0.8	20.0%	Hypothetical relative 20% decrease compared to uncomplicated distal pancreatectomy
Uncomplicated laparoscopic distal pancreatectomy—first 3 months	Beta	0.1	0.9	10.0%	Hypothetical 10% relative increase because of laparoscopic surgery
Complicated open distal pancreatectomy—first 3 months	Beta	0.2	0.8	20.0%	Hypothetical 20% relative decrease compared to uncomplicated distal pancreatectomy
Uncomplicated open distal pancreatectomy—first 3 months	Gamma	0.63	0.30	0.63	Ljungman et al [17].
Distal pancreatectomy subsequent stable period	Gamma	0.69	0.33	0.69	Ljungman et al [17].
Supportive care	Gamma	0.14	0.18	0.14	Tam et al [18]
Other parameters					
Length of hospital stay (laparoscopic pancreatectomy) (days)	Gamma	-2.43	11.67152474	-2.43	Data from Cochrane review [11]
Operating time (laparoscopic pancreatectomy) (minutes)	Gamma	-18.46	292.733099	-18.46	Data from studies included in the Cochrane review [11]
Length of hospital stay (laparoscopic pancreatectomy) (days)	Gamma	-2.43	11.67152474	-2.43	Data from Cochrane review [11]
Operating time (laparoscopic pancreatectomy) (minutes)	Gamma	-18.46	292.733099	-18.46	Data from studies included in the Cochrane review [11].
Proportion of surgeries in which one stapler was used	Beta	0.9	0.1	0.9	Hypothetical

A probabilistic sensitivity analysis (PSA) was also undertaken [12]. The PSA involves Monte Carlo simulation and takes variability of all selected inputs into account simultaneously. Distributions described in the tables were assigned to parameters (Table 1) to reflect the uncertainty with each parameter value.

A random value from the corresponding distribution for each parameter was selected. This generated an estimate of the mean cost and mean QALYs and the NMB associated with each treatment. This was repeated 5000 times and the results for each simulation were noted. The mean costs, QALYs and NMB for each treatment was calculated from the 5000 simulations; these are probabilistic results because they depend on chance. The NMB was also calculated for each of the 5000 simulations and the proportion of times each treatment had the highest NMB was calculated for a range of values for the maximum willingness to pay for a QALY. These were summarised graphically using cost-effectiveness acceptability curves. 95% confidence intervals around the base case values were derived using the 2.5 and 97.5 percentiles calculated from the PSA. In cases where standard errors were required for the PSA and these were not reported in the sources used it was assumed the standard error was equal to the mean.

For the deterministic univariate sensitivity analysis, each variable in the cost-effectiveness model was varied one at a time. The results of the sensitivity analysis are represented in the tornado diagram which reflects the variation in the NMB within the range of the lowest and highest value used for a parameter with all else equal. If the variation in the NMB includes 0, then there is uncertainty in the cost-effectiveness due to the variation of the parameter.

Results

The results of deterministic analysis are shown in Table 2. This shows that laparoscopic distal pancreatectomy results in decreased costs and increased QALYs compared to open distal pancreatectomy, with a higher net monetary benefit. Therefore, laparoscopic distal pancreatectomy dominates open distal pancreatectomy, and the incremental NMB is positive.

Table 2. Results of deterministic analysis (per patient).

Treatment	Costs	QALYs	Net monetary benefit*	
			£20,000	£30,000
Laparoscopic distal pancreatectomy	£7,676	1.6472	£25,267.54	£41,739.31
Open distal pancreatectomy	£8,539	1.4974	£21,409.10	£36,383.12
Incremental	**-£863**	**0.1498**	**£3,858.45**	**£5,356.20**

* Calculated at willingness to pay thresholds of £20,000 and £30,000 per QALY gained.
QALY = quality adjusted life year.

The results of probabilistic sensitivity analysis are shown in Table 3. The probabilistic sensitivity analysis shows that laparoscopic distal pancreatectomy results in decreased costs (not statistically significant) and increased QALYs (not statistically significant) compared to open distal pancreatectomy (i.e. laparoscopic distal pancreatectomy dominates open distal pancreatectomy), with a significantly higher net monetary benefit. Again, the incremental net monetary benefit is positive; however, the 95% confidence intervals include zero.

The scatter plot showing the incremental cost per incremental quality adjusted life years (QALY) per patient for a cohort of 5000 patients is shown in Fig 2. The scatter plot shows that the points lie almost symmetrical about the X-axis, i.e. the costs were similar between laparoscopic and open distal pancreatectomy, but most points lie to the right of the Y-axis, i.e. laparoscopic distal pancreatectomy was associated with increased QALYs.

Table 3. Results of probabilistic sensitivity analysis (per patient).

Treatment	Costs	QALYs	Net monetary benefit*	
			£20,000	£30,000
Laparoscopic distal pancreatectomy	£7,675 (95% CI £1,947 to £19,968)	1.6446 (95% CI 0.5998 to 3.3513)	£25,217.57 (95% CI £1,410.56 to £60,672.87)	£41,663.68 (95% CI £8,750.01 to £94,019.22)
Open distal pancreatectomy	£8,556 (95% CI £1,762 to £21,872)	1.4954 (95% CI 0.5487 to 3.0779)	£21,352.50 (95% CI -£1,768.51 to £53,381.03)	£36,306.83 (95% CI £4,801.25 to £83,318.20)
Incremental	**-£882 (95% CI -£12,494 to £12,357)**	**0.1492 (95% CI 0.0003 to 0.4180)**	**£3,865.07 (95% CI -£9,641.19 to £16,397.43)**	**£5,356.85 (95% CI -£8,678.12 to £19,137.46)**

* Calculated at willingness to pay thresholds of £20,000 and £30,000 per QALY gained.
QALY = quality adjusted life year.

We calculated data points to construct a cost-effectiveness acceptability curve, which showed that the probability laparoscopic distal pancreatectomy was cost-effective compared to open distal pancreatectomy was 70% to 80% at the willingness-to-pay thresholds generally used in England (£20,000 to £30,000 per QALY gained) (Fig 3). The cost-effectiveness acceptability curve shows that the probability laparoscopic distal pancreatectomy was cost-effective compared to open distal pancreatectomy was 70% to 80% at the

willingness-to-pay thresholds generally used in England (£20,000 to £30,000 per QALY gained).

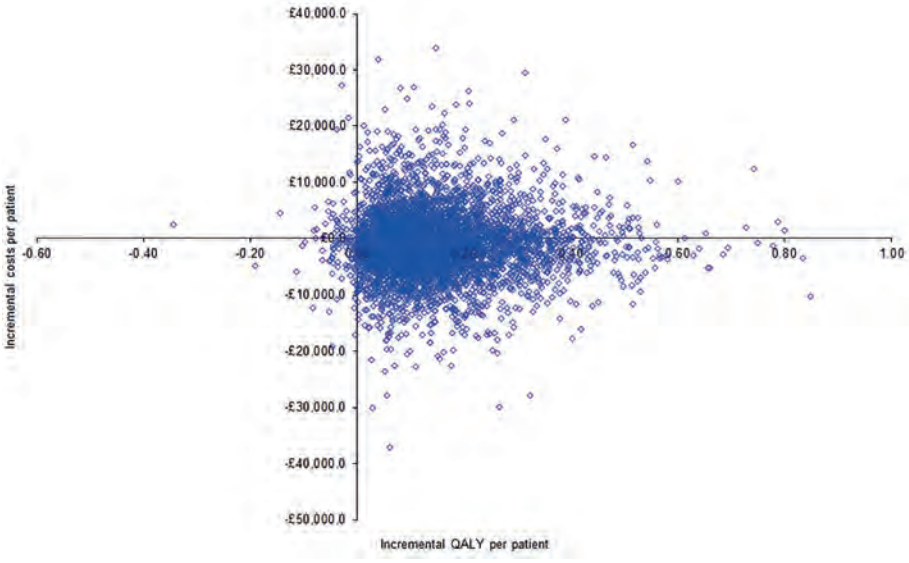

Figure 2. Scatter plot of incremental cost per incremental quality-adjusted life year.

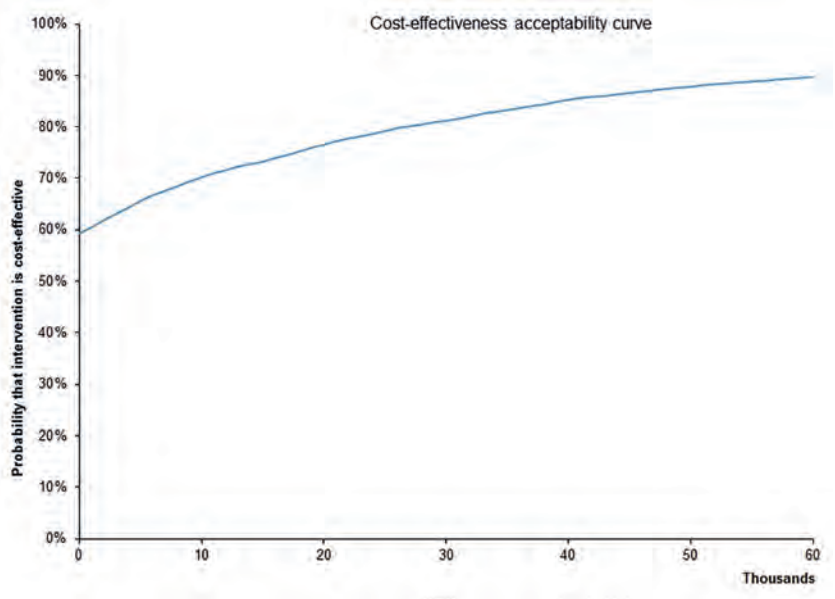

Figure 3. Cost-effectiveness acceptability curve.

Univariate sensitivity analysis

Using a cost-effectiveness threshold value of £20,000 per QALY gained, all else equal, laparoscopic distal pancreatectomy was cost-effective, as long as the probability of 90-day mortality was <30%, 1-year mortality was <55%, 2-year mortality was <75%, 3-year mortality was <95%, and the operating time was < 500 minutes in people who undergo laparoscopic distal pancreatectomy. Laparoscopic distal pancreatectomy was also cost-effective at this threshold all else equal if 2-year mortality was >20%, 3-year mortality was >35%, 4-year mortality was >50%, and 5-year mortality was >30% in the open distal pancreatectomy group. Laparoscopic distal pancreatectomy was cost-effective versus open distal pancreatectomy for all other values for the different parameters. The tornado diagram shows that there is significant uncertainty in the results, especially with regards to mortality (Fig 4).

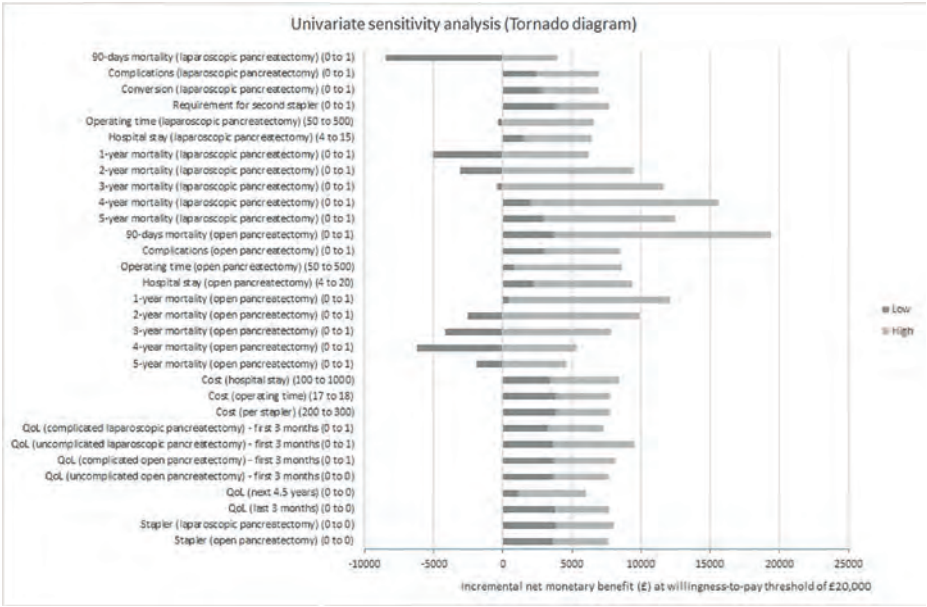

Figure 4. Univariate sensitivity analysis (Tornado diagram).

Scenario analysis

Scenario analysis 1: Difference in the use of stapler between laparoscopic and open distal pancreatectomy As indicated in Table 4, there was no change in the interpretation of the results compared to the main analysis.

Scenario analysis 2: Difference in the health-related quality of life between laparoscopic and open distal pancreatectomy As indicated in Table 5,

there was no change in the interpretation of the results compared to the main analysis.

Table 4. Results of probabilistic sensitivity analysis (per patient) (scenario analysis 1).

Treatment	Costs	QALYs	Net monetary benefit*	
			£20,000	£30,000
Laparoscopic distal pancreatectomy	£7,680 (95% CI £1,992 to £19,609)	1.6593 (95% CI 0.5832 to 3.3798)	£25,505.80 (95% CI £1,077.92 to £60,880.86)	£42,098.73 (95% CI £8,084.29 to £94,081.58)
Open distal pancreatectomy	£8,321 (95% CI £1,410 to £22,374)	1.5059 (95% CI 0.5316 to 3.0695)	£21,797.22 (95% CI -£2,999.81 to £54,686.77)	£36,856.49 (95% CI £3,931.88 to £84,698.84)
Incremental	**-£641 (95% CI -£12075 to £12214)**	**0.1534 (95% CI -0.0042 to 0.4261)**	**£3,708.58 (95% CI -£9,473.62 to £16,115.69)**	**£5,242.23 (95% CI -£8,443.26 to £18,761.80)**

* Calculated at willingness to pay thresholds of £20,000 and £30,000 per QALY gained.
QALY = quality adjusted life year.

Table 5. Results of probabilistic sensitivity analysis (per patient) (scenario analysis 2).

Treatment	Costs	QALYs	Net monetary benefit*	
			£20,000	£30,000
Laparoscopic distal pancreatectomy	£7,719 (95% CI £1,927 to £20,261)	1.6498 (95% CI 0.5955 to 3.3128)	£25277.36 (95% CI £1489.24 to £58981.13)	£41775.39 (95% CI £8808.85 to £91765.32)
Open distal pancreatectomy	£8,574 (95% CI £1,631 to £21,802)	1.5116 (95% CI 0.5539 to 2.9985)	£21658.93 (95% CI -£1351.14 to £53308.83)	£36775.18 (95% CI £5280.99 to £83402.58)
Incremental	**-£855 (95% CI -£12312 to £12176)**	**0.1382 (95% CI -0.0111 to 0.3989)**	**£3618.43 (95% CI -£9796.78 to £16258.35)**	**£5000.22 (95% CI -£8860.85 to £18803.70)**

* Calculated at willingness to pay thresholds of £20,000 and £30,000 per QALY gained.
QALY = quality adjusted life year.

Discussion

Summary of findings

This cost-utility analysis showed that laparoscopic distal pancreatectomy resulted in decreased costs compared to open distal pancreatectomy and resulted in a small increase in QALY (0.15 QALY per patient). Therefore, laparoscopic distal pancreatectomy dominated open distal pancreatectomy. However, the confidence intervals of NMB overlapped zero, i.e. there was uncertainty about the cost-effectiveness of laparoscopic distal pancreatectomy compared to open distal pancreatectomy. The probability of laparoscopic distal pancreatectomy being cost-effective compared to open distal pancreatectomy was 70% to 80% for at the willingness-to-pay thresholds generally used in England (£20,000 to £30,000 per QALY gained).

Limitations of the analysis

The major limitation of this analysis is the lack of data. The information used is from observational studies and not from randomised controlled trials. Because of this there are concerns about whether the estimates of laparoscopic distal pancreatectomy versus open distal pancreatectomy obtained in observational studies are reliable [11]. In fact, in the Cochrane review, it was noted that there was a high likelihood that patients with more advanced disease had open distal pancreatectomy and those with less advanced disease underwent laparoscopic distal pancreatectomy [11]. Thus, there is concern about the safety and oncological clearance offered by laparoscopic distal pancreatectomy for resections requiring resection of adjacent structures such as blood vessels.

There is currently no information on the health-related quality of life (reported as preference-based measures such as EQ-5D) after uncomplicated or complicated laparoscopic distal pancreatectomy and complicated open distal pancreatectomy. Health-related quality of life (reported as preference-based measures such as EQ-5D) was available in two studies of small sample sizes which did not relate to laparoscopic or open distal pancreatectomy. These studies which were not powered to identify differences in health-related quality of life between complicated and uncomplicated liver resection or gynaecological surgery [15, 16]. However, this is counterintuitive and therefore, we used a hypothetical 20% relative decrease in short-term HRQoL because of surgical complications based on the opinion of clinical experts. We also used a hypothetical 10% relative increase in short-term HRQoL because of laparoscopic distal pancreatectomy compared to open distal pancreatectomy. The cost-effectiveness was not sensitive to changes in the relative decrease in the HRQoL due to complications and increase in the HRQoL because of the use of laparoscopy.

The complication rates in people who underwent laparoscopic distal pancreatectomy were based on information from a Cochrane review involving observational studies in which people with more extensive cancer received open distal pancreatectomy more often and people with less extensive cancer received laparoscopic distal pancreatectomy more often [11]. Therefore, there is a high risk of systematic error (bias) favouring laparoscopic distal pancreatectomy. The number of participants included in the studies that contributed data for this review was small and the studies

were not powered to measure differences in harms. Thus, there is high risk of random error. In addition, it is unlikely that major complications related to laparoscopic distal pancreatectomy are reported in the literature because of the lack of incentive to publish these; so, there may be publication bias. Formal audits of laparoscopic distal pancreatectomy are necessary to ensure that complications related to laparoscopic distal pancreatectomy are recorded and are comparable with open distal pancreatectomy. Because of the above limitations in data, the results may change when better data becomes available.

Applicability of findings of the research

Studies included only patients with pancreatic cancer who were eligible for surgery. So, the findings of the review are applicable only in distal pancreatectomy performed in patients with pancreatic cancer who were eligible for surgery. The costs were based on NHS reference costs and the cost-effectiveness analysis used a willingness-to-pay threshold in UK. Therefore, the results are applicable in the NHS setting and other settings with similar methods of reimbursement.

Comparisons with previous research

This is the first cost-utility analysis on laparoscopic distal pancreatectomy versus open distal pancreatectomy specifically for pancreatic cancer. We identified one cost-utility analysis of laparoscopic distal pancreatectomy versus open distal pancreatectomy for benign and malignant pancreatic lesions in the body or tail of the pancreas, which revealed that laparoscopic distal pancreatectomy was cost-effective to open distal pancreatectomy if the willingness-to-pay threshold was €5400 per QALY, i.e. laparoscopic distal pancreatic was cost-effective compared to open distal pancreatectomy in the NHS setting [19].

Further research

Further research to collect data on costs, utilities, and probabilities associated with laparoscopic versus open distal pancreatectomy are required, particularly in relation to oncological efficacy of the laparoscopic procedure, survival probabilities, incidence of complications, and the utilities related to complicated and uncomplicated distal pancreatectomy. These should be collected from randomised controlled trials as randomisation is the only way to ensure that similar types of participants underwent laparoscopic distal pancreatectomy and open distal pancreatectomy.

Conclusions

It appears that there is uncertainty about whether laparoscopic distal pancreatectomy is cost-effective compared to open distal pancreatectomy for pancreatic cancer in the NHS setting. However, because of the limitations in the available data, the results may change when better data becomes available.

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Chapter 4

Minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease

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Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of laparoscopic versus robot-assisted versus open pancreatoduodenectomy for people with benign, premalignant, and malignant disease

Background

Description of the condition

Pancreatoduodenectomy is most commonly performed to remove premalignant and malignant neoplasms that involve the head of the pancreas, duodenum, periampullary region, or distal common bile duct (CBD) (Johnson 2008).

Cystic pancreatic lesions are very common in the general population with reported prevalence up to 50% (Komrey 2018). Cystic lesions that may be malignant include cystic neuroendocrine neoplasms, mucinous neoplasms, such as intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm. Solid pseudopapillary neoplasm has a known, but low risk for malignancy (Stark 2016). IPMN is the most common cystic pancreatic neoplasm. It is defined as a grossly visible noninvasive epithelial neoplasm constituted of mucin-producing cells which could arise from the main pancreatic duct (IPMN-MD) and/or more commonly from the branch ducts (IPMN-BD). IPMN-BD is associated with a relatively low risk of neoplastic transformation estimated in 0-7% per year (Crippa 2016), in contrast to IPMN-MD and mixed-type IPMN, which is an indication for surgical resection due to the high malignancy rate (Europ Guidelines Pancreatic Cystic Neoplasms 2018).

Neuroendocrine tumours (NET) are neoplasms arising from neuroendocrine cells. Functional NETs are capable of hormone production and therefore associated with distinct clinical syndromes (i.e. Whipple's triad, Zollinger-Ellison syndrome). Nonfunctional NETs do not secrete hormones, secrete them in minimal quantities, or secrete peptides that do not result in an obvious syndrome (Scott 2019). A substantial proportion of pancreatic NETs (PNETs) are nonfunctional, and the most common functional PNETs are insulinomas, followed by gastrinomas. Most PNETs are malignant, and up to

60% of patients present with metastatic disease (Halfdanarson 2008). The majority of PNETs are sporadic, but they can occur as part of an inherited syndrome such as multiple endocrine neoplasia type 1, Von Hippel-Lindau syndrome (VHL), tuberous sclerosis complex, neurofibromatosis type 1 (Jensen 2008). Functional tumours and nonfunctional PNETs larger than 2 cm should be resected (Falconi 2016).

Chronic pancreatitis (CP) is a complex inflammatory disease with pain as the most dominant symptom. The most common indication for surgery for CP is intractable pain, when medical or endoscopic management fails to provide pain relief. Other indications are a suspicion of neoplasm and local complications in adjacent organs, such as duodenal or common bile duct stenosis, pseudoaneurysm (most commonly of the splenic artery) or erosion of the large vessels producing gastrointestinal haemorrhage, large pancreatic pseudocysts, and internal pancreatic fistula. Surgical procedures for CP can be categorised into three major groups: drainage procedures (e.g., pancreaticojejunostomy), procedures combining drainage and resection (Frey or Beger procedure), and resection (e.g., pancreatoduodenectomy or pylorus-preserving pancreatoduodenectomy) (Kempeneers 2020). A recent RCT demonstrated that pancreatoduodenectomy for chronic pancreatitis is associated with similar outcomes as a surgical drainage procedure (Diener 2017).

Periampullary carcinomas arise within the vicinity of the ampulla of Vater and can originate from the ampulla of Vater, the distal common bile duct, the head of the pancreas and the duodenum. Pancreatic ductal adenocarcinoma is the most common and has the worst prognosis. In 2018, there were 458,918 new people diagnosed with pancreatic cancer and 432,242 deaths due to pancreatic cancer globally (IARC 2018). Mortality rates due to pancreatic cancer are increasing in the US (Ma 2013) and it is the fourth most common cause of cancer-related mortality in the west (Parkin 2001; Parkin 2005; Yamamoto 1998). Pancreatic adenocarcinoma is a biologically aggressive cancer, which is relatively resistant to chemotherapy and radiotherapy. In the minority which are resectable at presentation there is a high rate of local and systemic recurrence (Abrams 2009; Ghaneh 2007; Orr 2010). In early pancreatic cancer (with no invasion of adjacent structures such as the superior mesenteric vein, portal vein, or superior mesenteric artery), surgical resection remains the primary treatment of choice in people likely to withstand major surgery. However,

about half the people have metastatic disease at presentation and one-third have locally advanced unresectable disease, leaving only about 10% to 20% of people suitable for resection (Tucker 2008). Neoadjuvant therapy may improve survival compared with upfront surgery in patients with resectable and borderline resectable pancreatic cancer (van Dam 2021). Adjuvant therapy has been shown to significantly improve outcomes and is standard care in patients with resected pancreatic cancer (Pancreatic Cancer ESMO).

Description of the intervention

Surgical resection is the current standard therapy for resectable periampullary tumours and is performed by an en-bloc resection of the head of the pancreas, gallbladder with the common bile duct, duodenum, proximal jejunum, and loco-regional lymph nodes (Lillemoe 2000). The standard treatment for resectable tumours consists of a classic Whipple's operation (Whipple 1935), a pylorus-resecting pancreatoduodenectomy (PRPD)(Kawai 2011), or a pylorus-preserving pancreatoduodenectomy (PPPD) (Traverso 1980). During a classic Whipple's operation, the antrum of the stomach is resected in contrast with the PPPD, which is a pylorus preserving technique. During PRPD the proximal side of the pylorus ring and most part of the stomach is preserved.

In open surgery, access to the abdomen can be achieved by an upper midline incision, or a bilateral subcostal incision (rooftop or Chevron incision). In laparoscopic surgery, the surgical access to the abdominal cavity is by a number of trocars through which laparoscopic instruments can be inserted after the abdomen is insufflated using carbon-dioxide pneumoperitoneum. The robotic surgical system consists of a three or four-armed robot which is operated by the surgeon who sits at a separate console. The robotic approach affords the surgeon a three-dimensional stereoscopic view of the operating field and restores hand-eye coordination that is often lost in traditional laparoscopy when the camera is offset to the plane of dissection. The instrumentation replicates the movements of the human hand with seven degrees of freedom and eliminates hand tremor (Joyce 2014). Both classic Whipple's operation, PRPD and PPPD can be performed open or minimally invasive (Cameron 2015; Croome 2014; Mesleh 2013).

Improvements in surgical techniques and centralization of pancreatic surgery have led to mortality rates of less than 5% (de Wilde 2012; Buchler 2003; Cameron 2015). Nevertheless, operative morbidity remains high, reaching up to 30% to 45% from causes including sepsis, pancreatic fistula, intra-abdominal abscess, and delayed gastric emptying (Bassi 2001; Cameron 2015; Gouma 2000).

How the intervention might work

For many surgical procedures, minimally invasive surgery is currently preferred over open surgery. This includes surgical procedures such as cholecystectomy (removal of gallbladder), colon cancer, and hysterectomy (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009). Advantages of minimally invasive surgery include decreased pain, decreased blood loss, shorter hospital stay, earlier postoperative recovery, better cosmesis (physical appearance), and decreased costs (Bijen 2009; Keus 2006; Reza 2006; Talseth 2014; Walsh 2009).

Why it is important to do this review

Laparoscopic pancreatoduodenectomy is feasible and performed in several centres (Croome 2014; Mesleh 2013). The smaller incisions of pancreas surgery may reduce pain and result in earlier postoperative recovery. However, the safety of the laparoscopic approach for a procedure that has a high complication rate and which mandates adequate cancer clearance has to be ensured before the method can be widely recommended (van Hilst 2019).

Another issue is the adequacy of cancer clearance in terms of resection margins and the extent of lymph nodes removed with laparoscopy. There is also a lack of tactile sensation with laparoscopy which normally allows the surgeon to determine whether the tissue being cut is likely cancerous (Al-Taan 2010). Other concerns related to cancer clearance are the risk of port-site metastases (recurrence of cancer at the laparoscopic port-site), reported in <2% in a small cohort of patients operated for pancreatic and periampullary cancer (Kauffmann 2016). Therefore, oncological safety (cancer clearance) is an important issue with laparoscopic pancreatoduodenectomy. Also, prolonged operating times for laparoscopic pancreatoduodenectomy have been reported (Mesleh 2013). Robot-assisted laparoscopy has features which overcome some of the difficulties of conventional laparoscopy and robotic pancreatoduodenectomy has been

reported more frequently over the last years. However, it is unclear whether it is superior to laparoscopy (Joyce 2014).

There is no Cochrane review on minimally invasive versus open pancreatoduodenectomy in benign, premalignant, and malignant disease.

Methods

Criteria for considering studies for this review

Types of studies We will include only randomised controlled trials (RCTs), including cluster RCTs. We will include studies reported as full text, those published as abstract only, and unpublished data. Just one RCT will provide a better estimate of the effect than multiple observational studies (even if they are showing consistent and precise results) in this particular situation. Clearly, multiple RCTs with consistent effect estimates are more reliable than a single RCT. We anticipate significant selection bias when including non-randomized studies since there is a high possibility that participants with low risk are subjected to laparoscopic surgery, while participants at high risk (e.g., more advanced disease) are subjected to open surgery. The effect estimates of a meta-analysis of such observational studies can be misleading.

Types of participants We will include adults undergoing pancreato-duodenectomy for benign, premalignant, and malignant periampullary disease. Periampullary tumours are tumours that arise from the region around the ampulla of Vater. We will exclude adults undergoing other pancreatic surgeries such as metastasectomies, distal pancreatectomy, pancreatic pseudocyst drainage, pancreatic drainage procedures for chronic pancreatitis or pancreatic enucleation for benign neuroendocrine tumours as the issues surrounding minimally invasive versus open surgery for these procedures are different from those surrounding minimally invasive versus open pancreatoduodenectomy. We will include studies that only partially overlap with the review's population. If the study does not report separate data from the eligible section of the population and the majority of participants is eligible for inclusion, we will include the study and perform sensitivity analyses by excluding studies that include only a subset of eligible participants to assess the robustness of the results. Additionally, we will reach out to the authors of the studies to request additional information or data on the broader eligible population.

Types of interventions We will include trials comparing laparoscopic or robot-assisted pancreatoduodenectomy (minimally invasive) versus open pancreatoduodenectomy provided that the only difference between the randomised groups is the use of minimally invasive or open method of access to the pancreas. Therefore, we will have the following three comparisons:

1. Robotic versus open pancreatoduodenectomy
2. Robotic versus laparoscopic pancreatoduodenectomy
3. Laparoscopic versus open pancreatoduodenectomy

We will exclude trials comparing different methods of minimally invasive pancreatoduodenectomy (i.e. minimally invasive classical Whipple versus minimally invasive PPPD) or different methods of open pancreatoduodenectomy. We will exclude studies in which a hybrid procedure is planned at the outset. However, if the studies planned robotic procedures or laparoscopic procedures, which had to be converted to laparoscopic or open procedures from robotic procedures or to open procedures from laparoscopic procedures, we will include such studies and perform an intention-to-treat analysis, i.e., based on the procedure planned. We will obtain 'conversion' to other procedures as one of the secondary outcomes.

Types of outcome measures We based the choice of clinical outcomes on the necessity to assess whether minimally invasive surgery is safe, results in adequate cancer clearance and survival, and is beneficial in terms of decreased blood transfusion requirements, earlier postoperative recovery, and improvement in health-related quality of life. Studies meeting the inclusion criteria will be included irrespective of whether they report secondary outcomes. However, studies must report at least one of the primary outcomes to be included in the analysis. The primary outcomes are significant in clinical decision-making and plays a critical role in addressing the benefits and harms of laparoscopic, robot-assisted, and open pancreatoduodenectomy for people with benign, premalignant, and malignant diseases.

Primary outcomes

1. Mortality
    a. Short-term mortality (in-hospital mortality or mortality within three months)

b. Long-term mortality (latest available time point 1 year or more from randomisation)

2. Serious adverse events (within three months). We will accept the total number of serious adverse events using the following definitions:
   a. Clavien-Dindo classification (Clavien 2009; Dindo 2004) grade III or greater: any adverse events requiring surgical, endoscopic, or radiological intervention, life-threatening complications requiring intensive care or adverse events leading to death.
   b. International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guideline (ICH-GCP1996): serious adverse events defined as any untoward medical occurrences that result in death, are life-threatening, require hospitalisation or prolongation of existing hospitalisation or result in persistent or significant disability/incapacity.
   c. Individual complications that can clearly be classified as grade III or greater with the Clavien-Dindo classification (Clavien 2009; Dindo 2004), or as a serious adverse event with the ICH-GCP classification, such as postpancreatectomy hemorrhage, delayed gastric emptying and reintervention.
   d. Clinically significant pancreatic fistulas (type B or type C International Study Group on Pancreatic Fistula (ISGPF) definition) (Bassi 2005).

3. Health-related quality of life (latest available time point, using any validated scale)
   a. Short-term (four weeks to three months)
   b. Medium-term (longer than three months to one year)

Secondary outcomes

1. Any adverse events (within three months). We will accept the total number of all adverse events reported by the study author irrespective of the severity of the adverse event.

2. Recurrence (local recurrence, surgical wound recurrence (also called port-site metastases in the laparoscopic or robotic group) or distant metastases)
   a. Short-term recurrence (within six months)

b. Long-term recurrence (latest available time point 6 months or more from randomisation)

3. Oncological clearance in malignant diseases
   a. Positive resection margins (presence of macroscopic or microscopic cancer tissue at the plane of resection) at histopathological examination after surgery
   b. Tumour size at histopathological examination after surgery
   c. Total number of harvested lymph nodes and number of positive lymph nodes at histopathological examination after surgery
   d. Perineural invasion and lymphovascular invasion at histopathological examination after surgery

4. Perioperative blood loss
   a. Quantity of blood loss
   b. Proportion of people requiring blood transfusion (during surgery or within one week after surgery) (whole blood or red cell transfusion)
   c. Quantity of blood transfusion

5. Surgical duration

6. Conversion
   a. conversion to laparoscopic procedures
   b. conversion to open procedures

7. Measures of postoperative recovery
   a. Length of hospital stay (including the index admission for pancreatoduodenectomy and any surgical complication-related re-admissions)
   b. Time to return to normal activity (return to preoperative mobility without any additional carer support)
   c. Time to return to work (in people who were employed previously)
   d. Number of readmissions

Search methods for identification of studies

We will conduct a literature search to identify all published and unpublished randomised controlled trials. No restrictions will be placed on the language of publication when searching the electronic databases. We will translate the non-English language papers and fully assess them for potential inclusion in the review as necessary.

Electronic searches We will search the following electronic databases for identifying potential studies:

1. Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 2);
2. MEDLINE (1966 to present) (Appendix 3);
3. EMBASE (1988 to present) (Appendix 4)

Searching other resources We will check reference lists of all primary studies and review articles for additional references. We will contact authors of identified trials and ask them to identify other published and unpublished studies. We will search for errata or retractions from eligible trials on http://www.ncbi.nlm.nih.gov/pubmed and report the date this was done within the review.

1. Grey literature databases
2. Health Management Information Consortium (HMIC) database www.ovid.com/site/catalog/DataBase/99.jsp
3. National Technical Information Service (NTIS) database www.ntis.gov/products/ntisdb.aspx
4. OpenGrey www.opengrey.eu
5. Clinical trials registers/trial result registers

We will also conduct a search of clinical trial registers/trial result registers:

1. Clinical Trials.gov (Appendix 5);
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (Appendix 6)

Data collection and analysis

Selection of studies Two review authors (DR, PB) will independently screen titles and abstracts for inclusion all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/ unclear) or 'do not retrieve'. We will retrieve the full text study reports/ publication and two review authors (DR, PB) will independently screen the full text and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult third person (KG).

We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and characteristics of excluded studies table (Page 2021).

Data extraction and management We will use a standard data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. Two review authors [DR, PB] will extract study characteristics from included studies. We will extract the following study characteristics:

1. Methods: study design, total duration study and run in, number of study centres and location, study setting, withdrawals, date of study
2. Participants: N, mean age, age range, gender, American Society of Anesthesiologists (ASA) status (ASA 2014), BMI, inclusion criteria, exclusion criteria, tumour size, tumour stage, histological diagnosis
3. Interventions: intervention, comparison, concomitant interventions
4. Outcomes: primary and secondary outcomes specified and collected, time points reported
5. Notes: funding for trial, notable conflicts of interest of trial authors

Two review authors (DR, PB) will independently extract outcome data form included studies. If outcomes were reported multiple times for the same time point, for example, short-term health-related quality of life was reported at six weeks and three months, we will choose the later time point (i.e. three months) for data extraction. For timeto-event outcomes, we will extract data to calculate the hazard ratio (HR) and its standard error using the methods suggested by Parmar et al. (Parmar 1998). We will include all randomised participants for medium-term and long-term outcomes (e.g. mortality or quality of life) and this will not be conditional upon the short-term outcomes (e.g. being alive at three months or having a low or high quality-of-life index at three months). We will note in the "Characteristics of included studies" table if data outcome data was reported in an unusable way. We will resolve disagreements by consensus or by involving a third person (KG). One review author (DR) will copy across the data from the data collection form into the Review Manager file. We will double-check that the data is entered correctly by comparing the study reports with how

the data are presented in the systematic review. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies Two review authors (PB, DR) will independently assess risk of bias using Cochrane's risk of bias version 2 tool (Sterne 2019). We will use the Excel tool to implement RoB 2 (available at riskofbiasinfo.org) to manage risk of bias assessments. We will assess the risk of bias using the intention-to-treat effect (effect of assignment). We will conduct risk of bias assessments for all outcomes specified for inclusion in the summary of findings tables (mortality, health-related quality of life, and serious adverse events). Any disagreement will be resolved by discussion or by involving a third assessor (KG). We will assess the risk of bias according to the following domains:

1. Bias arising from the randomisation process;
2. Bias due to deviations from intended interventions;
3. Bias due to missing outcome data;
4. Bias in measurement of the outcome;
5. Bias in selection of the reported result;

For cluster-randomised clinical trials, we plan to consider an additional domain that specifically applies to the design of the cluster-randomised clinical trial: 'Bias arising from the timing of identification and recruitment of individual participants within clusters in relation to timing of randomisation' (RoB 2 Domain 1b).

We will grade each potential source of bias as 'high risk of bias', 'some concerns', or 'low risk of bias' by using signaling questions to rate each risk of bias domain, utilising the Excel tool to implement RoB 2, which comprises:

1. a series of ‘signaling questions’;
2. a judgement about risk of bias for the domain, which is facilitated by an algorithm that maps responses to the signaling questions to a proposed judgement;
3. free text boxes to justify responses to the signaling questions and risk-of-bias judgements;
4. an option to predict (and explain) the likely direction of bias.

We will include answers to signaling questions in a supplementary data file. We will summarise the risk of bias judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome. We will assess risk of bias for our main outcome measures, which are to be presented in a summary of findings table. This includes mortality, health-related quality of life and serious adverse events.

Assessment of bias in conducting the systematic review We will conduct the review according to this published protocol and report any deviations form it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect We will analyse dichotomous data as risk ratio and continuous data as mean difference when the outcome is reported or converted to the same units in all the trials (e.g. hospital stay, time to return to work) or standardized mean difference (SMD) when different scales are used for measuring the outcome (e.g. quality of life). We will ensure that higher scores for continuous outcomes have the same meaning for the particular outcome, explain the direction to the reader and report where the directions were reversed if this was necessary. We will calculate the HR for time-to-event outcomes such as long-term mortality, long-term recurrence, and time-to-first adverse event (or serious adverse event). We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. A common way that trialists indicate when they have skewed data is by reporting medians and interquartile ranges. When we encounter this we will note whether the data is skewed and consider the implication of this.

Unit of analysis issues The unit of analysis will be individual participants undergoing pancreatoduodenectomy. We do not anticipate finding any cluster randomised trials for this comparison but if we do identify cluster randomised trials, we will obtain the effect estimate adjusted for the clustering effect. If this is not available, we will perform a sensitivity analysis excluding the trial from the meta-analysis, as the variance of the effect estimate unadjusted for cluster effect is less than the actual variance

that is adjusted for cluster-effect giving inappropriately more weight to the cluster RCT in the meta-analysis.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. laparoscopic pancreatoduodenectomy method 1 versus open pancreatoduodenectomy and laparoscopic pancreatoduodenectomy method 2 versus open pancreatoduodenectomy) must be entered into the same meta-analysis, we will halve the control group to avoid double counting. The alternative way of including such trials with multiple arms is to pool the results of the laparoscopic pancreatoduodenectomy method 1 and laparoscopic pancreatoduodenectomy method 2 and compare it with open pancreatoduodenectomy. We will perform a sensitivity analysis to determine if the results of the two methods of dealing with multi-arm trials lead to different conclusions.

We will calculate the rate ratio (RaR) for outcomes such as adverse events and serious adverse events, where it is possible for the same person to develop more than one adverse event (or serious adverse event), using the inverse variance method provided by RevMan. If the authors have calculated the RaR of adverse events (or serious adverse events) in the intervention versus control based on Poisson regression, we will obtain the RaR by the Poisson regression method in preference to RaR calculated based on the number of adverse events (or serious adverse events) during a certain period.

Dealing with missing data We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). If we are unable to obtain the information from the investigators or study sponsors, we will impute mean from median (i.e. consider median as the mean) and standard deviation from standard error, interquartile range, or P values according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2022), but assess the impact of including such studies as indicated in a sensitivity analysis. If we are unable to calculate the standard deviation from standard error, interquartile range, or P values, we will impute standard deviation as the highest standard deviation in the remaining trials included in the outcome fully aware that this method of

imputation will decrease the weight of the studies in the meta-analysis of MD and shift the effect towards no effect for SMD.

Assessment of heterogeneity We will assess the presence of statistical heterogeneity by visual inspection of the forest plots. We will use the I^2 statistic (Higgins 2003) to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity as per Cochrane Handbook for Systematic Reviews of Interventions (greater than 50% to 60%; Higgins 2022), we report it and investigate possible causes by following the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2022). The assessments of clinical and methodological heterogeneity (i.e. variation in study participants, interventions, outcomes, and characteristics, such as length of follow-up) were supplemented, where appropriate, by information regarding statistical heterogeneity, assessed using the Chi2 test in conjunction with the I2 measure (Higgins 2003). We will assess the included studies for clinical diversity, by considering differences in the participants, setting, interventions and outcomes assessed. We will also consider whether there are methodological differences in the study design, or risk of bias. Diversity in these factors will impact on the decision to pool (or not to pool) data from different studies. We may also consider these sources of heterogeneity when assessing outcomes using the GRADE approach.

Assessment of reporting biases If we are able to pool more than ten trials, we will create and examine a funnel plot to explore possible publication biases. We will use Egger's test to determine the statistical significance of the reporting bias (Egger 1997). We will consider a P value less than 0.05 statistically significant reporting bias.

Data synthesis

We will perform analyses using Review Manager. We plan to restrict the primary analysis to studies judged to be at low risk of bias and some concerns. We plan to perform sensitivity analyses to show how conclusions might be affected if studies at some concerns or a high risk of bias were included. We will calculate the 95% confidence intervals for the treatment effect. We will use the random-effects model. We considered clinical and methodological differences between the studies that might account for the high heterogeneity; training and experience of surgeons may play a role. When standard meta-analysis is not possible, we will perform the following.

1. We will present the information in a table ordered by comparisons and by the sample size of studies.
2. We will perform a meta-analysis of P-values if possible.

If meta-analysis of P-values is not possible, we will use 'vote counting' and the 'sign test' to find out if the intervention is effective. We will not consider the statistical significance of the individual studies for the 'voting counting' method. We will present the information by harvest plot if we use 'vote counting' method. For continuous outcomes, we will also present the weighted median and quartiles of the means or medians when standard meta-analysis is not possible. If we calculated the weighted median and quartiles, we will present this information in a box plot.

Subgroup analysis and investigation of heterogeneity We plan to carry out the following subgroup analyses:

1. people with different anaesthetic risk (ASA I (a healthy person) or II (a person with mild systemic disease) versus ASA III or more (a person with severe systemic disease or worse), as persons with lower ASA are more likely to undergo minimally invasive surgery.
2. people with benign or premalignant disease versus malignant disease, as malignant tumors might be less likely to undergo successful minimally invasive surgery.
3. people with pancreatic ductal adenocarcinoma versus distal cholangiocarcinoma or periampullary cancer or other, as these cancer types exhibit distinct biological behaviours.
4. pylorus preserving versus classical Whipple, as there might be differences in complication rate (such as delayed gastric emptying).
5. tumour size < 2 cm versus > 2 cm, as smaller tumors are more likely to undergo successful minimally invasive surgery.

We will use mortality, serious adverse outcomes, and health-related quality of life in subgroup analyses. We will use the formal Chi2 test to test for subgroup interactions and consider a P-value of 0.05 as statistically significant.

Sensitivity analysis For all outcomes, we will perform sensitivity analysis defined a priori to assess the robustness of our conclusions. This will involve:

1. excluding trials at some concerns or high risk of bias (one of more of the risk of bias domains classified as unclear or high);
2. excluding trials in which either mean or standard deviation, or both are imputed;
3. excluding cluster RCTs in which the adjusted effect estimates are not reported;
4. different methods of dealing with multi-arm trials (see Measures of treatment effect).
5. excluding studies that include only a subset of eligible participants.

We will attempt to contact study authors asking them to provide missing outcome data. Where this is not possible, and the missing data are thought to introduce serious bias, the impact of including such studies in the overall assessment of results will be explored by a sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence We will create summary of findings tables, according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2022), for the following comparisons and critical outcomes:

1. Comparisons
   a. Laparoscopic versus open pancreatoduodenectomy
   b. Robotic versus open pancreatoduodenectomy
   c. Robotic versus laparoscopic pancreatoduodenectomy

2. Outcomes
   a. Short-term mortality (in-hospital mortality or mortality within three months)
   b. Long-term mortality (latest available time point 1 year or more from randomisation)
   c. Health-related quality of life (latest available time point)
   d. Serious adverse events (within three months)

We will use the overall RoB 2 judgement to feed into the GRADE assessment. We will use the five GRADE considerations (risk of bias, inconsistency, indirectness, imprecision, and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the pre-specified outcomes. We will use methods and recommendations described in Chapter 14 of the Cochrane

Handbook (Higgins 2022) and using GRADEpro software (GRADEprofiler). Two review authors (DR and PB) will independently assess the certainty of the evidence. Any disagreement will be resolved by discussion or by involving a third assessor (KG). We will justify all decisions to down- or up-grade the quality of studies using footnotes and make comments to aid reader's understanding of the review where necessary. We will consider whether there is any additional outcome information that was not able to be incorporated into meta-analyses and note this in the comments and state if it supports or contradicts the information from the meta-analyses.

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will give the reader a clear sense where the focus of any future research in the area should be and what the remaining uncertainties are.

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Editorial contributions

Cochrane GUT Group supported the authors in the development of this systematic review protocol. The following people conducted the editorial process for this article:

Sign-off Editor (final editorial decision): Grigorios Leontiadis, McMaster University, Canada; Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Marwah Anas El-Wegoud, Cochrane Central Editorial Service; Editorial Assistant (conducted editorial policy checks and supported

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Appendices

Appendix 2. Cochrane Central search strategy (via Ovid)

1. exp Pancreatic Neoplasms/
2. (pancreas* adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour*or malignan* or adenocarcinoma* or cystic or cyst or cysts)).tw,kw.
3. ((periampull* or peri-ampull*) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour*or malignan* or adenocarcinoma*)).tw,kw.
4. (intraductal papillary mucinous neoplasia* or IPMN or IPMNs).tw,kw.
5. exp Duodenal Neoplasms/
6. exp Bile Duct Neoplasms/
7. (((ampulla* adj5 (hepatopancreatic or vater*)) or ampullovateric) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
8. ((duodenal or duodenum or bile duct or biliary or (papillar adj vater*) or choledoch* or alcholedoch* or cholangio* or gall duct) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
9. exp Pancreatitis, Chronic/
10. chronic pancreatitis.tw,kw.
11. or/1-10
12. exp Pancreaticoduodenectomy/ or exp pancreaticojejunostomy/
13. exp Pancreatectomy/
14. (pancreaticoduodenectom* or pancreatoduodenectom* or duodenopancreatectom* or pancreatectom* or hemipancreatectom* or pancreaticojejunostom* or pancreatojejunostom*).tw,kw.
15. (pancreas* and (duodenectom* or Whipple or PPPD or Pylorus-Preserv*)).tw,kw.
16. (pancrea* adj3 (surger* or surgical or operat* or resect* or remov*)).tw,kw.
17. or/12-16
18. 11 and 17
19. exp Laparoscopy/
20. laparoscop*.tw,kw.
21. (peritoneoscop* or celioscop* or coelioscop*).tw,kw.
22. robot*.tw,kw.
23. (minimal* adj invasive).tw,kw.
24. exp Surgical Procedures, Minimally Invasive/
25. or/19-24
26. 18 and 25

Appendix 3. Medline Search strategy (via Ovid)

1. exp Pancreatic Neoplasms/
2. (pancreas* adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour*or malignan* or adenocarcinoma* or cystic or cyst or cysts)).tw,kw.
3. ((periampull* or peri-ampull*) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour*or malignan* or adenocarcinoma*)).tw,kw.
4. (intraductal papillary mucinous neoplasia* or IPMN or IPMNs).tw,kw.
5. exp Duodenal Neoplasms/
6. exp Bile Duct Neoplasms/
7. (((ampulla* adj5 (hepatopancreatic or vater*)) or ampullovateric) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
8. ((duodenal or duodenum or bile duct or biliary or (papillar adj vater*) or choledoch* or alcholedoch* or cholangio* or gall duct) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
9. exp Pancreatitis, Chronic/
10. chronic pancreatitis.tw,kw.
11. or/1-10
12. exp Pancreaticoduodenectomy/ or exp pancreaticojejunostomy/
13. exp Pancreatectomy/
14. (pancreaticoduodenectom* or pancreatoduodenectom* or duodenopancreatectom* or pancreatectom* or hemipancreatectom* or pancreaticojejunostom* or pancreatojejunostom*).tw,kw.
15. (pancreas* and (duodenectom* or Whipple or PPPD or Pylorus-Preserv*)).tw,kw.
16. (pancrea* adj3 (surger* or surgical or operat* or resect* or remov*)).tw,kw.
17. or/12-16
18. 11 and 17
19. exp Laparoscopy/
20. laparoscop*.tw,kw.
21. (peritoneoscop* or celioscop* or coelioscop*).tw,kw.
22. exp Robotic Surgical Procedures/
23. robot*.tw,kw.
24. (minimal* adj invasive).tw,kw.
25. exp Minimally Invasive Surgical Procedures/
26. or/19-25

27. 18 and 26
28. randomized controlled trial.pt.
29. controlled clinical trial.pt.
30. randomized.ab.
31. placebo.ab.
32. randomly.ab.
33. trial.ab.
34. groups.ab.
35. or/28-34
36. exp animals/ not humans.sh.
37. 35 not 36
38. 27 and 37
39. remove duplicates from 38

Note: lines #28-37. Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format, excluded "drug therapy.fs."

Appendix 4. Embase search strategy (via Ovid)

1. exp pancreas tumor/
2. (pancreas* adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour*or malignan* or adenocarcinoma* or cystic or cyst or cysts)).tw,kw.
3. ((periampull* or peri-ampull*) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour*or malignan* or adenocarcinoma*)).tw,kw.
4. (intraductal papillary mucinous neoplasia* or IPMN or IPMNs).tw,kw.
5. exp duodenum tumor/
6. exp bile duct tumor/
7. (((ampulla* adj5 (hepatopancreatic or vater*)) or ampullovateric) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
8. ((duodenal or duodenum or bile duct or biliary or (papillar adj vater*) or choledoch* or alcholedoch* or cholangio* or gall duct) adj5 (neoplas* or cancer* or carcinoma* or tumor* or tumour* or malignan* or adenocarcinoma*)).tw,kw.
9. chronic pancreatitis/
10. chronic pancreatitis.tw,kw.
11. or/1-10
12. exp pancreaticoduodenectomy/ or exp pancreaticojejunostomy/
13. exp pancreas resection/
14. (pancreaticoduodenectom* or pancreatoduodenectom* or duodenopancreatectom* or pancreatectom* or hemipancreatectom* or pancreaticojejunostom* or pancreatojejunostom*).tw,kw.
15. (pancreas* and (duodenectom* or Whipple or PPPD or Pylorus-Preserv*)).tw,kw.
16. (pancrea* adj3 (surger* or surgical or operat* or resect* or remov*)).tw,kw.
17. or/12-16
18. 11 and 17
19. exp laparoscopy/
20. laparoscop*.tw,kw.
21. (peritoneoscop* or celioscop* or coelioscop*).tw,kw.
22. exp robotics/
23. robot*.tw,kw.
24. (minimal* adj invasive).tw,kw.
25. exp minimally invasive surgery/
26. or/19-25
27. 18 and 26
28. random:.tw.
29. placebo:.mp.
30. double-blind:.tw.
31. or/28-30
32. exp animal/ not human.sh.
33. 31 not 32
34. 27 and 33

Lines #28-31, Hedge Best balance of sensitivity and specificity filter for identifying randomized trials in Embase. https://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx

Appendix 5. ClinicalTrials.gov search strategy

"Interventional" [STUDY-TYPES] AND pancreticoduodenectomy [INTERVENTION]

Appendix 6. WHO ICTRP search strategy

pancrea* AND laparoscop*
pancrea* AND minimal*
pancrea* AND robot

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Chapter 5

Diagnostic accuracy of different imaging modalities following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer

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Abstract

Background

Periampullary cancer includes cancer of the head and neck of the pancreas, cancer of the distal end of the bile duct, cancer of the ampulla of Vater, and cancer of the second part of the duodenum. Surgical resection is the only established potentially curative treatment for pancreatic and periampullary cancer. A considerable proportion of patients undergo unnecessary laparotomy because of underestimation of the extent of the cancer on computed tomography (CT) scanning. Other imaging methods such as magnetic resonance imaging (MRI), positron emission tomography (PET), PET-CT, and endoscopic ultrasound (EUS) have been used to detect local invasion or distant metastases not visualised on CT scanning which could prevent unnecessary laparotomy. No systematic review or meta-analysis has examined the role of different imaging modalities in assessing the resectability with curative intent in patients with pancreatic and periampullary cancer.

Objectives

To determine the diagnostic accuracy of MRI, PET scan, and EUS performed as an add-on test or PET-CT as a replacement test to CT scanning in detecting curative resectability in pancreatic and periampullary cancer.

Search methods

We searched MEDLINE, Embase, Science Citation Index Expanded, and Health Technology Assessment (HTA) databases up to 5 November 2015. Two review authors independently screened the references and selected the studies for inclusion. We also searched for articles related to the included studies by performing the "related search" function in MEDLINE (OvidSP) and Embase (OvidSP) and a "citing reference" search (by searching the articles that cite the included articles).

Selection criteria

We included diagnostic accuracy studies of MRI, PET scan, PET-CT, and EUS in patients with potentially resectable pancreatic and periampullary cancer on CT scan. We accepted any criteria of resectability used in the studies. We included studies irrespective of language, publication status, or study design (prospective or retrospective). We excluded case-control studies.

Data collection and analysis

Two review authors independently performed data extraction and quality assessment using the QUADAS-2 (quality assessment of diagnostic accuracy studies - 2) tool. Although we planned to use bivariate methods for analysis of sensitivities and specificities, we were able to fit only the univariate fixed-effect models for both sensitivity and specificity because of the paucity of data. We calculated the probability of unresectability in patients who had a positive index test (post-test probability of unresectability in people with a positive test result) and in those with negative index test (post-test probability of unresectability in people with a positive test result) using the mean probability of unresectability (pre-test probability) from the included studies and the positive and negative likelihood ratios derived from the model. The difference between the pre-test and post-test probabilities gave the overall added value of the index test compared to the standard practice of CT scan staging alone.

Main results

Only two studies (34 participants) met the inclusion criteria of this systematic review. Both studies evaluated the diagnostic test accuracy of EUS in assessing the resectability with curative intent in pancreatic cancers. There was low concerns about applicability for most domains in both studies. The overall risk of bias was low in one study and unclear or high in the second study. The mean probability of unresectable disease after CT scan across studies was 60.5% (that is 61 out of 100 patients who had resectable cancer after CT scan had unresectable disease on laparotomy). The summary estimate of sensitivity of EUS for unresectability was 0.87 (95% confidence interval (CI) 0.54 to 0.97) and the summary estimate of specificity for unresectability was 0.80 (95% CI 0.40 to 0.96). The positive likelihood ratio and negative likelihood ratio were 4.3 (95% CI 1.0 to 18.6) and 0.2 (95% CI 0.0 to 0.8) respectively. At the mean pre-test probability of 60.5%, the post-test probability of unresectable disease for people with a positive EUS (EUS indicating unresectability) was 86.9% (95% CI 60.9% to 96.6%) and the post-test probability of unresectable disease for people with a negative EUS (EUS indicating resectability) was 20.0% (5.1% to 53.7%). This means that 13% of people (95% CI 3% to 39%) with positive EUS have potentially resectable cancer and 20% (5% to 53%) of people with negative EUS have unresectable cancer.

Authors' conclusions

Based on two small studies, there is significant uncertainty in the utility of EUS in people with pancreatic cancer found to have resectable disease on CT scan. No studies have assessed the utility of EUS in people with periampullary cancer.

There is no evidence to suggest that it should be performed routinely in people with pancreatic cancer or periampullary cancer found to have resectable disease on CT scan.

Table 1: Summary of Findings

Population	People with pancreatic cancer found to resectable on computed tomography (CT) scan	
Setting	Secondary or tertiary setting	
Index test	Endoscopic ultrasound (EUS)	
Reference standard	Laparotomy (surgeon's judgement of unresectability)	
Number of studies	2 studies (38 participants)	
Summary sensitivity	0.87 (95% confidence interval (CI) 0.54 to 0.97)	
Summary specificity	0.80 (95% CI 0.40 to 0.96)	
Consistent results	Yes	
Overall risk of bias	Moderate to high	
Other limitations	1. Both studies included pancreatic cancers only. 2. One study included only participants with pancreatic cancer less than 3 cm. 3. We could only perform the univariate fixed-effect model and we were unable to compare the model fit with other models.	
Pre-test probability of unresectability from included studies	Post-test probability of unresectability in people with positive EUS (EUS indicating unresectability) (95% CI)	Post-test probability of unresectability in people with negative EUS (EUS indicating resectability) (95% CI)
Minimum = 53%	83% (53% to 95%)	16% (4% to 46%)
Mean = 61%	87% (61% to 97%)	20% (5% to 54%)
Maximum = 67%	90% (67% to 97%)	25% (7% to 61%)
Interpretation	There is significant uncertainty in the results because of inadequate data	

We reported all probabilities in the table as percentages.
Abbreviations: CI: confidence interval; EUS: endoscopic ultrasound.

Background

Periampullary cancer develops near the ampulla of Vater (National Cancer Institute 2014a). Periampullary cancer includes cancer of the head and neck of the pancreas, cancer of the distal end of the bile duct, cancer of the ampulla of Vater, and cancer of the second part of the duodenum. Pancreatic cancer (pancreatic cancer) is the tenth most common cancer in the USA, the fifth most common cause of cancer-related mortality in the east and the fourth most common cause of cancer-related mortality in the west (Parkin 2001; Parkin 2005; Yamamoto 1998). In 2012, 338,000 new patients were diagnosed with pancreatic cancer and there were 330,000 deaths due to pancreatic cancer globally (IARC 2014). There is global variation in the incidence of pancreatic cancers, with an age-standardised annual incidence rate of 7.2 per 100,000 population in the more developed regions and an age-standardised annual incidence rate of 2.8 per 100,000 population in the less developed regions (IARC 2014). A similar trend is noted in the age-standardised annual mortality rates, of 6.8 per 100,000 population in the more developed regions and an age-standardised annual mortality rate of 2.7 per 100,000 population in the less developed regions due to pancreatic cancer (IARC 2014).

Pancreaticoduodenectomy is the main treatment for cancers that arise in the head of the pancreas, ampulla, and second part of the duodenum. Surgical resection is generally considered the only treatment that can cure pancreatic cancer. However, only 15% to 20% of patients with pancreatic cancers undergo potentially curative resection (Conlon 1996; Engelken 2003; Michelassi 1989; Shahrudin 1997; Smith 2008). The overall five-year survival after radical resection ranges from 7% to 25% (Cameron 1993; Livingston 1991; Niederhuber 1995; Nitecki 1995; Orr 2010; Trede 1990), with a median survival of 11 to 15 months (British Management Guideline 2005). With adjuvant chemotherapy, the median survival after radical resection varies between 14 and 24 months (Liao 2013). In all other patients, the cancers are not resected because of infiltration of local structures, disseminated disease, or because the patient is deemed unfit to undergo major surgery. Computed tomography (CT) scan is generally used for staging pancreatic and periampullary cancers (National Cancer Institute 2014b). Despite undergoing routine CT scanning to stage the disease, a substantial proportion of patients (approximately 40%) undergo unnecessary laparotomy (opening the abdomen using a large incision)

with lack of curative resectability identified only during the laparotomy (Allen 2016). Staging laparoscopy or diagnostic laparoscopy may decrease the proportion of patients that undergo unnecessary laparotomy to approximately 17% (Allen 2016). Tests, such as magnetic resonance imaging (MRI), positron emission tomography (PET) scan, or endoscopic ultrasound (EUS), may be used in addition to CT scan to assess resectability with curative intent and decrease the proportion of patients who undergo unnecessary laparotomy.

Target condition being diagnosed

Inability to perform curative resectability of pancreatic and periampullary cancer ("unresectable" cancers).

Index test(s)

MRI MRI involves the use of a powerful magnet to produce images of different tissues of the body. This is also called nuclear MRI (NMRI) (National Cancer Institute 2014c). Features, such as extent of the cancer in terms of involvement of adjacent structures and spread of cancer to distant areas (metastases), are taken into account to assess resectability with curative intent. The radiologist usually interprets the images.

PET PET involves the use of a small amount of radioactive glucose (sugar) to differentiate between different tissues. It utilises the property that cancer cells often use more glucose than normal cells. It is also called PET scan (National Cancer Institute 2014d). This is a form of functional imaging. Cancerous lesions appear as areas of increased uptake. The presence of cancer in different locations and metastases are taken into account to assess resectability with curative intent. The radiologist usually interprets the images.

PET-CT scan PET scan can be combined with CT scan (PET-CT scan), with both tests performed at the same time (National Cancer Institute 2014e). This allows superimposition of the two images by identifying corresponding points of the body in the two scans (coregistration) and allows the combination of the functional imaging (PET scan) with an anatomical imaging (CT scan), which may result in better diagnostic accuracy than either modality alone (National Cancer Institute 2014e). Usually, the radiologist interprets the images.

EUS EUS involves the use of an endoscope, a camera introduced into the body cavities to view the inside of the body. An ultrasound (high-energy sound waves) probe at the end of the endoscope is used to differentiate different tissues. This is also called endosonography and EUS (National Cancer Institute 2014f). Local extent and metastases are taken into account to assess resectability with curative intent. The endoscopist usually interprets the images.

Clinical pathway

There is no standard algorithm currently available to assess the resectability of pancreatic and periampullary cancers, with different clinicians following their own algorithms based on either their clinical experience or what they have been taught. Currently, almost all algorithms include a CT scan as one of the tests (National Cancer Institute 2014b). CT may be the only test performed before laparotomy. Other tests, such as diagnostic laparoscopy, PET (PET scan or PET-CT scan), MRI, or EUS, may be used in addition to CT scan to assess resectability. We have presented the possible clinical pathway in the staging of pancreatic cancers in Figure 1.

Prior test(s) The minimum prior test should be CT and the cancer should be resectable with curative intent on the basis of the CT scan. Other imaging modalities, such as MRI, PET scan, PET-CT, or EUS, might be used in addition to CT scanning to assess resectability before performing the imaging modality being assessed.

Role of index test(s) MRI, PET scan, and EUS can be considered as add-on tests to the CT scan prior to laparotomy done with the intention of performing a potentially curative resection. PET-CT scan can be considered as a replacement for CT scan prior to laparotomy done with the intention of performing a potentially curative resection. It can also be considered as an add-on test to the CT scan prior to laparotomy. Although it appears strange to use PET-CT scan as an add-on test to CT scan, such an approach is possible if patients are referred to the referral centre with a CT scan. It should be noted that PET and CT scan should be performed simultaneously to allow coregistration. However, the problem with PET-CT scan as a replacement for CT scan is that PET-CT has to be performed without contrasts and hence PET-CT alone may not provide as good an information as PET-CT along with conventional CT scan.

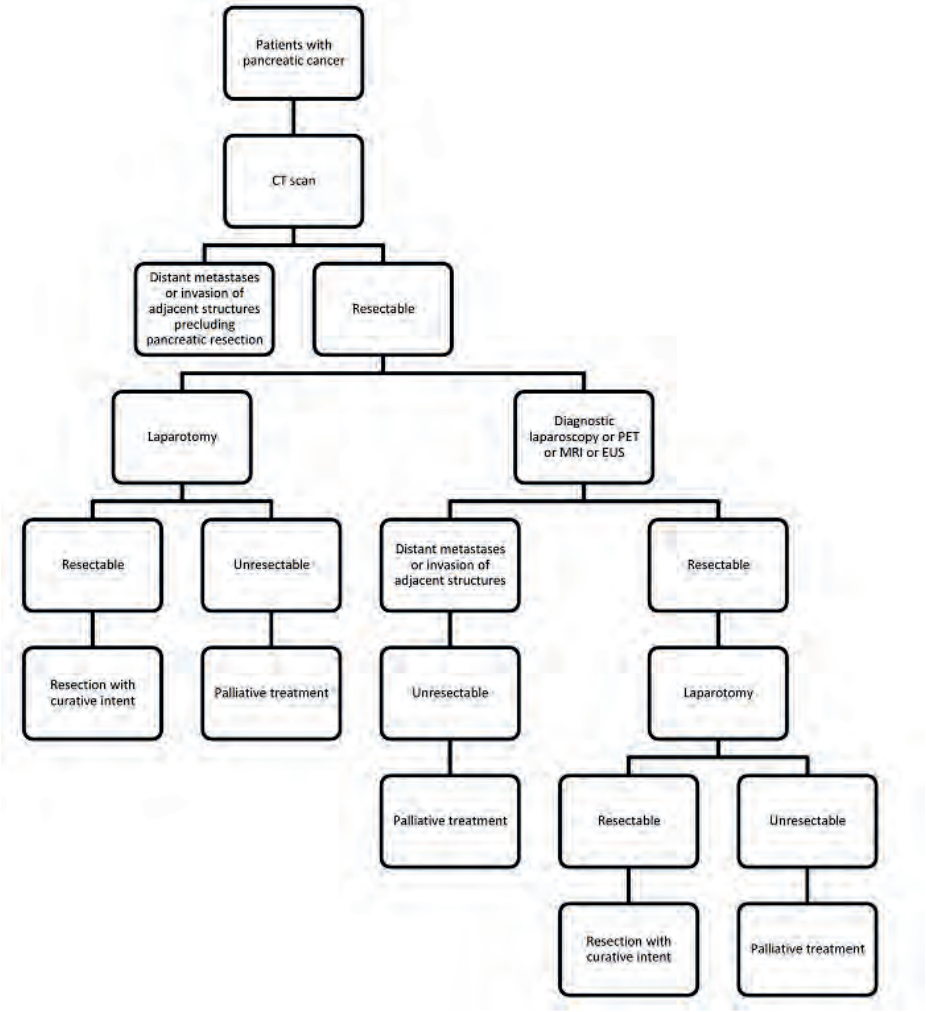

Figure 1. Clinical pathway for the staging of pancreatic cancers.

Alternative test(s) Diagnostic laparoscopy or laparoscopic ultrasound may be used as an alternative test to these imaging modalities in patients considered to have CT resectable pancreatic and periampullary cancer (Allen 2016; Hariharan 2010). Another Cochrane review has assessed the accuracy of diagnostic laparoscopy (Allen 2016).

Rationale

The different imaging modalities identify the extent of local spread, including invasion of adjacent blood vessels, and may identify distal metastases

(MRI, PET scan, PET-CT scan). If this add-on test (or replacement test in the case of PET-CT scan in patients who are referred without a CT scan) can identify unresectable cancers without laparotomy, it might decrease the costs and morbidity associated with unnecessary laparotomy. Currently there is no Cochrane review that has assessed the diagnostic accuracy of these imaging modalities in the assessment of the curative resectability of pancreatic and periampullary cancers.

Objectives

To determine the diagnostic accuracy of MRI, PET scan, and EUS performed as an add-on test or PET-CT as an add-on or replacement test to CT scanning in detecting curative resectability in pancreatic and periampullary cancer.

Secondary objectives

We planned to explore the following sources of heterogeneity.

1. Studies at low risk of bias versus those at unclear or high risk of bias (as assessed by the QUADAS-2 tool, recommended by the Cochrane Diagnostic Test Accuracy Group) (Whiting 2006; Whiting 2011).
2. Full text publications versus abstracts (this can give a clue about publication bias since there may be an association between the results of the study and the study reaching full publication status) (Eloubeidi 2001).
3. Prospective studies versus retrospective studies.
4. Proportion of patients with pancreatic cancer, ampullary cancer, and duodenal cancers (although classified as periampullary cancers they each have a different prognosis) (Klempnauer 1995). The additional value of the imaging modalities may be different because of the extent of spread in these different types of periampullary cancers.
5. Different definitions for resectable cancer on laparotomy. Different surgeons may consider cancer unresectable differently i.e. different surgeons would have different criteria for unresectability on laparotomy (other than the consensus criteria for resectability). For example, one surgeon may judge that the cancer is unresectable on laparotomy because of the involvement of the local vessels (mainly portal vein and superior mesenteric vein) and consider the reference standard to be positive. This would result in a false negative result for

the imaging modality. Another surgeon may judge the same cancer to be resectable despite the involvement of the vessel and proceed with resection. The reference standard would be negative in this situation, which would result in a true negative result for the imaging modality. This might have an intrinsic threshold effect.

6. Additional pre-tests performed (besides CT scan). This can alter the pre-test probability of unresectability and can help in the assessment of the additional value of the imaging modality under various situations.

Methods

Criteria for considering studies for this review

Types of studies We only included studies that provided diagnostic test accuracy data (true positive, false positive, false negative, and true negative) on the different imaging modalities mentioned above in the appropriate patient population (see below) irrespective of language, publication status, or whether data were collected prospectively or retrospectively. However, we excluded case reports which do not provide sufficient diagnostic test accuracy data. We also planned to exclude any identified case-control studies because case-control studies are prone to bias (Whiting 2011).

Participants Adults considered for curative resection of pancreatic or periampullary cancer on the basis of CT findings, who were fit to undergo major surgery. We included patients in this review irrespective of whether they underwent other imaging modalities prior to imaging modality being assessed.

Index tests MRI, PET scan, PET-CT scan, or EUS.

Target conditions The target conditions were unresectable pancreatic and periampullary cancers, that is, we considered the imaging modality a positive test if the pancreatic or periampullary cancer is unresectable with curative intent. In these cancers it is not possible to perform curative resectability. Clinically, it may not be easy to distinguish head of pancreas cancers, ampullary cancers, and cancer of the second part of the duodenum. The treatment for these different cancers is the same, i.e. pancreatoduodenectomy and the final confirmation as to the origin of these cancers may be done after resection without definitive diagnosis of the

origin of the cancer, as long as the cancers are resectable. So we considered these cancers together. There are no uniform criteria for resectability of pancreatic and periampullary cancer. Consensus exists for the definition of borderline resectable cancers (Abrams 2009). Therefore, where there is less tissue involvement than in a borderline resectable cancer the tumour can be considered as resectable. We accepted any criteria of resectability used by the study authors and acknowledge that this could potentially create a threshold effect. In general, the cancer will not be resected if liver, peritoneal, or distal nodal metastases were noted, or if the cancer had invaded important adjacent blood vessels that are beyond the criteria for borderline resectable cancers (for example, greater than 180° involvement of the superior mesenteric artery) (Abrams 2009).

Reference standards Confirmation of liver, peritoneal, or nodal metastatic involvement by histopathological examination of suspicious (liver, peritoneal, or nodal metastatic) lesions obtained at diagnostic laparoscopy or laparotomy. We accepted only paraffin section histology as the reference standard. In clinical practice, depending on the urgency of the results, a frozen section biopsy may be done to obtain immediate results. However, this is always confirmed by subsequent paraffin section histology (which can take several days) because frozen section biopsy is not as reliable as paraffin section histology. We also accepted the surgeon's judgement of unresectability at laparotomy when biopsy confirmation was not possible as an alternate reference standard. For example, if the tumour has invaded the adjacent blood vessels the surgeon may not resect the tumour because of the danger posed by resecting part of a large blood vessel, and so biopsy confirmation cannot be obtained. However, it should be noted that a surgeon's judgement of unresectability at laparotomy is a subjective decision and is a possible source of error in the reference standard. In the absence of an ethical and true gold standard, we accepted this as a reference standard.

Search methods for identification of studies

We included all studies irrespective of the language of publication and publication status. We translated any non-English articles we found to assess eligibility.

Electronic searches We searched the following databases on 5 November 2015.

1. MEDLINE (In-Process & Non-Indexed Citations) via OvidSP (January 1946 to 5 November 2015; Appendix 2*).
2. Embase via OvidSP (January 1947 to 5 November 2015; Appendix 3*).
3. Science Citation Index Expanded (including Conference Proceedings Citation Index - Science) via Web of Knowledge (January 1980 to 5 November 2015; Appendix 4*).
4. National Insitute for Health Research - Health Technology Assessment (NIHR HTA) (November 2015) through the University of York Centre for Reviews and Dissemination (www.crd.york.ac.uk/CRDWeb/) (Appendix 5*).

We included sensitivity maximising diagnostic filters for searching MEDLINE and Embase databases (Haynes 2004; Wilczynski 2005). This is because we retrieved more than 40,000 references when we used the original searches without the filters.

Searching other resources We searched the references of the included studies to identify additional studies. We also searched for articles related to the included studies by performing the "related search" function in MEDLINE (OvidSP) and Embase (OvidSP) and a "citing reference" search (by searching the articles which cite the included articles) (Sampson 2008) in Science Citation Index Expanded, MEDLINE (OvidSP), and Embase (OvidSP).

Data collection and analysis

Selection of studies Two review authors (DT and KSG) independently screened the results ofthe search strategy to identify relevant studies. We obtained the full-text articles of references that at least one of the review authors considered relevant. Two review authors (DT and KSG or DR) independently screened the full-text papers against the inclusion criteria. We did not have any differences in study selection based on our full-text article assessments. If the eligibility of the report was unclear, we attempted to contact the study authors to seek clarification. Since we were unable to contact the study authors, we excluded the reports. We listed all excluded studies and their reasons for exclusion in the Characteristics of excluded studies table). Also, we constructed a PRISMA diagram to illustrate the study selection process.

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*. Appendices were not printed here due to space limitations and may be accessed at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011515.pub2/full)

Data extraction and management Two review authors (DT and KSG) independently extracted the following data from each included study using a data extraction form that KSG designed and piloted. We resolved any differences by discussion.

1. First author.
2. Year of publication.
3. Study design (prospective or retrospective; cross-sectional studies or randomised controlled trials).
4. Inclusion and exclusion criteria for individual studies.
5. Total number of patients.
6. Number of females.
7. Average age of the participants.
8. Type of cancer (i.e. head and neck of pancreas, body and tail of pancreas, ampullary cancers, duodenal cancer).
9. Criteria for unresectability at the index test and at laparotomy (reference standard).
10. Preoperative tests carried out prior to index test.
11. Description of the index test.
12. Reference standard.
13. Number of true positives, false positives, false negatives, and true negatives.

The unit of analysis was the patient, meaning that if multiple metastases or multiple infiltrations of adjacent structures were found in a patient with a negative index test, we planned to consider the number of false negatives to be one. This is because it is the presence, rather than the number of metastases or the number of infiltrations of adjacent structures, that is important in determining the curative resectability of patients. We planned to consider patients with uninterpretable index test results (no matter the reason given for lack of interpretation) as negative for the test since in clinical practice laparotomy would be carried out on these patients. However, we planned to include such patients in the analysis only if the results of laparotomy were available. We sought further information from the study authors if necessary.

If the same study reported multiple index tests, we planned to extract the number of true positives, false positives, false negatives, and true negatives for each index test. If there was an overlap of participants between multiple

reports as suspected by common authors and centres, we planned to contact the study authors to seek clarification about the overlap. If we were unable to contact the authors, we planned to extract the maximum possible information from all the reports. However, we did not any find such reports.

Assessment of methodological quality Two review authors (DT and KSG) independently assessed study quality using the QUADAS-2 assessment tool (Whiting 2006; Whiting 2011). We resolved differences through discussion, based on the criteria published in the protocol (Gurusamy 2015). We have presented the criteria that we used to classify the different studies in Table 2. We considered studies which are classified as "low risk of bias" and "low concern" in all the domains as studies with high methodological quality. We planned to present the results in a "Risk of bias" summary and graphs, but because there were only two studies, we have presented the "Risk of bias" summary only.

Table 1. QUADAS-2 classification

Domain 1: patient selection	Patient sampling	Patients with pancreatic and periampullary cancer considered eligible for surgical resection following a computed tomography (CT) scan.
	Was a consecutive or random sample of patients enrolled?	Yes: if the study included a consecutive sample or a random sample of patients with pancreatic and periampullary cancer eligible for surgical resection after CT scan. No: if the study did not include a consecutive sample or a random sample of patients with pancreatic and periampullary cancer eligible for surgical resection after CT scan. Unclear: if this information was unavailable.
	Was a case-control design avoided?	Yes: if the study assessed a cohort of patients about to undergo surgical resection. No: if the study compared patients who underwent unsuccessful laparotomy (cases) with patients who underwent successful surgical resection (controls). We planned to exclude such studies but did not find any case-control studies that met the other inclusion criteria. Unclear: as anticipated, we were able to determine whether the design was case-control.
	Did the study avoid inappropriate exclusions?	Yes: if the study included all patients with pancreatic and periampullary cancer eligible for surgical resection. No: if the study excluded patients based on high probability of resectability (for example, small tumours). Unclear: if this information was unavailable.
	Could the selection of patients have introduced bias?	Low risk of bias: if "yes" classification for all the above 3 questions. High risk of bias: if "no" classification for any of the above 3 questions. Unclear risk of bias: if "unclear" classification for any of the above 3 questions but without a "no" classification for any of the above 3 questions.
	Patient characteristics and setting	Yes: we included only patients with pancreatic and periampullary cancer who were considered eligible for surgical resection following a CT scan. So, we anticipated that we would classify all the included studies as "yes". No: we excluded studies that considered patients unsuitable for surgery after a CT scan. So, we did not use this classification. Unclear: we excluded studies in which it is unclear whether the patients had undergone CT scan following which they were still considered suitable for surgical resection. So, we classified all studies included in the review as "yes" for this item, as anticipated.
	Are there concerns that the included patients and setting do not match the review question?	Considering the inclusion criteria of this review, as anticipated, we classified all the included studies as "low concern".

Table 1. Continued

Domain 2: index test	Index test(s)	Magnetic resonance imaging (MRI), positron emission tomography (PET), PET-CT, endoscopic ultrasound (EUS)
	Were the index test results interpreted without knowledge of the results of the reference standard?	The index test would always be conducted though not interpreted before the reference standard. Yes: if the index test was conducted and interpreted without the knowledge of the results of the reference standard. No: if the index test was interpreted with the knowledge of the results of the reference standard. Unclear: if it was unclear whether the index test was interpreted without the knowledge of the results of the reference standard.
	If a threshold was used, was it prespecified?	Not applicable.
	Could the conduct or interpretation of the index test have introduced bias?	Low risk of bias: if "yes" classification for the only relevant question in this domain. High risk of bias: if "no" classification for the only relevant question in this domain. Unclear risk of bias: if "unclear" classification for the only relevant question in this domain.
	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low concern: if the criteria for positive index test was clearly stated. High concern: if the criteria for positive index test was not stated.
Domain 3: target condition and reference standard	Target condition and reference standard(s)	Unresectability. The reasons for unresectability include involvement of adjacent structures or distant metastases. There is currently no universal criteria for unresectability. Consensus exists for the definition of borderline resectable cancers (Abrams 2009). Therefore, where there is less tissue involvement than in a borderline resectable cancer the tumour can be considered as resectable. Positive reference standard: confirmation of liver or peritoneal involvement by histopathological examination of suspicious (liver or peritoneal) lesions (irrespective of how the tissues were obtained for histopathological examination). We accepted only paraffin section histology as the reference standard. We also accepted the surgeon's judgement of unresectability on laparotomy when biopsy confirmation was not possible (for example, the surgeon may not resect the tumour if it invaded the adjacent blood vessels but would not obtain a biopsy confirmation of this because of the danger posed by resecting a part of a large blood vessel). However, it should be noted that surgeon's judgement of unresectability at laparotomy is a subjective decision and is a possible source of error in the reference standard but in the absence of an ethical and true gold standard, we accepted this as a reference standard. Negative reference standard: cancer was fully resected i.e. clear resection margins on histology.
	Is the reference standards likely to correctly classify the target condition?	Yes: if histological confirmation of distant spread or local infiltration of adjacent structures making the cancer unresectable was obtained. The report on the resection margins shows clearly that the cancer had been completely resected. As anticipated, none of the included studies met these criteria because of the danger that biopsy of infiltration of adjacent structures poses. No: if resection margins were not clear of cancer. Unclear: if surgeons' judgement was used to assess unresectability or if the information about the resection margins was unavailable. As anticipated, we classified both included studies as "unclear" because the studies used the surgeons' judgement as a criterion for unresectability.

Table 1. Continued

Target condition and reference standard(s)	Unresectability. The reasons for unresectability include involvement of adjacent structures or distant metastases. There is currently no universal criteria for unresectability. Consensus exists for the definition of borderline resectable cancers (Abrams 2009). Therefore, where there is less tissue involvement than in a borderline resectable cancer the tumour can be considered as resectable. Positive reference standard: confirmation of liver or peritoneal involvement by histopathological examination of suspicious (liver or peritoneal) lesions (irrespective of how the tissues were obtained for histopathological examination). We accepted only paraffin section histology as the reference standard. We also accepted the surgeon's judgement of unresectability on laparotomy when biopsy confirmation was not possible (for example, the surgeon may not resect the tumour if it invaded the adjacent blood vessels but would not obtain a biopsy confirmation of this because of the danger posed by resecting a part of a large blood vessel). However, it should be noted that surgeon's judgement of unresectability at laparotomy is a subjective decision and is a possible source of error in the reference standard but in the absence of an ethical and true gold standard, we accepted this as a reference standard. Negative reference standard: cancer was fully resected i.e. clear resection margins on histology.
Is the reference standards likely to correctly classify the target condition?	Yes: if histological confirmation of distant spread or local infiltration of adjacent structures making the cancer unresectable was obtained. The report on the resection margins shows clearly that the cancer had been completely resected. As anticipated, none of the included studies met these criteria because of the danger that biopsy of infiltration of adjacent structures poses. No: if resection margins were not clear of cancer. Unclear: if surgeons' judgement was used to assess unresectability or if the information about the resection margins was unavailable. As anticipated, we classified both included studies as "unclear" because the studies used the surgeons' judgement as a criterion for unresectability.
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes: if the reference standard was interpreted without the knowledge of the results of the index test. No: if the reference standard was interpreted with the knowledge of the results of the index test. Unclear: it was unclear if the reference standard was interpreted without the knowledge of the results of the index test. However, the results of the index test are unlikely to influence the results of the reference standard. So, we did not take the answer to this question into account to determine the risk of bias.
Could the reference standard, its conduct, or its interpretation have introduced bias?	We determined the risk of bias as "low" if the answer to the first question was "yes", "high" if the answer to the first question was "no", and "unclear" if the answer to the first question was "unclear".
Are there concerns that the target condition as defined by the reference standard does not match the question?	Considering the inclusion criteria for this review, we classified all the included studies as "low concern", as anticipated.

Table 1. Continued

Domain 4: flow and timing	Flow and timing	The cancer may progress if there is a long time interval between index test and laparotomy. So, we chose an arbitrary time interval of 2 months as an acceptable time interval between index test and laparotomy.
	Was there an appropriate interval between index test and reference standard?	Yes: if the time interval between index test and laparotomy was less than 2 months. No: if the time interval between index test and laparotomy was more than 2 months. Unclear: if the time interval between index test and laparotomy was unclear.
	Did all patients receive the same reference standard?	Yes: if all the patients received the same reference standard (we classified all the included studies as "yes", as anticipated). No: if different patients received different reference standards. Unclear: if this information was unclear.
	Were all patients included in the analysis?	Yes: if the study included all the patients in the analysis irrespective of whether the results were uninterpretable. No: if the study excluded some patients from the analysis because of uninterpretable results. Unclear: if this information was unclear.
	Could the patient flow have introduced bias?	Low risk of bias: if "yes" classification for all the above 3 questions. High risk of bias: if "no" classification for any of the above 3 questions. Unclear risk of bias: if "unclear" classification for any of the above 3 questions but without a "no" classification for any of the above 3 questions.

Abbreviations: CT: computed tomography; EUS: endoscopic ultrasound; MRI: magnetic resonance imaging; PET: positron emission tomography.

Statistical analysis and data synthesis We plotted study estimates of sensitivity and specificity on forest plots and in receiver operating characteristic (ROC) space to explore between study variation in the performance of each test. To estimate the summary sensitivity and specificity of each test, we planned to perform the meta-analysis by fitting the bivariate model (Chu 2006; Reitsma 2005). This model accounts for between-study variability in estimates of sensitivity and specificity through the inclusion of random effects for the logit sensitivity and logit specificity parameters of the bivariate model. If sparse data results in unreliable estimation of the covariance matrix of the random effects (as indicated by very large variance of logit sensitivity and specificity or if there was lack of convergence), we tried other alternate models including the random-effects model, ignoring the inverse correlation between sensitivities and specificities in the different studies due to intrinsic threshold effect, and the fixed-effect model for either sensitivity or specificity or both after visualising the forest plots and summary receiver operating characteristics (SROC) plots (Takwoingi 2015). We based our choice between the different models on the distribution of sensitivities and specificities as noted in the forest plots or ROC space. We also planned to use the model fit as indicated by the −2 log likelihood and planned to consider the model with the lower −2 log likelihood to be the better model.

We planned to compare the diagnostic accuracy of the tests by including covariate terms for test type (MRI, PET, PET-CT, or EUS) in the bivariate model to estimate differences in the sensitivity and specificity of the tests. We planned to allow both the sensitivity and specificity to vary by covariate. In addition, we also planned to permit the variances of the random effects and their covariance to also depend on test type thus allowing the variances to differ between tests. We planned to use likelihood ratio tests to compare the model with and without covariate (test type). We planned to use a P value of less than 0.05 for the likelihood ratio test to indicate differences in the diagnostic accuracy between the tests. If studies that reported different tests in the same study population were available from at least four studies, we planned to perform a direct head-to-head comparison by limiting the test comparison to such studies. We planned to calculate the relative sensitivities and specificities for each pairwise comparison of tests.

We performed the meta-analysis using the NLMixed command in SAS version 9.3 (SAS Institute Inc, Cary, North Carolina, USA). We created a

graph of pre-test probabilities (using the observed median and range of prevalence from the included studies) against post-test probabilities. We calculated the post-test probabilities using these pre-test probabilities and the summary positive and negative likelihood ratios. We calculated the summary likelihood ratios and their confidence intervals (CIs) from the functions of the parameter estimates from the model that we fitted to estimate the summary sensitivities and specificities. Post-test probability associated with positive test is the probability of having the target condition (unresectability) on the basis of a positive test result (unresectable disease) and is the same as the term "positive predictive value" used in a single diagnostic accuracy study. Post-test probability associated with a negative test is the probability of having the target condition (unresectability) on the basis of a negative test result (resectable disease) and is 1 - "negative predictive value". Negative predictive value is the term used in a single diagnostic accuracy study to indicate the chance that the patient has no target condition when the test is negative. We planned to report the summary sensitivity, specificity, positive and negative likelihood ratios, and post-test probabilities for the median, lower quartile, and upper quartile of the pre-test probabilities.

Investigations of heterogeneity We planned to explore heterogeneity by using the different sources of heterogeneity as covariate(s) in the hierarchical summary receiver operating characteristics (HSROC) model. Of the six sources of heterogeneity we listed in the Secondary objectives section, we planned to deal with all items other than proportion of patients with pancreatic cancer, ampullary cancer, and duodenal cancer as categorical covariates. We planned to use the proportion of patients with pancreatic cancer, ampullary cancer, and duodenal cancer as continuous covariates in the regression model. We planned to employ likelihood ratio tests to compare the model with and without covariate. We planned to use a P value of less than 0.05 for the likelihood ratio test to indicate that the covariate was a potential source of heterogeneity.

Sensitivity analyses We did not plan to perform any sensitivity analyses except when the data available from the studies was ambiguous (for example, the numbers in the text differed from the numbers in the figures), in which case we planned to assess the impact of different data used by a sensitivity analysis.

Assessment of reporting bias We planned to investigate whether the summary sensitivity and specificity differed between studies published as full texts and those available only as abstracts using the methods we described in the Investigations of heterogeneity section.

Results

Results of the search

We identified a total of 23,346 references through electronic searches of MEDLINE (OvidSP; N = 9763), Embase (OvidSP; N = 8097), Science Citation Index expanded (Web of Knowledge; includes Conference Proceedings Citation Index- Science; N = 5412), and HTA (Centre for Reviews and Dissemination; (N = 74). After we removed duplicate references, there were 14,590 articles remaining. We excluded 14,384 clearly irrelevant references through reading abstracts. We retrieved the full-text publication of 206 references for further detailed assessment. We excluded 204 references for the reasons in the Characteristics of excluded studies section. Two diagnostic accuracy studies (two references) fulfilled the inclusion criteria (see the Characteristics of included studies section). We have presented a study flow diagram in Figure 2.

Included studies Two studies with small sample sizes met the inclusion criteria. One study was a prospective study (Ahmad 2001), while the other was a retrospective study (Ardengh 2003). These two studies included a total of 38 participants with pancreatic cancer . Ardengh 2003 included 17 participants and Ahmad 2001 included 21 participants. The mean age of the participants in the two trials was 61 years and 64 years respectively (Ahmad 2001; Ardengh 2003). The proportion of females in the two trials was 23.8% and 64.7% respectively (Ahmad 2001; Ardengh 2003). The prevalence of unresectability (pre-test probability) was 0.529 in Ardengh 2003 and 0.667 in Ahmad 2001.

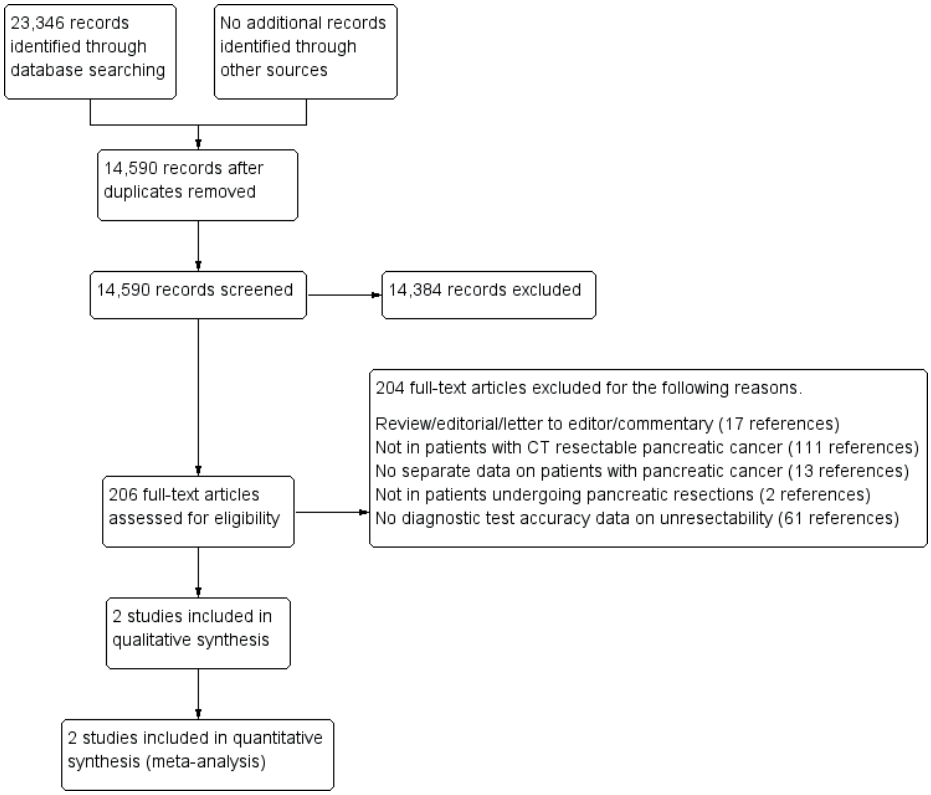

Figure 2. Study flow diagram.

The tests that participants underwent prior to endoscopic ultrasound (EUS) were cross-sectional imaging (CT scan in all patients and ultrasound in some patients depending upon the referral centre) in Ahmad 2001, and CT scan and ultrasound in Ardengh 2003 (on people undergoing pancreatic resection after an ultrasound and a CT scan). Both studies evaluated endoscopic ultrasound (EUS) as the index test. The reference standard was surgeon's judgement of unresectability in both studies. In Ahmad 2001, this was vascular invasion during laparotomy, while Ardengh 2003 did not report the criteria that the surgeon used for assessing unresectability during laparotomy.

We have provided the methodological quality of the included studies in the Methodological quality of included studies section.

Excluded studies We excluded a total of 204 references** for the following reasons:

1. Seventeen studies were not primary studies (Barthet 2007; Brugge 1995; Faigel 1996; Fockens 1993; Freeny 2001; García-Cano 2002; Gaspar 2015; Goh 2006; Lévy 2001; Malfertheiner 2005; Neoptolemos 2005; Pappas 2011; Rösch 1992c; Shin 2013; Snady 1993; Wang 2007a; Wiersema 2000).
2. We excluded 111 studies because participants were not patients with CT resectable pancreatic cancer (Abe 2010; Ahmad 1999; Ahmad 2000a; Ahmad 2000c; Ahmad 2000d; Akahoshi 1998; Anand 2013; Aubertin 1996; Awad 1997; Baarir 1998; Bao 2008; Bettini 2005; Broglia 2001; Burge 2015; Carroll 1999; Catalano 1997; Catalano 1998; Chandler 1999; Chhibber 2006; Chiang 2014; Cieslak 2014; Crippa 2013; Crippa 2014; DeWitt 2004; Egorov 2012; Einersen 2013; Farma 2008a; Fischer 2002; Frohlich 1999; Grenacher 2004; Lopez-Hänninen 2002; Hochwald 1999; Howard 1997; Hu 2015; Ichikawa 1997; Iglesias-Garcia 2010; Imazu 2010; Izuishi 2010; Javery 2013; Jemaa 2008; Kala 2007; Karoumpalis 2011; Kim 2001; Kim 2012; Koelblinger 2011; Koranda 2009; Koranda 2010; Kulig 2004; Kysucan 2010; Latronico 2005; Lee 2002; Lee 2010; Lentschig 1996; Makowiec 2000; Maluf-Filho 2004; Mansfield 2008; McFarland 1996; Megibow 1995; Melzer 1996; Mertz 2000; Motosugi 2011; Mukai 1991; Murakami 1996; Nakamoto 1999; Napolitano 2002; Nishiharu 1999; Palazzo 1993; Park 2009; Patel 2002a; Patel 2002b; Paul 2012; Ramsay 2004; Razzaque 2012; Reiser-Erkan 2009; Reiser-Erkan 2010; Ren 2006; Ridtitid 2015; Rivadeneira 2003; Romijn 2000; Rösch 1992a; Rösch 1992b; Schmidt 2004; Schwarz 2001; Seicean 2008; Shami 2011; Sheng 2012; Smedby 1997; Solodinina 2014b; Soriano 2001; Soriano 2004; Strobel 2008; Tapper 2010; Tian 2008a; Tian 2008b; Tian 2008c; Tierney 2001; Tio 1986; Tio 1988; Tio 1990; Tomić 2005; Trede 1997; Turowska 2009; Valinas 2002; Wakabayashi 2008; Wang 2007b; Wang 2015; Warshaw 1990; Woerlein 2002; Younes 1999; Yusoff 2003; Zhong 2005).
3. Thirteen studies had no separate data on patients with pancreatic cancer (Arabul 2012; Buchs 2007; Casneuf 2007; Cieslak 2012; Cieslak

** References of excluded studies were not printed here due to space limitations and may be accessed at the Cochrane Library (https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011515.pub2/full)

2013; Dewitt 2003; Ho 2008; Lu 2006; Lytras 2005; Pan 2014; Schima 2002; Takaori 2007; Tomazic 2000).

4. Two studies were not conducted in patients undergoing pancreatic resections (Agarwal 2005; Xu 2014).
5. In 61 studies diagnostic accuracy data on unresectability was unavailable (Ahmad 2000b; Arslan 2001; Artifon 2009; Asagi 2013; Aslanian 2005; Baghbanian 2014; Brugge 1996; Buscall 1999; Cahn 1996; Chang 1997; Chen 2001a; Chen 2001b; Chen 2009; Chiang 2012; Costilla 2011; Croome 2010; Czako 2009; Delbeke 1999; Egorov 2013; Einersen 2014; Eloubeidi 2006; Eloubeidi 2007; Erickson 2000; Farma 2008b; Gress 1997; Gress 1999; Harrison 1999; Heinrich 2005; Helmreich 2004; Hemmingsson 1982; Hirokawa 2010; Holzapfel 2011; Kadish 1995; Kim 2015; Lakhtakia 2011; Mehmet 2006; Morris-Stiff 2011; Prithiviraj 2013; Raj 2013; Rösch 2000; Saif 2008; Shoup 2000; Sironi 1995; Sironi 1996; Skordilis 2002; Snady 1994; Solodinina 2014a; Spencer 1998; Staib 1997; Takayama 2009; Tellez-Avila 2012; Tio 1996; Wang 2008; Wang 2014; Wee 2012; Yao 2012; Yasuda 1988; Yasuda 1993; Yoneyama 2014; Zhang 2012; Zhang 2015).

Methodological quality of included studies

We have summarised the risk of bias and applicability concerns in the included studies in Figure 3. As shown in Figure 3, there were no applicability concerns in the included studies. However, the risk of bias in the "patient selection" was high in Ardengh 2003 since it excluded pancreatic cancers that were 3 cm or more in diameter. The risk of bias in this domain was low in Ahmad 2001. The risk of bias in the "index test" domain was unclear in Ardengh 2003 since it was unclear whether the index test results were interpreted without knowledge of the results of the reference standard. The risk of bias in this domain was low in Ahmad 2001. As anticipated, both studies used surgeons' judgement on unresectability as the reference standard and so both studies were at unclear risk of bias in the "reference standard" domain. Ardengh 2003 did not report the interval between EUS and surgery and the participant flow. We considered this study to be at unclear risk of bias in the "flow and timing" domain. The risk of bias in this domain was low in Ahmad 2001.

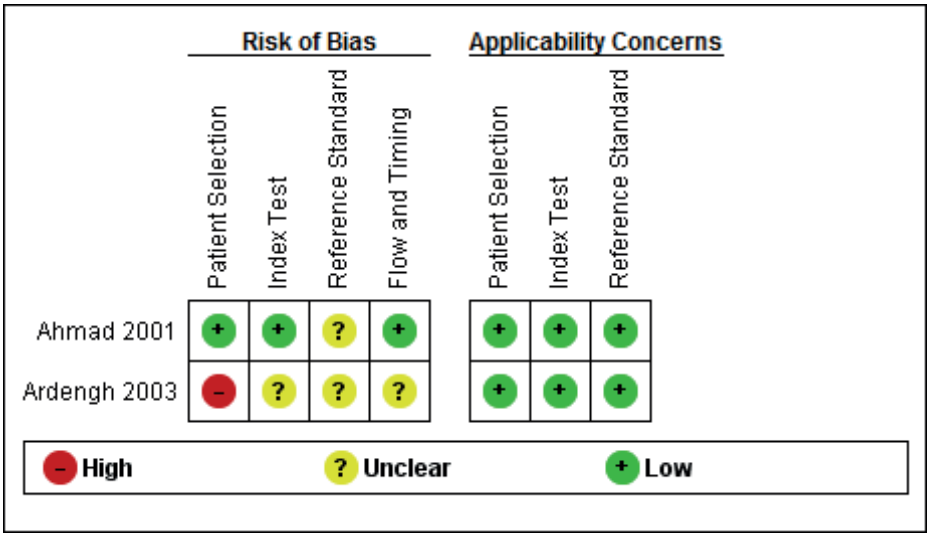

Figure 3. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

Findings

There was no heterogeneity in sensitivity as shown by very good overlap of confidence intervals (CIs) in the forest plots, visualisation of the receiver operating characteristic (ROC) plot, and by the values of sensitivity which were almost identical (0.86 in Ahmad 2001 versus 0.89 in Ardengh 2003) (Figure 4; Figure 5). Although we planned to evaluate the use of univariate random-effects model for specificity based on the forest plots (there was good overlap of CIs but the difference in point estimate was more with specificity than sensitivity: 0.71 in Ahmad 2001 versus 0.88 in Ardengh 2003) and ROC plot, the only model that converged was univariate fixed-effect model for both sensitivity and specificity. So, we were unable to choose the best model by comparing the –2 log likelihood.

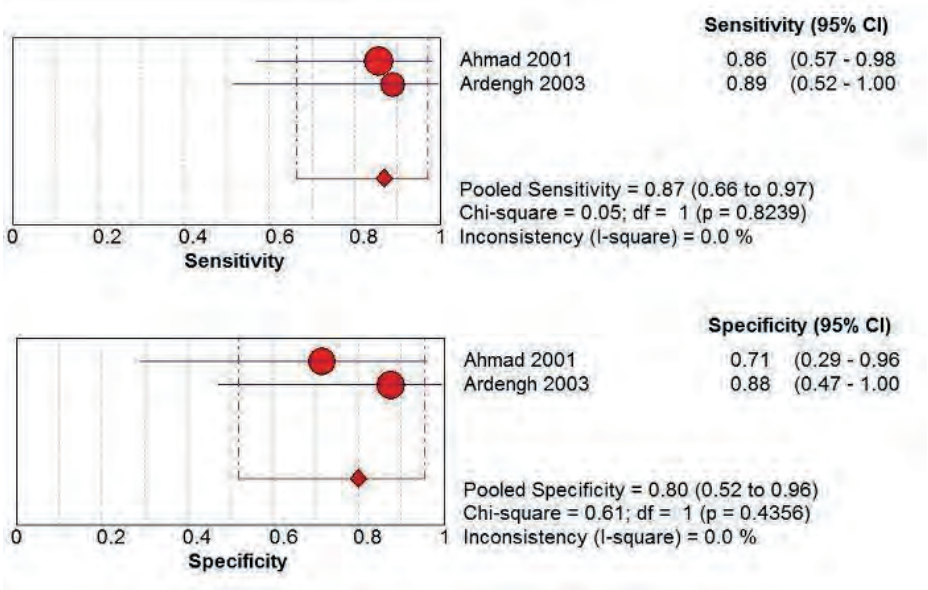

Figure 4. Pooled sensitivity and specificity of endoscopic ultrasound for assessing the resectability with curative intent in pancreatic and periampullary cancer.
Abbreviations: df: degrees of freedom.

The summary estimate of sensitivity for unresectability was 0.87 (95% CI 0.54 to 0.97) and the summary estimate of specificity for unresectability was 0.80 (95% CI 0.40 to 0.96). The positive likelihood ratio and negative likelihood ratio were 4.3 (95% CI 1.0 to 18.6) and 0.2 (95% CI 0.0 to 0.8) respectively. Although we planned to calculate the post-test probabilities using the median and quartiles of the pre-test probabilities, we calculated the post-test probabilities using the mean and range of the pre-test probabilities because of the inclusion of two studies only. The mean pre-test probability was 60.5%. At this pre-test probability, the post-test probability of unresectable disease for people with a positive EUS (EUS indicating unresectability) was 86.9% (95% CI 60.9% to 96.6%) and the post-test probability of unresectable disease for people with a negative EUS (EUS indicating resectability) was 20.0% (5.1% to 53.7%). This means that 13% of people (95% CI 3% to 39%) with positive EUS have potentially resectable cancer and 20% (5% to 53%) of people with negative EUS have unresectable cancer. The "Summary of findings" table shows the post-test probability of unresectable disease at different pre-test probabilities of unresectable disease (Table 1).

Neither of the included studies reported any complications related to EUS. We did not perform any investigation of heterogeneity because only two studies met the inclusion criteria of this review.

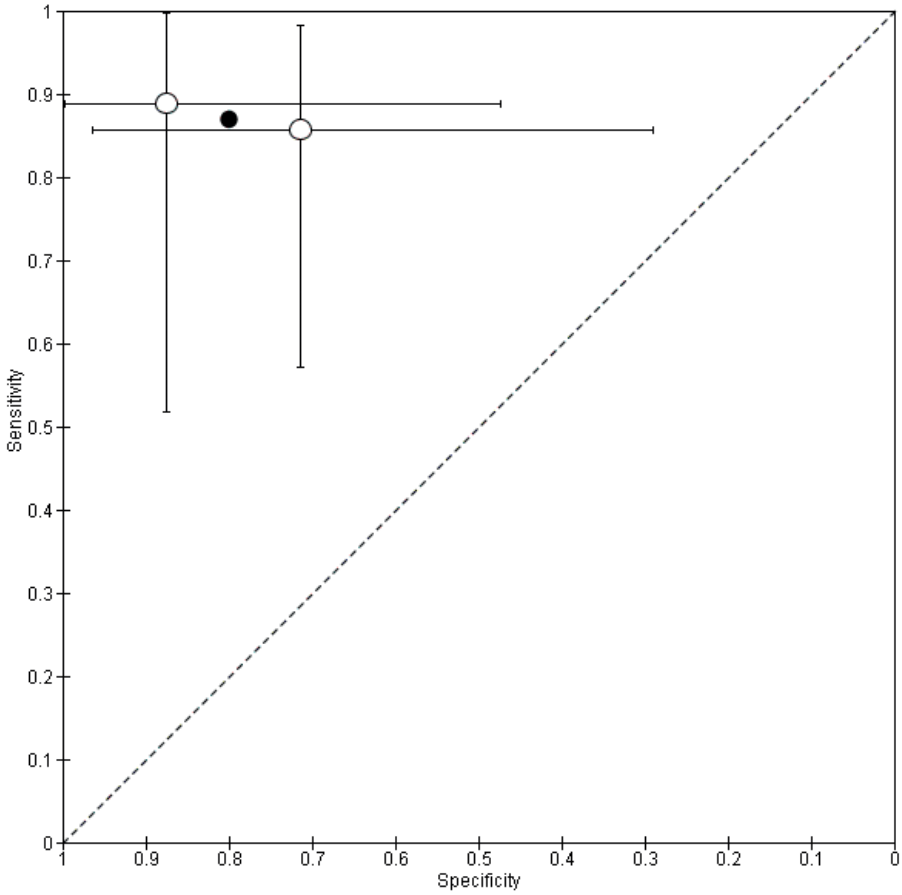

Figure 5. Summary ROC Plot of endoscopic ultrasound for assessing the resectability of pancreatic and periampullary cancer.

Discussion

Summary of main results

Only two studies (38 participants) that evaluated the diagnostic accuracy of EUS in people with CT-resectable pancreatic cancers met the inclusion criteria of this review. The summary estimate of sensitivity was 0.87 (95% CI 0.54 to 0.97) and the summary estimate of specificity was 0.81 (95% CI 0.40 to 0.96). The positive likelihood ratio and negative likelihood ratio were 4.3 (95% CI 1.0 to 18.6) and 0.2 (95% CI 0.0 to 0.8) respectively. At the mean pre-test probability in included studies (60.5%), the post-test probability of unresectable disease for people with a positive EUS (EUS indicating unresectability) was 86.9% (95% CI 60.9% to 96.6%) and the post-test probability of unresectable disease for people with a negative EUS (EUS indicating resectability) was 20.0% (5.1% to 53.7%).

Direct laparotomy after CT resulted in approximately 60% of cancers being unresectable, which appears to be higher than the usual unresectability rates after CT scan of around 30% to 40% (Allen 2016). We are unable to identify why the pre-test probability of unresectability was high in these centres which are specialist centres, considering that they have facilities to perform EUS. When the EUS indicates that the pancreatic cancer is not resectable although CT scan shows that pancreatic cancer is resectable (EUS positive in CT resectable pancreatic cancer), approximately 13% of people (95% CI 3% to 39%) had resectable pancreatic cancer. Since pancreatic resection is the only potentially curative option for pancreatic cancer, omission of laparotomy and resection in these people can have a major negative impact on their survival.

We were unable to assess the diagnostic accuracy of MRI, PET, PET-CT and compare their diagnostic accuracy with EUS since none of the studies on MRI or PET were on CT resectable pancreatic cancers and none of the studies on PET-CT indicated the added value of PET clearly.

Strengths and weaknesses of the review

We used formal search strategies and reported this, so that it is possible to independently verify our results. Two review authors independently identified studies and extracted data, thereby minimising human error in the selection of studies and data extraction. We reached agreement based on the information available in the protocol of this review (Gurusamy 2015).

The methodological quality in one included study was as good as can be achieved ethically (Ahmad 2001), and the methodological quality in the second included study was mostly unclear (Ardengh 2003). There were no concerns about applicability in either study. There was no heterogeneity in the diagnostic test accuracy between the studies as indicated by the almost identical sensitivities and good overlap of CIs for specificities. These are the major strengths of this review.

The major limitation of this review was the paucity of data: only two studies met the inclusion criteria and both these studies were on EUS. We had to use univariate fixed-effect models for both sensitivity and specificity since this was the only model that converged. Such models may give reliable and stable results if used in the appropriate situation (Takwoingi 2015). Although we would have liked to compare the model fit of the univariate fixed-effect models that we performed with the model fit of univariate random-effects model for at least specificity, this was not possible because convergence was obtained only for univariate fixed-effect models for both sensitivity and specificity. However, our decision is vindicated to a certain extent by the almost identical sensitivity and good overlap of CIs for specificity and the I^2 statistic values of 0% for both sensitivity and specificity. The alternative was to present the results of studies individually, which would have negated the advantage of meta-analysis, i.e. improved precision, particularly when there was no heterogeneity in the results between the two studies.

Another limitation of this review is that we included sensitivity maximising diagnostic filters for searching MEDLINE and Embase databases (Haynes 2004; Wilczynski 2005). This is because the original searches without the filters retrieved more than 40,000 references. We had to balance the possibility of missing some studies against the risk of being unable to complete the review. We decided that it would be more useful to have evidence from major studies rather than having no information at all. Notably, the diagnostic filters we used have a sensitivity of 98.6% for MEDLINE and 100% for Embase. So, the chances of us missing some relevant diagnostic studies are extremely low. We reduced this further by performing a "related search" and "citing reference search" in which we did not find any studies that we could include in this review.

This is the first systematic review on the topic. EUS is not routinely performed to assess resectability of pancreatic cancers in most centres and the findings from our review would suggest that there is insufficient evidence of clinical benefit to justify its inclusion in the standard diagnostic algorithm.

Applicability of findings to the review question

The findings of this review are applicable only to people with pancreatic cancer who were found to be resectable after a CT scan. In addition, all the participants included in this review underwent laparotomy; so the findings of this review are applicable only in those who are fit to withstand major surgery. This review assessed the diagnostic accuracy of EUS in assessing the resectability of pancreatic cancer and does not provide the diagnostic accuracy of EUS in diagnosis of pancreatic cancer or finding the tumour, node, and metastasis (TNM) staging of pancreatic cancer.

Authors' conclusions

Implications for practice

Based on two small studies, there is significant uncertainty in the utility of endoscopic ultrasound (EUS) in people with pancreatic cancer found to have resectable disease on computed tomography (CT) scan. No studies have assessed the utility of EUS in people with periampullary cancer.

There is no evidence to suggest that it should be performed routinely in people with pancreatic cancer or periampullary cancer found to have resectable disease on CT scan.

Implications for research

Well-designed diagnostic test accuracy studies are needed to reliably estimate the accuracy of diagnostic laparoscopy in people with pancreatic and periampullary cancers. Comparison of different imaging modalities with each other and with diagnostic laparoscopy and laparoscopic ultrasound may further demonstrate the value of the different imaging tests in staging pancreatic and periampullary cancers.

The conclusion of this systematic review needs regular review as the quality of CT scanning improves and the different imaging tests should be compared with each other and diagnostic laparoscopy and laparoscopic ultrasound in staging pancreatic and periampullary cancers.

Cost-effectiveness studies should be undertaken to determine whether EUS alone for EUS-negative CT resectable pancreatic cancer and EUS plus diagnostic laparoscopy for EUS-positive CT resectable pancreatic cancer should be routinely performed in state funded clinical practice.

Acknowledgements

We thank the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group, the UK Support Unit for Diagnostic Test Accuracy (DTA) Reviews, the DTA editorial team, the peer reviewers, and the copy editors for their advice in the preparation of this review.

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Chapter 6

Limited role of the Apparent Diffusion Coefficient (ADC) for tumor grade and overall survival in resectable pancreatic ductal adenocarcinoma

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Abstract

This study evaluated the relationship between apparent diffusion coefficient (ADC) values in pancreatic ductal adenocarcinoma (PDAC) and tumor grades based on WHO, Adsay, and Kalimuthu classifications, using whole-mount pancreatectomy specimens. If glandular formation plays a key role in the degree of diffusion restriction, diffusion-weighted imaging could facilitate non-invasive grading of PDAC. A freehand region of interest (ROI) was drawn along tumor borders on the preoperative ADC map in each tumor-containing slice. Resection specimens were retrospectively graded according to WHO, Adsay, and Kalimuthu classifications and correlated with overall survival and the 10th percentile of whole-volume ADC values. Findings from 40 patients (23 male, median age 67) showed no correlation between ADC p10 values and WHO differentiation ($p = 0.050$), Adsay grade ($p = 0.955$), or Kalimuthu patterns ($p = 0.117$). There was no association between ADC p10 and overall survival ($p = 0.082$) and other clinicopathological variables. Survival was significantly lower for poor tumor differentiation ($p = 0.046$) and non-glandular Kalimuthu patterns ($p = 0.016$) and there was a trend towards inferior survival for Adsay G3 ($p = 0.090$) after correction for age, tumor location, and stage. Preoperative ADC measurements for determining PDAC aggressiveness had limited clinical utility, as there was no correlation with histological parameters or overall survival in resectable PDAC.

Introduction

In pancreatic cancer, poor tumor differentiation is a statistically significant independent prognosticator of overall survival after resection, disease-specific survival, early recurrence, and post-recurrence survival [1-4]. Therefore, patients with poorly differentiated resectable tumors may particularly benefit from neoadjuvant therapy instead of upfront resection [5]. However, the histopathological grade is typically unknown when treatment decisions are made and, therefore, not useful for determining whether neoadjuvant therapy should be considered.

Diffusion-weighted magnetic resonance imaging (DWI) reflects changes in water mobility caused by alterations to the tissue environment, interactions with cell membranes, and macromolecules, thus providing a tissue contrast that differs from conventional T1- and T2-weighted images [6]. Generating qualitative and quantitative parametric image maps based on the calculated diffusion coefficient, the apparent diffusion coefficient (ADC) is uncomplicated. Glandular formation is the critical morphological characteristic for grading differentiation of PDAC. Neoplastic tubular and duct-like structures of well-differentiated adenocarcinoma may provide fewer structural limitations and higher ADC, while poorly differentiated ductal adenocarcinoma with limited to no glandular formation may show less diffusion due to its high cellularity. The change in tissue organization to a more solid and compact architecture may account for the restriction of diffusion of water molecules and lower ADC values [7]. If the degree of glandular formation in different grades of pancreatic cancer, indeed, plays a key role in the degree of diffusion restriction and ADC value, we might be able to identify relevant pretherapeutic high-risk patients.

Adsay et al. proposed a grading system reporting the primary and secondary patterns of glandular formation within PDAC, which demonstrated a good correlation with clinical outcome [8]. Similarly, Kalimuthu et al. found that their morphological pattern-based groups correlated better with clinical outcomes than the conventional differentiation-based World Health Organization (WHO) classification. The patterns were categorized into two components based on the presence or absence of well-formed glands [9]. While previous studies showed conflicting results regarding the relationship between ADC and WHO tumor grade of pancreatic cancer [7,10-19], no studies have investigated this relationship for other classifications.

The purpose of this study was to determine if the ADC value of pancreatic ductal adenocarcinoma could be a predictor of tumor aggressiveness and to assess its association with tumor grades according to WHO, Adsay, and Kalimuthu classifications, using whole-mount pancreatectomy specimens.

Materials and Methods

Patients

Our institutional review board approved this single-center retrospective study and the need to obtain informed consent was waived. Contrast-enhanced MRI with DWI has been a part of our standard diagnostic workup for patients with potentially resectable pancreatobiliary disease since January 2012. We reviewed our radiology imaging database to identify patients who underwent contrast-enhanced MRI of the upper abdomen combined with a DWI from January 2012 to December 2016. All patients aged 18 years and older with pancreatic ductal adenocarcinoma were eligible for inclusion. Patients who had undergone previous treatment for pancreatic ductal adenocarcinoma (surgery, neoadjuvant chemotherapy, radiotherapy, and ablation) were not eligible for inclusion. Special subtypes of PDAC, including colloid carcinoma, medullary carcinoma, undifferentiated carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells of the pancreas, were excluded as they constitute a small subset of PDACs (1–3%) with distinct clinicopathological features. Clinical information and survival rates until 31 December 2021 were retrieved from the electronic patient files. Survival was calculated from the date of diagnosis to the date of death.

MRI Technique

The MR imaging examination was performed on a 3.0 Tesla system (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). Single-shot spin-echo echoplanar imaging DWI was conducted in the transverse plane with monopolar diffusion gradients along three orthogonal directions, utilizing a combination of three b-values (0/50, 400/500, and 800 s/mm2). ADC maps were automatically generated based on the available b-values on a voxel-by-voxel basis using the software supplied with the MR unit (Syngo VD; Siemens Healthcare, Erlangen, Germany). Additionally, axial, and coronal T2-weighted sequences and axial fat-suppressed T1-weighted sequences before and after intravenous administration of gadoterate meglumine (0.5 mmol/mL; Dotarem, Guerbet, Villepinte, France) were acquired, serving as anatomical reference.

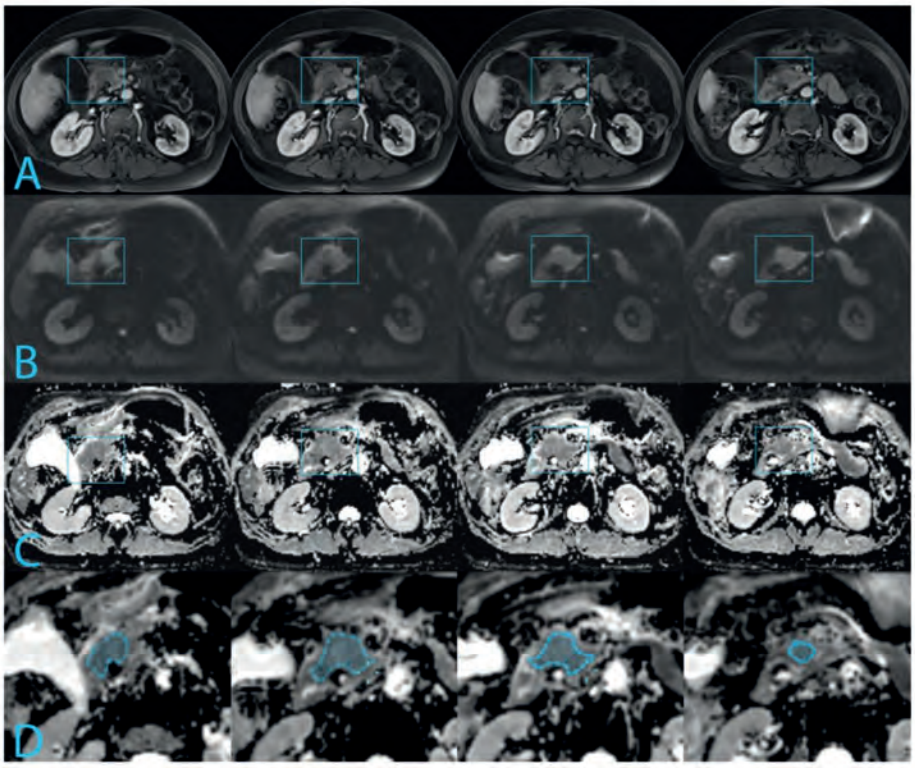

Figure 1. Four slices of MR images depict a pT2N2 tumor measuring 35 mm in the pancreatic head, highlighted by the blue rectangle. The tumor exhibits an ADC p10 of 1038 μm2/s. Histopathologically, the tumor is classified as WHO moderately differentiated, Adsay G1 and a Kalimuthu tubulopapillary pattern. (A). T1-VIBE arterial phase. (B). DWI at b800 s/mm2. (C). ADC map. (D). Freehand regions of interest along the border of the tumor on the ADC map.

Image Analysis

All imaging data were retrospectively reviewed by a radiology resident with 5 years of experience, supervised by a radiologist with 20 years of experience in abdominal and pancreatic imaging. Interobserver variability is reported to be good to excellent for all MRI sequences [20]; therefore, consensus reading was deemed sufficient. Anonymized MR images were imported in MeVisLab (Bremen, Germany). The tumor was localized on the DWI using the other MR sequences (HASTE and pre- and post-contrast T1 VIBE) and contrast-enhanced CT images. Freehand regions of interest (ROIs) were drawn along the border of the tumor on the ADC map to cover the largest possible area of tumor in each tumor-containing slice. Care was taken to avoid dilated pancreatic duct, cystic lesions, or artefacts in the

regions of interest, See Figure 1. ADC values for the tumor were measured with in-house developed software MeVisLab using the ROIs drawn to create a whole-volume ROI. The 10th percentile of the ADC of the whole-volume ROI was used in the analysis, assuming that tumor areas with poorest differentiation coincided with the lowest ADC.

Assessment of Histologic Tumor Grade

The whole-mount specimens were fixed in formalin and stained using haematoxylin and eosin. Histological examination included: grade of differentiation (World Health Organization); pTNM classification; number of lymph nodes retrieved from the specimen and number and site of lymph nodes containing metastases; and resection margins. Positive resection margins were defined as direct extension or distance of the tumor from the resection margin ≤ 1 mm [21,22].

Tumor grade was retrospectively evaluated by an expert pancreatic pathologist with 10 years of experience in evaluating pancreatic cancer specimens. Tumor grades were based on the global assessment of glandular formation, mitosis, mucin, and nuclear characteristics, and subcategorized as well, moderately, and poorly differentiated PDAC. If >95% of the tumor was composed of glands, then, it was classified as well differentiated, 50–95% as moderately differentiated, and <50% as poorly differentiated [23,24]. Additionally, the whole-mount specimen was scored according to Adsay's grading system and Kalimuthu's grading system.

Adsay et al. defined three patterns [8]. Pattern one was defined as well-formed tubular units with complete, easily discernible borders. Pattern two was defined as incomplete, with ill-defined borders, fusion of glands, or irregular multi-lumina formation. And pattern three was defined as non-glandular patterns, including cord-like areas, individual cell infiltration, with nested or solid (sheet-like) growth patterns. The final score is the summation of the major and minor pattern identified. Grade 1 is defined as a total score of three or less. Grade 2 is defined as a total score of four. Grade 3 is defined as a total score of five or more.

Table 1. Patient characteristics.

Demographics	
Age	median 67 years, range 36–79
Gender	
Male	23
Female	17
Tumor location	
Pancreas head	31
Pancreas body/tail	9
Ca19.9	median 190 kU/l, IQR 42.5–520 (missing = 8)
Survival	
Median overall survival	14.1 months (95% CI 11.7–17.1 months)
5-year survival	11%
Pathological characteristics	
pTNM (8th edition)	
1A	4
1B	4
2A	1
2B	11
3	19
4	1 *
Tumor size	median 32 mm, IQR 25–36 mm
Lymph node metastasis (pN+)	31
Residual disease	
R0	15
R1	21
R2	4
MRI characteristics	
ADC	
Mean ADC	1344 $\mu m^2/s$ (SD = 240)
Mean ADC p10	1075 $\mu m^2/s$ (SD = 209)
Mean volume	412 voxels (range 34–1235)

** Based on distant lymph node metastasis sampled during surgery.*

Kalimuthu et al. defined four specific morphological patterns divided in glandular (conventional and tubulopapillary) and non-glandular (squamous and composite) patterns [9]. The conventional pattern was characterized by well-differentiated glands with a tubular, stellate configuration, lined

by pancreaticobiliary-type epithelium. The tubulo-papillary pattern was characterized by glands with a rounded and dilated configuration, lined by a combination of foveolar gastric-type and pancreaticobiliary-type epithelium. The squamous component was characterized by nests of large polygonal cells with squamous differentiation. The composite pattern is characterized by glands that begin to lose their integrity and cohesion, forming a spectrum of patterns including sheets, nests/islands, ribbons, cords, angulated glands, single file, or dispersing as buds and single cells and cribriforming.

Statistical Analysis

All data were processed using SPSS (version 27) for Windows. To find relationships between ADC values and normally distributed continuous data, Pearson's correlation coefficient was used. For nominal data, independent t-tests were used. For ordinal data and non-normally distributed continuous data, Spearman was used. For survival data, Cox regression analysis was used. Median overall survival was calculated and survival curves were generated using the Kaplan–Meier method, followed by the log-rank test to assess statistical significance. Overall, p-values less than 0.05 were considered statistically significant.

Results

Patient Characteristics

We reviewed our radiology imaging database (Agfa Healthcare, Mortsel, Belgium) and identified 630 patients who underwent MR imaging of the upper abdomen. The final study population consisted of 40 patients who underwent surgery with curative intent and had a final diagnosis of PDAC; see Table 1 for demographics and pathological characteristics. Tumor stage was redefined according to the UICC 8th edition in patients previously classified according to the 7th edition. The median time interval between MRI and surgery was 27 days (range 6–44 days). Of these patients, 31 underwent pancreatoduodenectomy, 8 underwent distal pancreatectomy, and 1 underwent subtotal pancreatectomy. Postoperative systemic therapy was administered to 21 patients. Data on adjuvant therapy were missing for 4 patients. The preoperative CA19-9 level nearest to the time of surgery was used in the analysis.

Table 2. Histopathological classification.

	Kalimuthu								
	Conventional			Tubulopapillary			Composite		
	Adsay								
WHO	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
Well differentiated	1	0	0	2	0	0	0	0	0
Moderately differentiated	9	1	1	6	1	0	3	1	3
Poorly differentiated	0	1	3	0	0	1	1	0	6

There were no Kalimuthu squamous tumors identified.

Histopathologic Results

According to WHO grading, tumors were classified as well differentiated (n = 3), moderately differentiated (n = 25), and poorly differentiated (n = 12). Adsay's grading system resulted in G1 (n = 22), G2 (n = 4), and G3 (n = 14). Kalimuthu's grading scheme resulted in conventional (n = 16), tubulopapillary (n = 10), squamous (n = 0), and composite patterns (n = 14), see Table 2.

Correlation between ADC, Tumor Grades, and Clinicopathological Variables

There was a near-significant difference (p = 0.050) between the ADCs of well (mean p10 1355 μm2/s), moderately (mean p10 1052 μm2/s), and poorly differentiated tumors (mean p10 1052 μm2/s). The ADCs of Adsay G1 (mean p10 1081 μm2/s), G2 (mean p10 1046 μm2/s), and G3 (mean p10 1074 μm2/s) were not significantly different (p = 0.955), nor were the ADCs of Kalimuthu patterns conventional (mean p10 1068 μm2/s), tubulopapillary (mean p10 1183 μm2/s), and composite (mean p10 1006 μm2/s), p = 0.117).

There was no correlation between ADC p10 and WHO tumor grade (r = −0.119; p = 0.463), Adsay tumor grade (r = 0.034; p = 0.837), or Kalimuthu patterns (r = −0.094; p = 0.562); see Figure 2. ROC analysis showed population distributions almost completely overlapped; therefore, optimal cut-off values for ADC were not calculated for well/moderately vs. poorly differentiated tumors (AUC 0.488, 95% CI 0.305–0.671, p = 0.899), Adsay G1/G2 vs. G3 (AUC 0.475, 95%CI 0.294–0.657, p = 0.790), and Kalimuthu conventional/tubulopapillary vs. composite tumors (AUC 0.367, 95% CI 0.185–0.548, p = 0.150). ADC p10 was significantly associated with age (r = −0.316; p = 0.047). However, further analysis revealed this was caused by an outlier, a large duct-type pancreatic cancer with an ADC p10 1627 μm2/s (r = −0.149; p = 0.365). There was no correlation with gender (p = 0.503), tumor size (p = 0.358), tumor location (p = 0.054), tumor stage (p = 0.232), R-status (p = 0.643), lymph node status (p = 0.346), or Ca19.9 levels (p = 0.685). Additionally, ADC p10 was not a significant predictor for overall survival (p = 0.082).

Overall Survival

At the end of the follow-up period, 35 patients were deceased, with a maximum follow-up of more than 6 years. The median OS for WHO tumor grades was 38.4 months (95% CI 7.6–69.3 months) for well differentiated

tumors, 14.1 months (95% CI 4.2–24.0 months) for moderately differentiated tumors, and 13.3 months (95% CI 5.5–21.0 months) for poorly differentiated tumors (p = 0.235). For tumor grade according to Adsay, the median overall survival was 19.2 months (95% CI 0.0–40.0 months) for G1, 13.8 months (95% CI 0.0–28.6 months) for G2, and 10.6 months (95% CI 3.4–17.8 months) for G3 (p = 0.272). In 20 patients, Adsay's grading system resulted in downgrading the tumor, and in four patients, it resulted in upgrading the tumor compared to the WHO classification (Table 2); however, this did not lead to an improvement in correlation with overall survival. The median overall survival for Kalimuthu patterns was 27.1 months (95% CI 0.0–56.0 months) for conventional tumors, 19.2 months (95% CI 6.0–32.4 months) for tubulopapillary tumors, and 10.6 months (95% CI 3.4–17.8 months) for composite tumors (p = 0.170). Overall survival was significantly lower for poor tumor differentiation (HR 0.418, 95% CI 0.178–0.985, p = 0.046) and non-glandular Kalimuthu patterns (HR 0.352, 95% CI 0.151–0.823, p = 0.016) and showed a trend for poorer survival for Adsay G3 (HR 0.498, 95% CI 0.223–1.115, p = 0.090) after correction for age, tumor location, and stage.

Discussion

MRI is commonly used as a diagnostic tool for suspected pancreatic cancer, particularly in cases with inconclusive findings on contrast-enhanced CT. DWI has shown promise in distinguishing benign and malignant pancreatic lesions [25], as well as detecting liver metastases [26,27] and local recurrence [28], and could be useful for assessing the response to neoadjuvant therapy [29]. However, this study revealed no significant associations between ADC p10 values of PDAC and tumor grades according to WHO, Adsay, or Kalimuthu classifications, using whole-mount specimens from surgical resections as the reference standard. PDAC ADCs did not demonstrate a correlation with different grades, showing no significant differences among low-, intermediate-, and high-grade tumors. Thus, based on our present data, it is impossible to non-invasively grade PDAC with DWI.

Previous studies have shown conflicting results regarding the relationship between the ADC and tumor differentiation, using various methods of ADC measurements, ADC values, and field strengths [7,10-19]. The variable

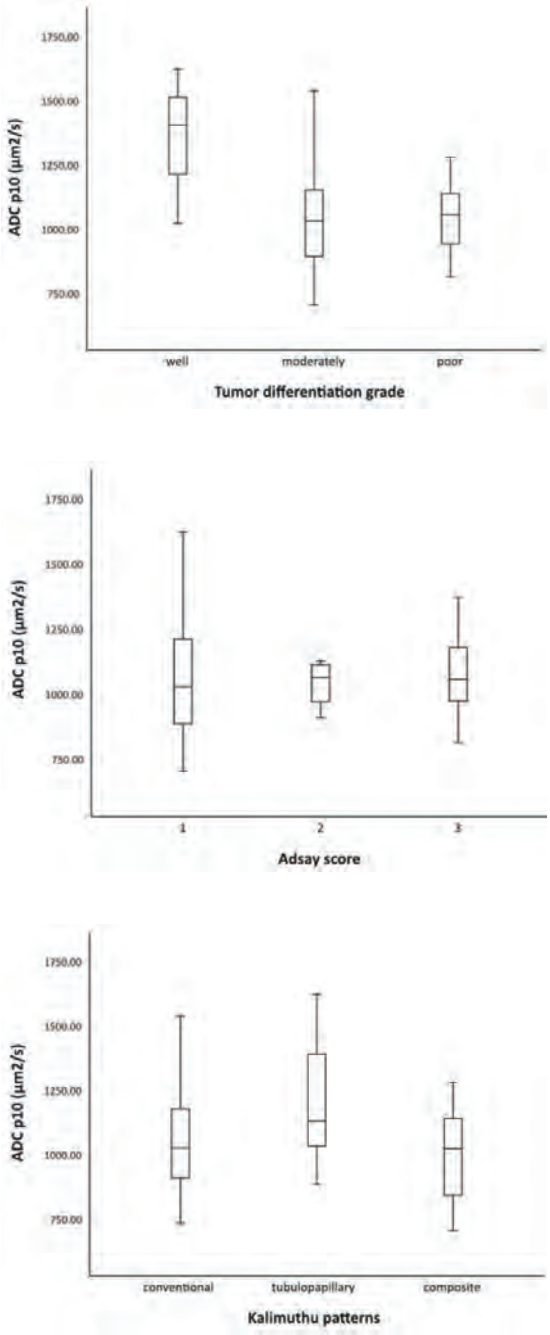

Figure 2. Boxplot of ADC p10 values by tumor differentiation grade, Adsay score, and Kalimuthu patterns.

percentage of poorly differentiated tumors across studies further suggests potential influences from differences in the study population. It is also important to highlight that in everyday clinical practice, many pathologists will use a subjective “gut-feeling approach”, relying on the degree of gland formation as the key criterion for the histological differentiation of PDAC [30]. Consistent with prior studies, our study revealed no associations between the ADC and other adverse clinicopathological features, such as tumor size, location, lymph node metastases, and R-status [16,18]. Interestingly, in pancreatic cancer liver metastases, the ADC also did not predict relevant histopathological features [31]. In agreement with Sakane et al. and Dunet et al., our study found no significant prognostic value for the ADC [10,32], while other studies found better OS in patients with tumors exhibiting high ADC values compared to those with low ADC values [14,18,19,33]. We observed a prognostic value for tumor grade, with significantly lower OS for poor tumor differentiation and non-glandular Kalimuthu patterns, and a near-significant lower OS for Adsay G3 after correction for age, tumor location, and stage. Although these three grading systems all incorporate gland formation for differentiation, it is worth noting there is not much agreement between methods.

To establish a relationship between the ADC and pancreatic cancer aggressiveness, it is critical to understand the organization of the tumor components that exist in different grades or types of tumors. The complex, dynamic, and heterogeneous tumor microenvironment of pancreatic cancer results from the cellular and extracellular components of the tumor, contributing to the inter- and intratumor variability. The predominant histopathological feature of pancreatic cancer is desmoplastic reaction, consisting of abundant fibrosis and abnormal accumulation of extracellular matrix components, which can constitute up to 90% of the tumor area. This creates a mechanical barrier and results in relatively low microvascular density [34], potentially decreasing the ADC value. Conversely, edema, small areas of necrosis, cystic parts, or large ducts have the opposite effect and tend to increase the ADC, potentially overwhelming the ADC decrease associated with cell proliferation [6].

In addition to factors related to the tumor microenvironment, technical factors such as vendors, field strength, b-values selection, and placement of region of interest [35,36] influence the ADC values. Although whole-volume measurements could, theoretically, result in higher ADCs [37],

we did not observe obvious differences compared to the other studies. Moreover, whole-volume measurements better capture the morphologic intra- and intertumoral heterogeneity, characteristic for pancreatic cancer, compared to single section-based measurements [37]. Furthermore, it reduces measurement errors in the ADC values that could be introduced when a small subjective region within the morphologic heterogeneous tumor is chosen for evaluation. This is reflected in the better interobserver variability of whole-volume ADC measurements compared to solid-part ADC measurements [35,37]. Additionally, the total number of voxels used per volume of ADC value showed a great variety ranging from 34 to 1235 voxels, which is inherently related to and relative to tumor size. In prostate cancer, where the ADC is used to discriminate between low-grade and high-grade tumors, primarily in the peripheral zone [38,39], the 10th percentile ADC was the parameter that correlated best with the Gleason score and performed significantly better than the mean ADC in differentiating clinically significant cancer from clinically insignificant tumor foci. Within tumors with heterogeneous cellularity, focal areas of high cellularity are represented to a greater extent by the 10th and 25th percentile ADCs than by the mean and median ADCs [40]. Accordingly, the range of observed ADC values was the smallest for the 10th percentile.

Conducting retrospective imaging analyses is known to have its limitations. Within this study, the sample size of included patients was relatively small, resulting in the inclusion of only three well differentiated tumors, four Adsay grade 2 tumors and no Kalimuthu squamous tumors. Unfortunately, this prevents the drawing of sound conclusions regarding these subcategories. The p-value for the correlation between tumor ADC and overall survival initially showed proximity, but with expansion of the cohort size after the preliminary study (n = 10), there was a subsequent increase in the p-value from p = 0.063 to p = 0.082. Further enlargement of the cohort may not necessarily result in improved outcomes. Unfortunately, it was not possible to include more patients due to interference with another study. Another limitation concerned the inclusion of resected patients only. This could potentially have introduced selection bias and could confound the outcomes as these patients have a better prognosis. However, this strict inclusion criterion was also deemed a relative strength as we analyzed whole-mount resection specimens. Histopathological grade is known to more dependable in a whole-mount resection specimen whereas biopsied tissue samples can suffer from sampling bias histopathologically. Another limitation of imaging

studies using DWI concerns the lack of harmonization of imaging protocols. In this specific study, the imaging protocol was different in three patients with the use of different b-values. High b-values of 800–1000 s/mm^2 are widely used; however, the use of higher (calculated) b-values can be useful for improved delineation of PDAC because diffusion-restricted tissues show relatively higher signal intensity than the normal pancreatic parenchyma with the increasing b-values [6], thus, better capturing pure water diffusion, regardless of perfusion effects.

Conclusions

The measurement of the ADC for determining tumor aggressiveness in individual patients with resectable pancreatic cancer is not useful, as there is no correlation with histological grade or OS and there is substantial overlap in the ADC values between grades. The outcome of this study along with contradicting reports of other studies indicate there are other, yet-to-be identified factors contributing to the ADC values. To gain a better understanding of ADC values in pancreatic tumors, it might be necessary to compare in vivo MR images with whole-mount digital pathology slides to identify spatially discriminating imaging features, as has been done for prostate [41,42] and renal tumors [43].

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Chapter 7

Qualitative flow metabolic phenotype of pancreatic cancer. A new prognostic biomarker?

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Abstract

Background

Retrospective analysis to investigate the relationship between the flow-metabolic phenotype and overall survival (OS) of pancreatic ductal adenocarcinoma (PDAC) and its potential clinical utility.

Methods

Patients with histopathologically proven PDAC between 2005 and 2014 using tumor attenuation on routine pre-operative CECT as a surrogate for the vascularity and [18F]FDG-uptake as a surrogate for metabolic activity on [18F]FDG-PET.

Results

In total, 93 patients (50 male, 43 female, median age 63) were included. Hypoattenuating PDAC with high [18F]FDG-uptake has the poorest prognosis (median OS 7 ± 1 months), compared to hypoattenuating PDAC with low [18F]FDG-uptake (median OS 11 ± 3 months; p = 0.176), iso- or hyperattenuating PDAC with high [18F]FDG-uptake (median OS 15 ± 5 months; p = 0.004) and iso- or hyperattenuating PDAC with low [18F] FDG-uptake (median OS 23 ± 4 months; p = 0.035). In multivariate analysis, surgery combined with tumor differentiation, tumor stage, systemic therapy and flow metabolic phenotype remained independent predictors for overall survival.

Discussion

The novel qualitative flow-metabolic phenotype of PDAC using a combination of CECT and [18F]FDG-PET features, predicted significantly worse survival for hypoattenuating-high uptake pancreatic cancers compared to the other phenotypes.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis which has gradually improved in the past 20 years.[1] The incidence for PDAC has been estimated to increase by 66% between 2020 and 2040 and it is predicted to be the second cause of cancer related death in 2026.[2] Only 15–20% of the patients diagnosed with PDAC are considered for resection as the remainder of the patients present with locally advanced and/or metastatic disease and curative surgical treatment is no longer possible.[1] The 5-year survival rate is only 9%[3] up to 16.5% for resected patients.[1] Traditional prognostic factors associated with poorer survival include larger tumor size, major blood vessel invasion, the presence of nodal or distant metastasis, the presence of residual disease after resection, high histologic grade, and poor performance status. New therapeutic approaches such as FOLFIRINOX in the neoadjuvant or palliative setting are under investigation. [4- 8] Accurate patient stratification prior to treatment is crucial to benefit from these new strategies. Thus, the demand for non-invasive imaging biomarkers that better correlate with tumor biology, as opposed to conventional anatomic-morphologic approaches, is evident.

Previous CT studies have suggested that the physiological vascular information from dynamic contrast-enhanced imaging can have a role in diagnosis, grading and response assessment.[9] The presence of dense desmoplastic stroma, a hallmark of PDAC, leads to a substantial interstitial pressure resulting in vascular collapse and tumor hypoperfusion, which limits oxygen and nutrient availability[10- 12] and hinders drug delivery to cancer cells.[13] Tumors that are hypoattenuating on the portal-venous phase on CT scan are more aggressive with poor tumor differentiation, more lymph node metastases, and shorter disease-free survival.[14] Conversely, visually isoattenuating tumors have a better survival after surgery with curative intent.[15] Although [18F]FDG-PET is not able to accurately define tumor extent relative to the surrounding tissues, it has proved useful in modifying the staging of PDAC for 10% of cases, changing the decision making in about 50% of cases and sparing non-useful surgery in 20% of cases, usually due to the detection of previously undetected metastases.[16] Using the tumor glucose metabolism [18F]FDG-PET can be useful to detect local recurrence, assess therapeutic effects, and predict prognosis in PDAC patients.[17-20] [18F]FDG-PET SUVmax was significantly associated with the therapeutic response to chemoradiotherapy in PDAC patients[21] and in a subset of patients with

interval metabolic imaging after initial chemotherapy, complete metabolic response highly correlated with major pathologic response.[22,23] Additionally, tumors with higher rates of glycolysis but lower cholesterol synthesis are known to be more aggressive and less sensitive to chemotherapy than tumors with a more cholesterogenic phenotype.[24,25]

Until recently, perfusion and metabolism have mostly been used separately. The balance between tumor vascularity and glucose metabolism offers complementary information concerning tumor adaption to the microenvironment. Matched high glucose metabolism with increased vascularity represents a different biologic status compared to mismatched high metabolism with lower vascularity, with the latter indicating adaptation to hypoxia.[26] Long term adaptation to hypoxic conditions, may facilitate cancer progression and treatment resistance.[27] However, a flow-metabolic phenotype has not been defined for PDAC.

The purpose of this study is to investigate the relationship between the qualitative flow-metabolic phenotype and overall survival of PDAC and its potential clinical utility, using tumor attenuation on routine contrast-enhanced CT (CECT) as a surrogate for the vascularity and [18F]FDG uptake as a surrogate for metabolic activity on [18F]FDG-PET.

Methods

Study design and outcome measures

All adult patients with histopathologically proven PDAC who received both a CECT and a [18F]FDG-PET scan in accordance with prevailing guidelines between 2005 and 2014 were eligible for inclusion. Patients were identified in the electronic medical records of our institution. CT scans and [18F]FDG-PET scans were either performed in our university hospital or in community hospitals. Exclusion criteria were pathological diagnosis other than PDAC and a time interval between CECT and [18F]FDG-PET of more than 60 days.

The primary outcome measure evaluated in this study was overall survival. The institution's electronic medical records and the Statistics Netherlands (CBS), until 31st of December 2021, were used to establish the overall survival. Overall survival was measured from the day of diagnosis until death. Censoring was performed for loss to follow up or survival at 31st of December 2021.

Tumor characteristics such as tumor size and tumor grade were obtained from the pathology report. Tumor size on CECT in portal-venous phase was used in analyses in patients that did not undergo curative resection. Tumor grade was coded well differentiated, moderately differentiated, and poorly differentiated. Tumor stage was recorded according to the 8th edition of the AJCC Staging Manual. For patients that did not undergo resection pathological stage was supplemented with clinical stage. Information on treatment (surgery, systemic therapy) was obtained from the electronic medical records.

CT quantitative and qualitative analysis of flow

CT scans were reviewed by a single observer (JH) with 20 years of experience in abdominal radiology. Qualitative and quantitative assessment of attenuation has excellent interobserver agreement,[28] therefore single reader assessment of CT images suffices. Image quality was deemed insufficient in case of severe motion artefacts or low signal to noise ratio (SNR). For image analysis images in the portal-venous phase were used, defined as enhancement of both the portal vein and the hepatic veins, which were extracted from either the CT pancreas protocol or routine abdominal CT images in the absence of a multiphase pancreas CT. The largest tumor diameter was measured in the axial plane, and the images were evaluated in the portal-venous phase. Tumor enhancement was used as a surrogate for the vascularity. Hypoattenuation and isoattenuation qualitatively indicated a state of low and normal blood flow respectively and hyperattenuation a state of increased flow. For quantitative analysis, the Hounsfield unit (HU) value in the tumor was determined, and if possible, the HU value upstream or downstream in the surrounding pancreas parenchyma. A circular region of interest (ROI) with the largest possible diameter was placed in the tumor and in the surrounding pancreas parenchyma of the pancreatic head, body, and tail. Isoattenuating PDAC was defined as a difference in attenuation value of less than 10 HU between surrounding pancreas parenchyma (HUP) and pancreas tumor (HUT): $-10 \leq HUP - HUT \leq 10$. Hypoattenuating PDAC was defined as a difference in attenuation value of more than 10 HU between surrounding pancreas parenchyma and tumor: $HUP - HUT > 10$. Hyperattenuating PDAC was defined as a difference in attenuation value of more than 10 HU in the tumor compared to surrounding pancreas parenchyma: $HUP - HUT < -10$. If it was impossible to measure the difference in HU between the tumor and surrounding parenchyma, tumors were visually evaluated. Isoattenuating PDAC was qualitatively defined as

a tumor visually not discernible from surrounding pancreas parenchyma. Hypoattenuating PDAC was qualitatively defined as a tumor darker than surrounding pancreas parenchyma, hyperattenuating PDAC was qualitatively defined as a tumor brighter than surrounding parenchyma.

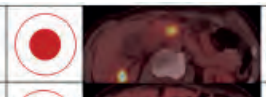
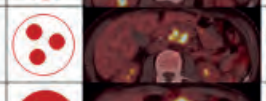
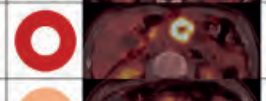
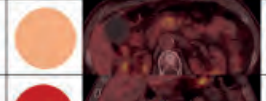
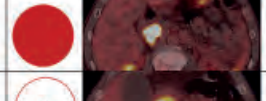
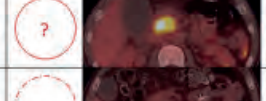
1		Focal hotspot	High uptake	Heterogeneous	n = 14
2		Multifocal hotspots	High uptake	Heterogeneous	n = 13
3		Ring shaped	High uptake	Heterogeneous	n = 11
4		Low	Low uptake	Homogeneous	n = 8
5		High	High uptake	Homogeneous	n = 22
6		Indeterminate			n = 16
7		No uptake	Low uptake	Homogeneous	n = 9

Figure 1. [18F]FDG-uptake patterns

PET qualitative analysis of metabolism

[18F]FDG-PET images were obtained in our university hospital using Siemens EXACT, Siemens Biograph2 and Siemens mCT40 or in community hospitals (n = 3; Philips Gemini GXL, Philips unknown model, unknown vendor, and model). The median FDG dose was 236 megabecquerel (range 75–384). [18F]FDG-PET images were reviewed and individually scored using Hermes (Hermes P5 Gold, version 4.6-A) by two observers (MG and LGO) with more than 25 years of experience. Image quality was deemed insufficient in case of severe motion artefacts or low SNR. After visual identification of the primary pancreatic lesion with guidance of CT or MR images, a qualitative evaluation was performed based on [18F]FDG uptake. The [18F]FDG uptake of the tumor was defined low uptake or high uptake compared to uptake of the liver. SUVmax was not measured, because EARL reconstructions were not available for all patients. Discordant results were solved by consensus reading. Different uptake patterns were recorded: focal hotspot, multifocal hotspots, ring-shaped, homogeneous low, homogeneous high, indeterminate, no uptake. High uptake was defined as uptake pattern 1, 2, 3, 5 and low

uptake was defined as uptake pattern 4 and 7. Indeterminate pattern contained both high uptake tumors (n = 15) and low uptake tumors (n = 1). Heterogeneous uptake was defined as uptake pattern 1, 2 and 3 (Fig. 1).

Statistics

SPSS (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.) was used for all statistical analysis. The summary statistics are presented as the median (± SD and range) for continuous variables, or frequency and percentage for categorical variables. For between-group analyses student t-test was used for comparing means and chi-square test was used for categorical data. Kaplan–Meier curves for overall survival analysis were generated and compared using the Mantel Cox log-rank test. Cox regression survival analysis was performed on various factors to examine possible confounding factors for survival. A statistically significant result was defined as $p < 0.05$.

Results

Population

A total of 137 patients were retrieved from the hospitals' electronic patient database with suspected PDAC who underwent both a CECT scan and a [18F]FDG-PET scan between January 2005 and December 2014 as primary diagnostic workup. After 2014 [18F]FDG-PET was not part of the diagnostic workup anymore. Patients without a histopathological proof of PDAC were excluded (n = 16), as were patients with a pathological diagnosis other than PDAC; cholangiocarcinoma (n = 10), ampulla of Vater carcinoma (n = 3), double tumor of the pancreas (n = 2), duodenum tumor (n = 1), malignant intraductal papillary mucinous neoplasm IPMN (n = 1) and anaplastic carcinoma (n = 1). Three patients were excluded because imaging quality was not sufficient, and seven patients were excluded because the imaging interval was more than 2 months. Finally, 93 patients (50 male, median age 63 years) were included (Table 1). PDAC mostly occurred in the pancreatic head (86%). In 8 patients the tumor diameter could not be reliably measured due to poor demarcation or ill-defined tumor borders. The mean time interval between imaging was 13.2 days (SD 15.2). A curative resection was performed in 39 patients: pancreatoduodenectomy n = 33, distal pancreatectomy n = 5 and subtotal pancreatectomy n = 1. In 30 patients exploratory laparotomy or laparoscopy was performed with or

without surgical bypass. The other 24 patients did not undergo surgery. In total, 32 patients received adjuvant and/or palliative systemic therapy. One of these patients also received neoadjuvant chemoradiotherapy, imaging included in this study was performed before treatment. Most patients were too weak to undergo systemic therapy (although performance status was not registered in most patients), some patients choose quality of life over systemic therapy, and in 10 patients data on systemic therapy was missing. At the time of analysis, 89 patients had died, with a median follow up of 9 months (range 1–94 months), with a loss to follow up of n = 4. The median overall survival was 10 months.

CT patterns

Of the 93 patients, 65 patients had hypoattenuating tumors and 28 patients had iso- or hyperattenuating tumors (Table 2). In 22 patients the difference in HU value between tumor and surrounding pancreatic tissue was not measurable due to upstream atrophy, chronic pancreatitis, or diffuse tumor infiltration. In these patients, attenuation was graded visually. Most of these tumors (n = 21) were located in the pancreatic head. There was a statistically significant difference in OS between hypo- and iso- or hyperattenuating tumors with a median OS of 8 ± 0.9 months versus 20 ± 4.2 months ($p = <0.001$). Iso- or hyperattenuating tumors were all located in the head of pancreas ($p = 0.011$), had significantly lower tumor stage ($p = 0.007$) and underwent curative resection more often ($p < 0.001$). There was no significant difference in overall survival between iso- or hyperattenuating tumors versus hypoattenuating tumors in stage I/II ($p = 0.444$), stage III ($p = 0.089$) and stage IV ($p = 0.182$).

Table 1. Demographic characteristics

	All patients (n = 93)	**Resectable PDAC (n = 39)**
Age years (median)	63 SD 10.3, range 30–80	64 SD 10.3, range 30–78
Gender		
Male	50 (54%)	20 (51%)
Female	43 (46%)	19 (49%)
Tumor location		
Head	80 (86%)	35 (90%)
Body–tail	13 (14%)	4 (10%)
Diameter mm (median)	26 (n = 85) SD 10.0, range 6–60	26 SD 9.9, range 6–60
Tumor grade		
Well	3 (3%)	2(5%)
Moderate	16 (17%)	14 (36%)
Poor	21 (23%)	19 (49%)
Unknown	53 (57%)	4 (10%)
Tumor stage		
I	10 (11%)	9 (23%)
II	17 (18%)	16 (41%)
III	31 (33%)	14 (36%)
IV	35 (38%)	–
Curative surgery	39 (42%)	
Systemic therapy		
Yes	32 (34%)	19 (49%)
No	51 (55%)	17 (44%)
Unknown	10 (11%)	3 (8%)
Overall survival		
Median	10 months	21.2 months
1 year survival	45%	79%
3 year survival	12%	28%
5 year survival	4%	10%

Table 2. Demographic characteristics of patients with iso- or hyperattenuating versus hypoattenuating tumors

	Iso- or hyperattenuating (n = 28)	**Hypoattenuating (n = 65)**	***p*-value**
Age years (median)	64 SD 11.5, range 30–80	63 SD 10.1, range 35–79	0.394
Gender			0.182
Male	18 (64%)	32 (49%)	
Female	10 (36%)	33 (51%)	
Tumor location			**0.011**
Head	28 (100%)	52 (80%)	
Body–tail	–	13 (20%)	
Diameter mm (median)	25 (n = 23) SD 10.2, range 6–55	28 (n = 62) SD 9.8, range 14–60	0.055
Tumor grade			0.111
Well	3 (11%)	–	
Moderate	6 (21%)	10 (15%)	
Poor	8 (29%)	13 (20%)	
Unknown	11 (39%)	42 (65%)	
Tumor stage			**0.007**
I	7 (25%)	3 (5%)	
II	6 (21%)	11 (17%)	
III	10 (36%)	21 (32%)	
IV	5 (18%)	30 (46%)	
Curative surgery	19 (68%)	20 (31%)	**<0.001**
Systemic therapy	11 (39%)	21 (32%)	0.503
Overall survival			
Median	20 months	8 months	**<0.001**
1 year survival	75%	32%	
3 year survival	29%	5%	
5 year survival	7%	3%	

FDG patterns

There were 18 patients with low uptake and 75 patients with high uptake (Table 3). Patients with high [18F]FDG-uptake (median OS 9 ± 0.9 months) had a trend of a worse OS compared to patients with low [18F]FDG-uptake (median OS 19 ± 6.3 months; p = 0.175). There was a significant difference in overall survival between low [18F]FDG-uptake tumors versus high

[18F]FDG-uptake tumors in stage IV (p = 0.041).There was no significant difference in stage I/II (p = 0.931) or stage III (p = 0.378). There were several homogenous or heterogeneous (i.e., uni- and multifocal hotspots, ring-shaped) uptake patterns observed (Fig. 1). Patients with heterogeneous tumors (median OS 8 ± 1.2 months) had a significant lower overall survival compared to patients with homogeneous tumors (median OS 13 ± 2.1 months; p = 0.026).

Table 3. Demographic characteristics of patients with high versus low [^{18}F]FDG-U=uptake tumors

	High (n = 75)	**Low (n = 18)**	***p*-value**
Age years (median)	63 SD 10.6, range 30–79	63 SD 9.3, range 44–80	0.467
Gender			0.486
Male	39 (52%)	11 (61%)	
Female	36 (48%)	7 (39%)	
Tumor location			0.714
Head	65 (87%)	15 (83%)	
Body–tail	10 (13%)	3 (17%)	
Diameter mm (median)	27 (n = 69) SD 10.4, range 6–60	25 (n = 16) SD 7.8, range 12–39	0.105
Tumor grade			0.104
Well	1 (1%)	2 (11%)	
Moderate	13 (17%)	3 (17%)	
Poor	18 (24%)	3 (17%)	
Unknown	43 (57%)	10 (56%)	
Tumor stage			0.259
I	9 (12%)	1(5%)	
II	13 (17%)	4 (22%)	
III	22 (29%)	9 (50%)	
IV	31 (41%)	4 (22%)	
Curative surgery	30 (40%)	9 (50%)	0.440
Systemic therapy	26 (35%)	6 (33%)	0.607
Overall survival			0.175
Median	9 months	19 months	
1 year survival	40%	67%	
3 year survival	12%	11%	
5 year survival	5%	0%	

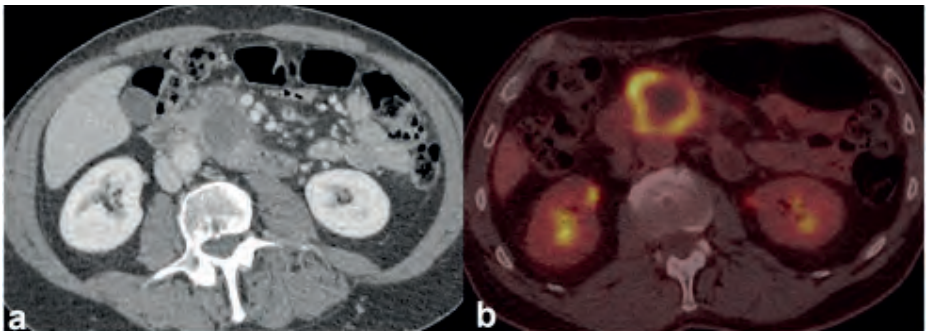


Figure 2. A 64-year-old male with stage 4 PDAC of the pancreatic head (42 mm) and an overall survival of 4 months. The tumor was hypoattenuating on CECT (a) and showed ring-shaped high [18F]FDG-uptake on PETCT (b)

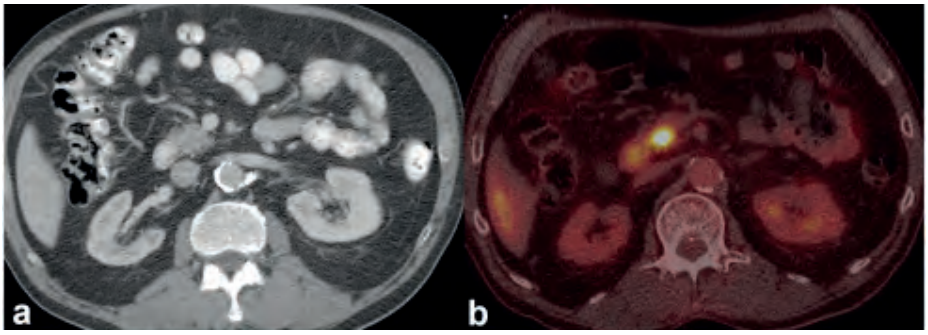


Figure 3. A 77-year-old male with a small (25 mm) poorly differentiated T2N2 PDAC of the pancreatic head who underwent pancreatoduodenectomy with an overall survival of 6 months. The tumor was isoattenuating on CECT (a) and showed homogeneous high [18F] FDG-uptake on PETCT (b)

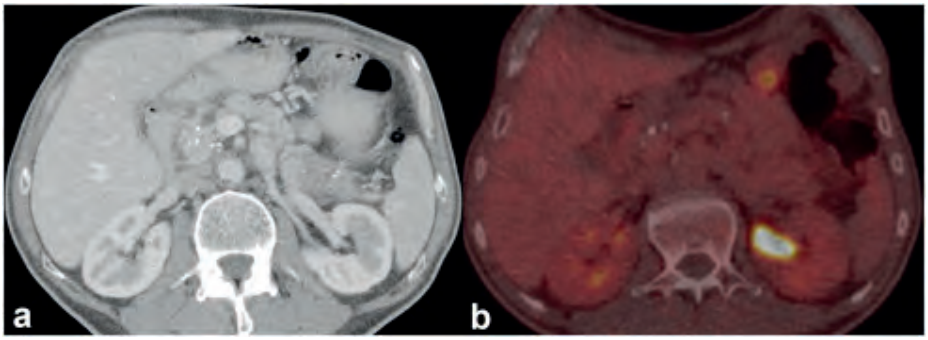


Figure 4. A 56-year-old male with T2N1 PDAC of the pancreatic tail who underwent distal pancreatectomy with an overall survival of 6 months. The tumor (25 mm) was hypoattenuating on CECT (a) and showed low [18F]FDG-uptake on PETCT (b)

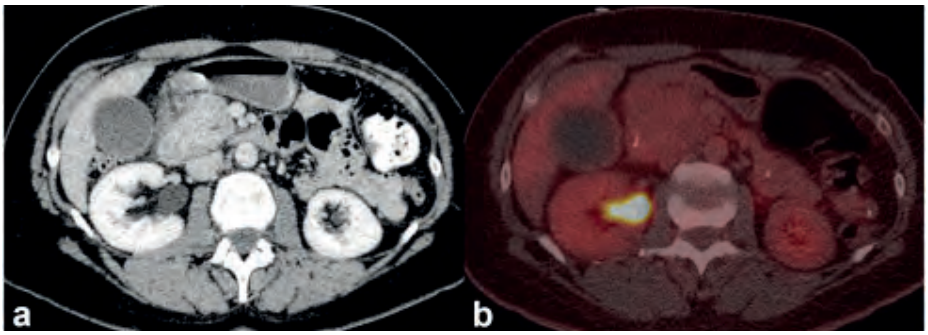


Figure 5. A 44-year-old female with locally advanced PDAC of the pancreatic head who underwent pancreatoduodenectomy after neoadjuvant chemotherapy with an overall survival of 25 months. The tumor was isoattenuating on CECT (a) and showed low [18F] FDG-uptake on PETCT (b)

Qualitative flow-metabolic phenotype

When taking both CECT and PET features into consideration, there were 55 patients with hypoattenuating tumors and high [18F]FDG-uptake (Fig. 2), 20 patients with iso- or hyperattenuating tumors and high [18F]FDG-uptake (Fig. 3), 10 patients with hypoattenuating tumors and low [18F] FDG-uptake (Fig. 4), and finally 8 patients with iso- or hyperattenuating tumors and low [18F]FDG-uptake (Fig. 5). A cross correlation of CECT attenuation and [18F]FDG-uptake pattern revealed that hypoattenuating PDAC with high [18F]FDG-uptake has the poorest prognosis (median OS 7 ± 0.9 months), compared to hypoattenuating PDAC with low [18F]FDG-uptake (median OS 11 ± 2.6 months; p = 0.176), iso- or hyperattenuating PDAC with high [18F]FDG-uptake (median OS 15 ± 4.5 months; p = 0.004) and iso- or hyperattenuating PDAC with low [18F]FDG-uptake (median OS 23 ± 3.5 months; p = 0.035) (Fig. 6). There was no significant difference in overall survival between the other groups.

Hypoattenuating PDAC with high [18F]FDG-uptake has significantly higher tumor stage (Stage I/II vs II-IV HR 2.846, 95% CI 1.720–4.708, p < 0.001), lower curative resection rates (HR 3.996, 95% CI 2.420–6.597, p < 0.001) and worse overall survival compared to the other flow-metabolic phenotypes (HR 2.042, 95% CI 1.324–3.150, p = 0.001). Surgery, systemic therapy, and tumor grade were found to be possible confounders. In multivariate Cox regression analysis surgery combined with tumor differentiation (good-moderate diff HR 0.381, 95% CI 0.176–0.821, p = 0.014; poor diff HR 0.410, 95% CI 0.201–0.839, p = 0.015), tumor stage (HR 2.074, 95% CI 1.019–4.222, p = 0.044), systemic therapy (HR 0.562,

95% CI 0.332–0.952, p = 0.032) and flow metabolic phenotype (HR 1.861, 95% CI 1.131–3.060, p = 0.014) remained independent predictors for overall survival. Tumor differentiation was combined with the variable surgery to compensate for missing values in the non-surgically treated patients (no resection was indicator p = 0.017). Missing data occurred in 14 cases in multivariate analysis.

There was no significant difference in overall survival between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage I/II (p = 0.750). There was a significant difference in overall survival between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage III (p = 0.028) and a near significant difference in stage IV (p = 0.056). Additionally, treatment-naïve patients with stage IV tumors had a tendency for a worse prognosis if they had hypoattenuating-high uptake flow-metabolic phenotype with a median overall survival of 4 months versus 6 months in the other phenotypes (p = 0.075). Interestingly, there was no significant difference in overall survival between patients with stage I/II hypoattenuating-high uptake flow-metabolic phenotype and stage III/IV iso- or hyperattenuating-high uptake flow-metabolic phenotype (p = 0.470) or iso- or hyperattenuating-low uptake (p = 0.603).

Subgroup analysis

Only 15/55 (27%) of hypoattenuating-high uptake tumors underwent curative resection versus 24/38 (63%) of the other phenotypes, and 21/55 (38%) were unexpectedly advanced stage at explorative laparotomy versus 9/38 (24%) of the other phenotypes (p = 0.002). Subgroup analysis of resected patients showed age, gender, tumor location, stage, lymph node ratio, grade and systemic therapy were all possible confounders for overall survival but were not independent predictors in multivariate analysis. After curative resection there was no significant difference in overall survival between hypoattenuating-high uptake tumors versus other phenotypes, whether patients received systemic therapy or not. Subgroup analysis of palliative patients showed age, stage, tumor size and systemic therapy were possible confounders. In multivariate Cox regression analysis tumor stage (HR 3.350, 95% CI 1.439–7.802, p = 0.005), systemic therapy (HR 0.231, 95% CI 0.092–0.580, p = 0.002), tumor size (HR 1.036, 95% CI 1.004–1.069, p = 0.026) and flow metabolic phenotype (HR 4.333, 95% CI 1.525–12.309, p = 0.006) remained independent predictors for overall survival.

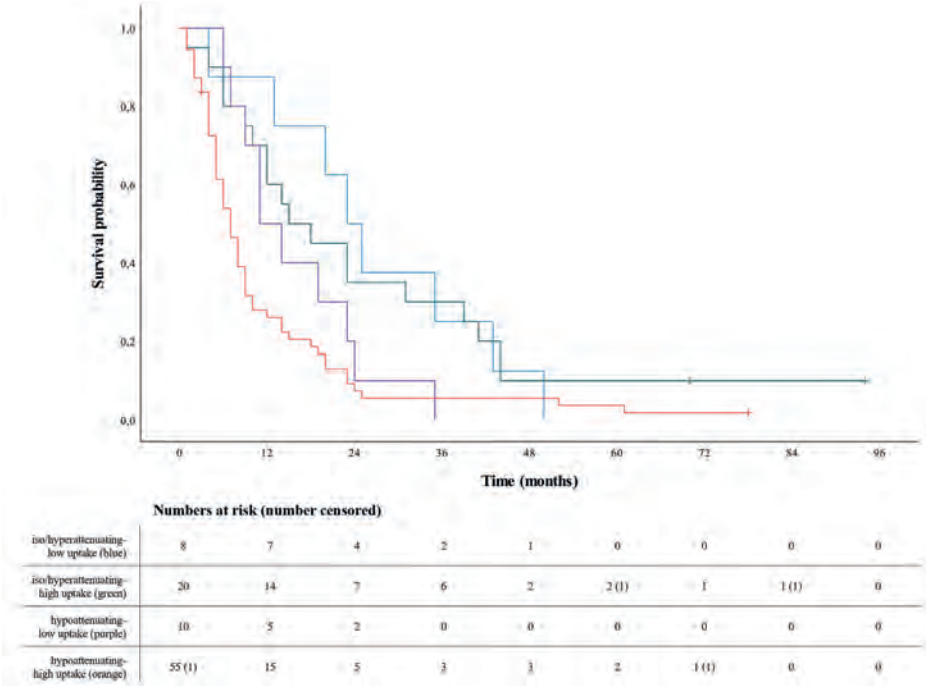


Figure 6. Kaplan–Meier survival curve, with follow-up duration of 8 years after diagnosis of PDAC (total n = 93). Censored values (+) indicate the last known follow-up time for subjects still alive after diagnosis or lost to follow up. Flow-metabolic phenotype, χ^2 12,694, p = 0.005). Median survival iso-or hyperattenuating-low uptake tumors 23 months, 95% CI 16–30 months (blue), median survival iso-or hyperattenuating-high uptake tumors 15 months, 95% CI 6–24 months (green), median survival hypoattenuating-low uptake tumors 11 months, 95% CI 6–16 months (purple), median survival hypoattenuating-high uptake tumors 7 months, 95% CI 5–9 months (orange)

Discussion

In this study, we demonstrated that the qualitative flow-metabolic phenotype of PDAC using the combination of CECT and [18F]FDG-PET features, predicted significantly worse survival for hypoattenuating-high uptake PDAC compared to the other phenotypes. Hypoattenuating-high uptake tumors had a median OS of 7 months compared to an OS of 23 months in patients with iso- or hyperattenuating-low uptake tumors. Hypoattenuating PDAC with high [18F]FDG-uptake has significantly higher tumor stage and more advanced stage found at exploratory laparotomy leading to lower curative resection rates. In multivariate analysis surgery combined with tumor grade, tumor stage, systemic therapy and flow

metabolic phenotype remained independent predictors for overall survival. Patients with stage I/II hypoattenuating-high uptake flow-metabolic phenotype did not show a significant difference in overall survival compared to those with stage III/IV iso- or hyperattenuating-high uptake flow-metabolic phenotype. In stage III, a significant difference in overall survival was observed between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage III ($p = 0.028$). A near-significant difference was observed in stage IV. Notably, among patients with stage IV tumors who did not undergo palliative systemic therapy, there was a trend towards a worse prognosis in the hypoattenuating-high uptake flow-metabolic phenotype. These findings support the hypothesis that the combination of high tumor metabolism and low blood flow does represent an aggressive PDAC tumor biology with unfavorable prognostic characteristics. Above all, curative resection remains the best chance of better overall survival. No significant difference in overall survival was observed between hypoattenuating-high uptake flow-metabolic phenotype versus other phenotype tumors in stage I/II.

In one previous study with a small number of patients with pancreatic cancer, in which [15O]water was used to measure blood flow, a high SUVmax/blood flow ratio was a strong predictor of poor survival.[29] In this study tumor attenuation on CECT was used as a surrogate for the vascularity, because it is routinely available, in contrast to [15O]water.

[18F]FDG-PET is currently not routinely performed for PDAC. However, it is increasingly being integrated into staging algorithms. For instance, the NICE guidelines in the UK recommend the use of [18F]FDG-PET for individuals with localized disease on CECT who will undergo cancer treatment, whether that involves surgery, radiotherapy, or systemic therapy. In combination with the discovery of novel molecular subtypes of PDAC, which use different metabolic pathways as their main source of energy, it is not possible to omit the use of [18F]FDG-PET in PDAC. The subtypes are largely divided into two broad subtypes; the better prognostic classical/progenitor subtype and the worse prognostic squamous/basal-like/quasi-mesenchymal subtype[30, 31, 32] characterized by a higher tumor grade, worse overall survival, higher risk of metastasis[33] and liver recurrence.[34] Recent literature showed the worse prognostic squamous subtype is highly catabolic and utilizes glycolysis as their main source of energy and is more sensitive to glycolysis inhibition, which is used as a novel metabolic therapeutic agent.[35]

Although it is known that [18F]FDG uptake might be absent in PDAC, it is rarely emphasized in current literature. In this study low [18F]FDG uptake tumors were present in 19% of patients, who demonstrated a trend of better overall survival compared to high [18F]FDG uptake. The squamous subtype is more likely to be associated with body/tail pancreatic cancer,[36] while the prognostically favorable Bailey's immunogenic subtype was almost exclusively found in the pancreatic head tumors.[37,38] Interestingly, in agreement with the previous studies iso- and hyperattenuating tumors (n = 28) all presented in the pancreatic head, had higher curative resection rates and a significant better overall survival.[39,40] This adds to the hypothesis that iso- and hyperattenuating tumors are not early PDAC, but might be different molecular, genomic, metabolic or pathological entities compared to hypoattenuating tumors.[41] Molecular subtyping and information on tumor biology, including tumor aggressiveness and chemosensitivity, may aid in treatment planning and selection.

Stratifying tumors in hypoattenuating versus iso- and hyperattenuating and high versus low uptake does not take into account the heterogeneity of the tumor, which is a well-known hallmark of PDAC[42] and reflected in the macroscopically different uptake patterns that we observed. The [18F] FDG uptake in tumors is heterogeneous due to both neoplastic and non-neoplastic components such as tumor cells, (activated) stromal cells and necrosis and is related to the degree of vascularity, hypoxia, metabolic reprogramming, and proliferative capacity. Equally important, there is the intrinsic metabolic plasticity of pancreatic cancer cells. Tumor cells in hypoxic regions, due to poor perfusion caused by dense stroma, tend to undergo epithelial–mesenchymal transition (EMT) and exhibit elevated glycolysis compared to tumor cells in normoxic areas.[43] EMT is associated with features that negatively effects overall survival, such as tumor invasion, metastases formation and treatment resistance.[44] Our study demonstrated that using both PET and CT have an advantage compared to using either PET or CT alone in predicting overall survival. When comparing the imaging features, demographic and prognostic aspects, the hypoattenuating-high uptake tumors could represent the squamous/basal-like/quasi mesenchymal subtypes enriched with mesenchymal signatures. This is clinically relevant, as chemotherapy responses may differ among the different subtypes. The basal-like population is more sensitive to gemcitabine treatment and less sensitive to modified-FOLFIRINOX (mFFX), while there is a favorable impact of mFFX in classical PDAC.[45, 46, 47] Unfortunately, due to the low

number of patients who underwent chemotherapy and the missing data on the specific chemotherapeutic regimens, we were unable to assess the potential of using the flow-metabolic phenotype to stratify patients into therapy-resistant groups. Nonetheless, the limited number of patients receiving chemotherapy is consistent with nationwide numbers for the years of inclusion.[1] In future studies, a more comprehensive analysis of this aspect may be particularly relevant in the context of the current era of (neo) adjuvant therapies. The main limitation of this study is the heterogeneous study population, which includes all tumor stages and different treatment strategies, which influences overall survival data and complicates interpretation of the results. Selection bias were introduced in this study, as only patients who were potentially eligible for resection on CECT received an [18F]FDG-PET scan for the exclusion of distant metastasis. This is reflected in the high percentage of resected tumors, 41.0%, whereas normally only 15–20% of the patients undergo surgery. Isoattenuating tumors were found in 28% of patients, which was somewhat higher than the reported prevalence of 5%–23%.[15,48, 49, 50] Both may reflect a certain heterogeneity in the study population.

This study demonstrated promising results using routine CECT and [18F] FDG-PET to define a novel qualitative flow-metabolic phenotype that reflects perfusion and metabolism of pancreatic ductal adenocarcinoma. Future integration of [18F]FDG-PET and perfusion CT holds the potential to generate a fully quantitative flow-metabolic phenotype. This approach can be instrumental in facilitating tumor classification and advancing precision medicine. Furthermore, if the flow-metabolic phenotype can effectively distinguish molecular subtypes, it can serve as the foundation for more personalized treatment strategies. Future research may explore the application of machine learning or deep learning to analyze CT and [18F] FDG-PET, as there are different contrast enhancement patterns and [18F] FDG-uptake patterns. Texture analysis could offer a more comprehensive evaluation, considering the typical tissue heterogeneity in PDAC.

Concluding, the qualitative flow-metabolic phenotype of PDAC using the combination of CECT and [18F]FDG-PET features, predicted significantly worse survival for hypoattenuating-high uptake pancreatic cancers compared to the other phenotypes. Hypoattenuating PDAC with high [18F] FDG-uptake has significantly lower resection rates and represents an

aggressive tumor biology. This novel flow-metabolic phenotype of PDAC might be useful as a prognostic biomarker.

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Chapter 8

Improving preoperative detection of synchronous liver metastases in pancreatic cancer with combined contrast-enhanced and diffusion-weighted MRI

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Abstract

Purpose

To explore the value of gadolinium-enhanced MRI combined with diffusion-weighted MRI (Gd-enhanced MRI with DWI) in addition to contrast-enhanced CT (CECT) for detection of synchronous liver metastases for potentially resectable pancreatic cancer.

Methods

By means of a retrospective cohort study we included patients with potentially resectable pancreatic cancer on CECT, who underwent Gd-enhanced MRI with DWI between January 2012 and December 2016. A single observer evaluated MRI and CT and was blinded to imaging, pathology, and surgery reports. Liver lesions were scored in both modalities, using a 3-point scale: 1-benign, 2-indeterminate, 3- malignant (i.e., metastasis). The primary outcome parameters were the presence of liver metastases on Gd-enhanced MRI with DWI and the sensitivity of Gd-enhanced MRI with DWI for synchronous liver metastases.

Results

We included 66 patients (42 men, 24 women; median age 65 years, range 36–82 years). In 19 patients, liver metastases were present, which were confirmed by histopathology (n = 12), 18FDG-PET (n = 6), or surgical inspection (n = 1). Gd-enhanced MRI with DWI showed metastases in 16/19 patients (24%), which resulted in a sensitivity of 84% (95% CI 60–97%). Contrast-enhanced MRI showed 156 and DWI 397 metastases (p = 0.051), and 339 were particularly small (< 5 mm).

Conclusions

In this study, Gd-enhanced MRI with DWI detected synchronous liver metastases in 24% of patients with potentially resectable pancreatic cancer on CECT with a sensitivity of 84%. Diffusion-weighted MRI showed a greater number of metastases than any other sequence, particularly small metastases (< 5 mm).

Introduction

Pancreatic cancer is one of the most lethal forms of cancer with a 5-year relative survival rate of 6% reported by the American Cancer Society [1]. Total deaths due to pancreatic cancer are increasing dramatically and expected to become the second leading cause of cancer-related deaths before 2030 [2, 3]. Surgery of localized pancreatic cancer offers the only realistic chance to cure. Approximately 10–20% of patients do have unexpected liver metastases, peritoneal carcinomatosis, or locally advanced disease at the time of surgery [4,5,6]. More than 50% of all liver metastases develop in the first six months postoperatively, even in patients with early tumor stage [7]. These findings suggest that liver metastases are already present at the time of surgery, which is supported by the mathematical model by Haeno et al., predicting that patients likely harbor metastases at diagnosis [8]. These synchronous liver metastases are not identified pre-operatively, as they are too small to be detected by routine preoperative ultrasound and contrast-enhanced CT (CECT) [9].

International guidelines advise CECT for routine diagnosing and staging of pancreatic cancer, whereas MRI is mostly used for characterization of indeterminate liver lesions [10]. CECT allows accurate assessment of the relationship between the tumor and critical arterial and venous structures [11]. However, the detection of subcentimeter metastases by CECT poses a greater challenge. Even if subcentimeter liver lesions are identified on a preoperative CT scan, the ability to precisely characterize those lesions as malignant is limited [12].

Nowadays, diffusion-weighted MR imaging (DWI) is increasingly used for hepatic imaging and has been shown to be a valuable tool in both detection and characterization of focal liver lesions with a sensitivity ranging from 86 to 97% and 60 to 91% for subcentimeter lesions [13,14,15,16]. Most studies have been performed for liver metastases of colorectal cancer. There are limited studies performed in pancreatic cancer, all concluding that additional MRI is useful in detecting liver metastases. Most studies used 1,5T scanners [9, 17,18,19,20]. In the 3,0T scanners, the increased signal-to-noise ratio can be translated into a higher resolution, and the improved contrast-to-noise ratio of gadolinium-based contrast agent can both contribute to improved lesion detection and characterization [21]. Liver-specific contrast agent was used in the studies by Ito et al., Motosugi

et al. and Chew et al. for the detection of liver metastases [17, 19, 22]. In the ESGAR consensus statement, gadoxetate disodium is recommended for the diagnosis and characterization of malignant liver lesions in non-cirrhotic livers [23]. Aside from the associated higher costs, the relative hepatic enhancement could be negatively influenced by high serum bilirubin levels, which is common in patients with obstructive jaundice in pancreatic cancer of the head [24]. In this retrospective study, we evaluated the sensitivity of nonspecific extracellular gadolinium contrast-enhanced MRI (Gd-enhanced MRI) combined with DWI for synchronous liver metastases in potentially resectable pancreatic cancer on a 3T MR scanner.

Materials and methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Setting and participants

All patients older than 18 years with potentially resectable pancreatic cancer without liver metastases on CECT and additional Gd-enhanced MRI with DWI performed in our hospital from January 2012 to December 2016 were eligible for inclusion. Patients were recruited from the Radiology Information System. MRI was routinely performed in our center in all patients with potentially resectable disease or indeterminate liver lesions on CECT. Patients with locally resectable or borderline resectable pancreatic cancer were included. Resectability was established using criteria of the Dutch Pancreatic Cancer Group (PREOPANC trial, DPCG 2012). Exclusion criteria were local or systemic treatment for pancreatic cancer prior to imaging, locally advanced pancreatic cancer on CECT, incomplete liver imaging, and a time interval between CT and MRI or imaging and surgery of more than 2 months. The primary outcome parameters were the presence of liver metastases on Gd-enhanced MRI with DWI and the sensitivity of Gd-enhanced MRI with DWI for synchronous liver metastases. The secondary endpoint was the number of lesions suspicious for metastases detected by the different MRI sequences. Confirmation of liver metastases was obtained by histopathology, 18FDG-PET, and surgical findings. Explorative

surgery was performed in all patients with (borderline) resectable tumors without histopathological proof or 18FDG-PET confirmation of metastases. Demographic characteristics were collected from the electronic medical records. Survival rates were obtained from the general practitioners in October 2015 and were updated in January 2018 from data in the electronic medical records.

CT technique

CECT was performed in different hospitals and produced at different models of 16- and 64-row multidetector CT scanners. Only high-quality datasets with image acquisition in the portal-venous phase and slice thickness of 3–5 mm were included for analysis.

Table 1. MR Imaging Parameters

Parameter	**T1- weighted imaging In- and opposed phase (VIBE)**	**T2-weighted imaging (HASTE)**		**T1-weighted imaging (VIBE)Pre- and postcontrast**		**Diffusion-weighted imaging (SPAIR)**
Plane	Axial	Axial	Coronal	Axial	Coronal	Axial
Section thickness (mm)	3	5		3	1.5	5
Intersection gap (mm)	0	0.5		0	0	1
Repetition time (msec)	4.35	1600	1400	4.34	2.92	>2100
Echo time (msec)	2.45 – 1.33	95	87	1.89	1.05	71
Flip angle (degree)	9	90/160	90/180	9	11	90/180
Field of view (cm)	30	35		30	30	38
Matrix	320 x 195	320 x 256		320 x 195	256 x 243	192 x 156
Bandwidth (Hz/pix)	975	710/710		445	650	1736

MRI technique

All MR imaging of the abdomen was performed in our academic tertiary referral center on a 3.0 Tesla system (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). The imaging protocol is displayed in Table 1. The protocol consisted of a T1-weighted axial in- and opposed phase gradient-echo VIBE, a half Fourier acquisition single-shot turbo spin-echo (HASTE), pre- and post-contrast T1-weighted 3D gradient-echo VIBE, and a respiratory triggered single-shot spin-echo echoplanar DWI in the transverse plane with monopolar diffusion gradients along three orthogonal

directions with b-values of 0/50, 500, and 800 s/mm2, using δ = 10.1 ms and Δ = 33.5 ms. Fifteen ml of gadoterate meglumine 0.5 mmol/mL (Dotarem, Guerbet, Villepinte, France) was injected in an antecubital vein at 2.5 ml/s with a saline flush (NaCl 0.9%) of 20 ml at 2.5 ml/s using a pump injector (Optistar Elite, Mallinckrodt, Dublin, Ireland). MR cholangiopancreatographic images were also obtained; these images were not used in this study.

Image interpretation

MR images were consecutively reviewed by a radiologist (JH) with 14 years of experience in abdominal and pancreas imaging, on a commercial PACS workstation (Impax, Agfa Healthcare, Belgium). The observer was blinded to all clinical information, pathology reports, and the original radiology report, aside from the diagnosis of pancreatic cancer. In both modalities, liver lesions were scored using a 3-point scale: 1-benign, 2-indeterminate, 3-malignant (i.e., metastasis). Number, size, location, and imaging characteristics and the presumed diagnosis of the lesion were noted. Benign lesions were diagnosed using established imaging criteria [25,26,27]. On CECT, hypodense lesions that show typical features of a simple cyst (fluid attenuation measurements, round-oval, well-defined borders, no contrast enhancement), a hemangioma (localization next to vessels, peripheral nodular enhancement, centripetal fill-in), or focal fatty infiltration (geographic hypodense area, angular margins, typical location) are classified as benign lesions. Indeterminate liver lesions on CECT included hypodense liver lesions that were too small to be characterized. Metastases are hypodense lesions with rim enhancement. On MRI, metastases of pancreatic cancer are typically of moderately high to isointense signal intensity on T2W-images and mildly hypointense to isointense on T1W-images. Metastases can either be hypo- or hypervascular, and show homogeneous or peripheral enhancement (ring or wedge-shaped) in the arterial phase, homogeneous enhancement or peripheral enhancement with complete or incomplete centripetal progression in the portal-venous and interstitial phase [28]. On DWI, a lesion was classified as malignant (i.e., metastasis) when it was (moderately) hyperintense at b = 0/50 s/mm^2 and remained hyperintense at the highest b = 800 s/mm2 and a lesion was considered benign when it was hyperintense at b = 0/50 s/mm2 and showed a substantial decrease in signal intensity at higher b-values (b = 500 and 800 s/mm2). If none of the criteria were met, a lesion was classified as indeterminate. For the analysis, indeterminate lesions were classified as benign, as in clinical practice indeterminate lesions that cannot be further

classified will be regarded as benign unless proven otherwise by biopsy. Whenever more than ten malignant lesions (i.e., metastasis) per slice were present, the number of malignant lesions per slice was estimated in dozens.

Statistical methods

All data were processed using SPSS software (version 20, SPSS, Chicago, IL). The sensitivity of Gd-enhanced MRI with DWI was calculated with a 95% confidence interval (CI). ANOVA test was performed to determine the differences between the group with liver metastases and the group without liver metastases. Paired samples t test was used to determine the difference between contrast-enhanced MRI and DWI regarding detection of malignant lesions. The differences between various MRI sequences regarding lesion detection were compared using the Friedman test. Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied. Survival analysis was performed using Kaplan–Meier curves with the day of diagnosis on imaging as entry date and log-rank test to test for statistical significance. A p value of less than 0.05 was considered statistically significant.

Results

Patients

Sixty-six consecutive patients (median age 65 years, range 36–82 years) out of 93 patients with potentially resectable pancreatic cancer were eligible for inclusion. Twenty-seven patients were excluded for the following reasons: no confirmation of the presence or absence of malignant lesions (n = 4), local or systemic treatment prior to imaging (n = 3), artifacts or incomplete liver imaging (n = 8), and a time interval between imaging or imaging and surgery of more than two months (n = 12). Nineteen (29%) patients were diagnosed with liver metastases. Altogether 32 out of 47 patients without liver metastases underwent resection of the tumor. In the remaining 15 patients, the tumor was unexpectedly locally advanced (n = 12), metastasized intraperitoneally (n = 2), or the patient was too weak for surgery (n = 1). There was a significant difference in the survival between patients with liver metastases and without liver metastases ($\chi^2(2) = 28.354$, $p = 0.000$). Descriptives of included patients are described in Table 2.

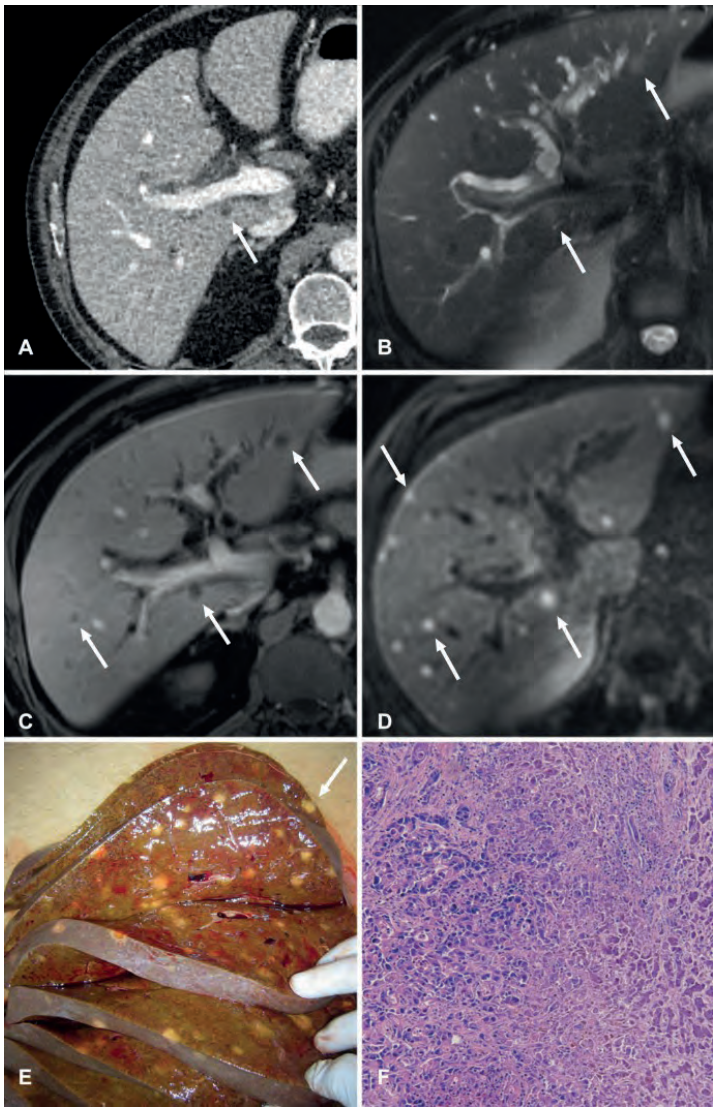

Figure 1. A 64-year-old male patient with borderline resectable pancreatic cancer on CECT and indeterminate liver lesions. The lesions were characterized as liver metastases by Gd-enhanced MRI. DWI additionally showed > 100 metastases. The time interval between CT and MRI was 11 days. In this patient, there was a large discrepancy between CECT and Gd-enhanced MRI and DWI. Within 4 weeks after initial diagnosis, the patient died of cholangitis septicemia. An autopsy was performed and confirmed MRI findings of more than 100 liver metastases. CECT (a) shows multiple hypodense liver lesions too small to characterize. These lesions show moderately high signal intensity on T2W-HASTE (b), and post-contrast T1W-VIBE portal-venous phase (c) shows rim enhancement. Diffusion-weighted MRI shows multiple lesions (white arrows) with a high signal intensity that remain hyperintense on the high b-value b = 800 s/mm2 (d). The autopsy confirmed there were more than 100 liver metastases (E&F).

Table 2. Descriptives

	Liver metastases 19 (29%)	**No liver metastases 47 (71%)**	**Total population 66 (100%)**	***p*- value**
Gender				
Men	13 (68%)	29 (62%)	42(64%)	
Women	6 (32%)	18 (38%)	24 (36%)	
Age (years)	median 64 (50-81)	median 66 (36-82)	median 65 (36-82)	0.828
Primary tumor location				
Head	15 (79%)	37 (79%)	52 (79%)	
Body/Tail	2(11%)	7 (15%)	10 (15%)	
Both	1 (5%)	3 (6%)	4 (6%)	
Ca19.9	median 430 (0-5297) (n = 16)	median 155 (1-7400) (n = 42)	median 191 (0-7400) (n = 58)	0.044
Tumor stage				
I	-	-	-	
II	-	27 (57%)	27 (41%)	
III	-	17 (36%)	17 (26%)	
IV	19 (100%)	3 (6%)	22(33%)	
Treatment primary tumor				
Resection	-	32 (68%)	32 (48%)	
Palliative bypass	7 (37%)	6 (13%)	13 (20%)	
Explorative laparotomy	3 (16%)	5 (11%)	8 (12%)	
Supportive care or palliative chemotherapy	9 (47%)	4 (9%)	13 (20%)	
Survival (weeks)	median 18± 1,9	median 60 ± 8,1	median 47 ± 3,0	0.000

Out of the included 66 patients, 19 patients had confirmed synchronous liver metastases. In this table, the groups with and without liver metastases and the total study population are depicted. The number of patients and the corresponding percentages, the median and corresponding ranges are reported. The survival is displayed in weeks, with corresponding standard errors

Confirmation of findings

Confirmation of liver metastases was obtained by histopathology in twelve patients; only in two cases transabdominal ultrasound with biopsy was successful. In the remaining patients, histopathology was obtained intraoperatively (n = 9) or by autopsy (n = 1). In six patients without histological proof, preoperative 18FDG-PET showed avid lesions in the liver, suggestive of liver metastases. In one patient multiple liver metastases were confirmed by intraoperative inspection and palpation of the liver and peritoneal metastases were histologically proven. The absence of liver metastases in the remaining 46 patients was confirmed intraoperatively by inspection and palpation of the liver (n = 43) and 18FDG-PET (n = 4). The

mean time interval between CECT and Gd-enhanced MRI with DWI was 15 days (SD 12 days) and 26 days (SD 14 days) between Gd-enhanced MRI with DWI and surgery.

Lesion analysis

Gd-enhanced MRI with DWI detected malignant lesions in 16 out of 19 patients with liver metastases. The sensitivity of Gd-enhanced MRI with DWI was 84% (95% CI 60–97%). The positive predictive value was 94% (95% CI 69–99%), and the negative predictive value was 94% (95% CI 85–98%). There was one false positive on a per-patient basis, in this patient one liver lesion with perilesional ring enhancement and persistent high signal intensity on DWI was characterized as malignant on Gd-enhanced MRI with DWI. There was no evidence of liver metastases during surgery and follow-up CECT after 1 year. There were three false negatives on a per-patient basis. In the first case, one indeterminate lesion in liver segment six on CECT was characterized as benign on Gd-enhanced MRI with DWI. However, intraoperative biopsy-proven metastasis in segment two was not detected on MRI. In the second case, there were neither liver lesions on CECT nor Gd-enhanced MRI with DWI. In the last case, one lesion was indeterminate on Gd-enhanced MRI with DWI, yet showed high uptake on preoperative ^{18}FDG-PET and thus was classified as metastasis.

In the negative-on-CT group, the per-patient prevalence of liver metastases was 20% (9/44). MRI was of additional value in 16% (7/44). In the indeterminate-on-CT group, the per-patient prevalence of liver metastases was 45% (10/22). MRI was of additional value in 90% of the patients (20/22).

Table 3. Number of malignant lesions on different sequences of CE-DWI-MRI

Sequence	T2W-MRI	T1W-MRI precontrast	T1W-MRI arterial	T1W-MRI portal-venous	DW-MRI
≤ 5 mm	13	9	100	90	339
6 – 10 mm	30	27	32	30	38
> 10 mm	20	18	20	20	20
Total	63	54	152	140	397

Number of suspected liver metastases on different sequences of CE-DWI-MRI in patients with liver metastases.

On a per lesion basis, Gd-enhanced MRI with DWI detected 397 malignant lesions in 16 out of 19 patients with liver metastases. Contrast-enhanced MRI detected 156 malignant lesions, whereas DWI detected 397 malignant lesions ($p = 0.051$). In three patients, 20 to 50 malignant lesions were detected only by DWI. In one patient, even more than 100 malignant lesions were visible only on DWI (Fig. 1). Table 3 summarizes the detection rate of malignant lesions in the different sequences of Gd-enhanced MRI with DWI. There was a statistically significant difference in the number of malignant lesions detected by T2W-HASTE, T1W-VIBE precontrast, arterial phase, portal-venous phase, and DWI ($\chi^2(2) = 32.861$, $p = 0.000$). Post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a statistically significant difference with a p value of 0.005. DWI detected significantly more metastases compared to T2W-HASTE ($Z = -3.181$, $p = 0.001$), T1W-VIBE precontrast ($Z = -3.183$, $p = 0.001$), arterial phase ($Z = -2.943$, $p = 0.003$), and portal-venous phase ($Z = -3.063$, $p = 0.002$). Figures 2, 3, and 4 show examples of three different patterns of liver metastases of pancreatic cancer on Gd-enhanced MRI with DWI.

Ninety-five percent of all liver metastases detected on Gd-enhanced MRI with DWI were subcentimeter lesions: 85% ≤ 5 mm, 10% 6–10 mm, and 5% > 10 mm. Nine patients (47%) had oligometastatic liver disease (i.e., ≤ 5 liver metastases [29]) and eleven patients had polymetastatic liver disease.

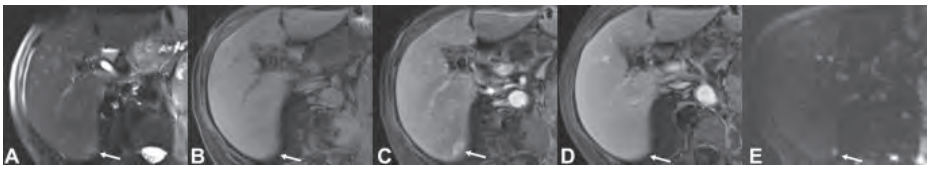

Figure 2. A 70-year-old female patient with borderline resectable pancreatic cancer with three indeterminate liver lesions on CECT. Seven lesions were characterized as liver metastases by Gd-enhanced MRI with DWI. Liver metastases were confirmed by intraoperative inspection and palpation of the liver. a–e Subcapsular hypervascular lesion in liver segment six (arrow). Near isointense on T2W-HASTE (a), near isointense on the T1W-VIBE precontrast images (b), hyperintense with wedge-shaped enhancement in the arterial phase (c), near isointense in the portal-venous phase (d). Persistent high signal intensity on DWI (b = 800 s/mm2) (e)

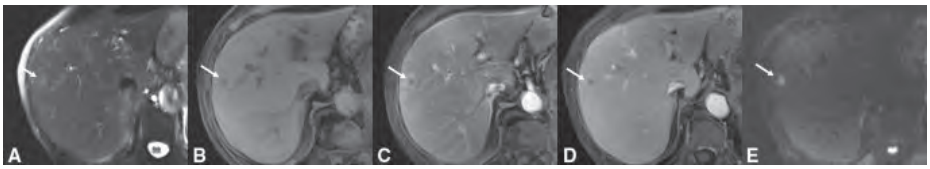

Figure 3. This is the same patient as the patient in Fig. 2. a–e A malignant lesion with arterial perilesional ring enhancement with incomplete centripetal progression in liver segment eight (arrow). Moderately high on T2W-HASTE (a). Hypointense on T1W-VIBE precontrast (b), perilesional ring enhancement in the arterial phase with hypointense center (c), which remains hypointense on the portal-venous phase (d). Persistent high signal intensity on DWI (b = 800 s/mm2) (e)

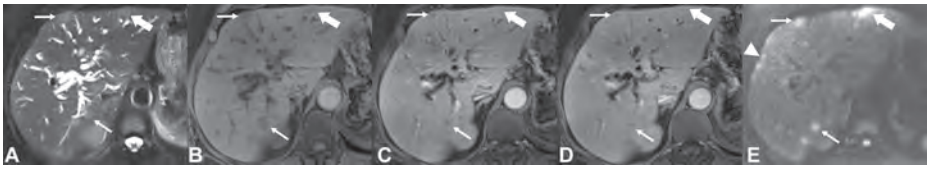

Figure 4. A 53-year-old female patient with locally resectable pancreatic cancer on CECT. CECT showed indeterminate liver lesions, which were characterized as liver metastases by Gd-enhanced MRI with DWI. 18FDG-PET showed avid liver metastases and possible pulmonary metastasis. a–e Multiple capsular based and deep liver lesions with peripheral enhancement with complete or incomplete centripetal progression. Multiple malignant lesions with moderately high signal intensity on T2W-HASTE (a), low signal intensity on T1W-VIBE precontrast (b), incomplete progression in the arterial (c), and portal-venous phase (thin arrows) (d). Another malignant lesion with complete progression to isointense enhancement in the portal-venous phase (thick arrow) (d). Persistent high signal intensity on DWI (b = 800 s/mm2). Some capsular lesions are only visible on DWI (arrowhead) (e)

Discussion

In this study, liver metastases were accurately diagnosed by Gd-enhanced MRI with DWI in 16 out of 66 (24%) patients initially diagnosed with potentially resectable pancreatic cancer on CECT. Adding a diffusion-weighted MRI to the contrast-enhanced MRI increased the number of detected metastases from 156 to 397. The combination of contrast-enhanced MRI and diffusion-weighted MRI yielded a high detection rate in previous studies, particularly in small metastases [30]. Metastases of pancreatic cancer are mostly small and multiple, which is consistent with the study by Danet et al. [28], subcentimeter lesions comprising 95% of all lesions. DWI seems particularly useful in the estimation of the metastatic load with the detection of metastases that are smaller than 5 mm.

The prevalence of liver metastases in this study was relatively high, 29%. The reported prevalence of liver metastases in the previous studies varies from 4.9% to 30% [9, 17,18,19,20, 22]. Patients with borderline resectable tumors and patients with indeterminate liver lesions were included, with a higher probability of having liver metastases. Additionally, on Gd-enhanced MRI there were metastases with a hypervascular enhancement pattern. A CECT with only porto-venous phase might have decreased the detection of these hypervascular metastases and overall the ability to characterize focal liver lesions on CECT. These factors might attribute to the higher additional value of MRI in this study as compared to the previous studies. The sensitivity of combined contrast-enhanced and diffusion-weighted MRI was 84%, which was comparable to other studies with sensitivities ranging from 73 to 100% [9, 17, 18, 22]. Given the aggressiveness of pancreatic cancer and its tendency for rapid metastatic spread, differences in sensitivity might be caused by differences in the time interval between Gd-enhanced MRI with DWI and the reference standard. The mean time interval in this study between CECT and Gd-enhanced MRI with DWI was 15 days and 26 days between Gd-enhanced MRI with DWI and surgery. A time interval of less than 20–25 days between imaging and any planned definitive therapy seems appropriate to grant accurate staging [4, 5, 31, 32]. Observer bias might have influenced the results of the study in favor of Gd-enhanced MRI with DWI, as only one observer re-evaluated the images, although in routine clinical practice images are also viewed by one observer, and the reported interobserver agreement for focal liver lesions in previous studies was good to excellent [15, 17, 18, 33,34,35].

A major problem was histopathological confirmation of the findings on Gd-enhanced MRI with DWI, as biopsy of all liver lesions is not possible and unethical in a living patient. Therefore, determining diagnostic accuracy on a per lesion basis is nearly impossible. Moreover, in our experience not all lesions on MRI are visible using either transabdominal or intraoperative ultrasound, therefore determining diagnostic accuracy on a per-patient basis remains challenging. In future clinical practice, MRI-guided biopsy with follow-up imaging could become an alternative strategy. In this study, there was one false positive on a per-patient basis; in previous studies false positives were also reported [17, 20, 22]. Therefore, at this moment we cannot deny patients surgery without histopathological proof of the radiological malignant liver lesions.

The increased safety of operations has led to more extensive local pancreas resections with venous and arterial reconstructions. Also, more effective chemotherapy protocols have been introduced, including combination therapies such as FOLFIRINOX. After neoadjuvant therapy in patients with borderline resectable pancreatic cancer or even locally advanced pancreatic cancer, secondary resection proved feasible with acceptable morbidity and survival rates [36]. Although still controversial, small studies and case reports have described select patients with oligometastatic hepatic metastases undergoing curative resection of the pancreas and the synchronous hepatic metastases [37, 38]. To benefit from these developments, adequate staging is a prerequisite and information on size, number, and distribution of liver metastases are of the utmost importance. Improved detection of liver metastases could reduce futile resection of the tumor with its associated morbidity and mortality in these patients with a markedly reduced life expectancy. Moreover, it offers the possibility to start palliative systemic chemotherapy earlier as there is no recovery period from the operation. Also, it can reduce palliative bypass surgery as the prognosis for metastatic disease is even worse than for locally advanced disease [39]. Patients with obstructive symptoms can successfully be treated with endoscopically placed biliary and enteric stents, which is a safe, efficacious, and cost-effective procedure with good clinical outcome [40]. Finally, improved detection of liver metastases during monitoring of (neo)adjuvant treatment could lead to a change in therapeutic strategy.

The retrospective nature of this study prevents a reliable calculation of the specificity, positive and negative predictive value of Gd-enhanced MRI with DWI versus CECT. Therefore, we started a large international multicenter prospective study to validate these results and to determine the diagnostic accuracy, implications for clinical decision making, and cost-effectiveness of Gd-enhanced MRI with DWI.

This study showed that Gd-enhanced MRI with DWI detected synchronous liver metastases in 24% of patients with potentially resectable pancreatic cancer on CECT with a sensitivity of 84%. Contrast-enhanced MRI showed 156 malignant lesions versus 397 malignant lesions with DWI, most of which were particularly small (< 5 mm).

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Chapter 9

Diagnostic accuracy of contrast-enhanced diffusion-weighted MRI for liver metastases of pancreatic cancer: towards adequate staging and follow-up of pancreatic cancer – DIA-PANC study: study protocol for an international, multicenter, diagnostic trial

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Abstract

Background

At the time of surgery, approximately 10–20% of the patients with pancreatic cancer are considered unresectable because of unexpected liver metastasis, peritoneal carcinomatosis or locally advanced disease. This leads to futile surgical treatment with all the associated morbidity, mortality and costs. More than 50% of all liver metastases develop in the first six months postoperatively. These (subcentimeter) liver metastases are most likely already present at the time of diagnosis and have not been identified pre-operatively, due to the poor sensitivity of routine preoperative contrast-enhanced CT (CECT).

Methods

The DIA-PANC study is a prospective, international, multicenter, diagnostic cohort study investigating diffusion-weighted contrast-enhanced MRI for the detection of liver metastases in patients with all stages of pancreatic cancer. Indeterminate or malignant liver lesions on MRI will be further investigated histopathologically. For patients with suspected liver lesions without histopathological proof, follow up imaging with paired CT and MRI at 3-, 6- and 12-months will serve as an alternative reference standard.

Discussion

The DIA-PANC trial is expected to report high-level evidence of the diagnostic accuracy of MRI for the detection of liver metastases, resulting in significant value for clinical decision making, guideline development and improved stratification for treatment strategies and future trials. Furthermore, DIA-PANC will contribute to our knowledge of liver metastases regarding incidence, imaging characteristics, their number and extent, and their change in time with or without treatment. It will enhance the worldwide implementation of MRI and consequently improve personalized treatment of patients with suspected pancreatic ductal adenocarcinoma.

Trial registration

ClinicalTrials.gov Identifier: NCT03469726.

Registered on March 19th 2018 - Retrospectively registered.

Background

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal forms of cancer and expected to become the second leading cause of cancer-related deaths before 2030. Developments in pancreatic cancer diagnostics, surgical techniques and treatment have hardly improved the survival rate in the past 40 years. The 5-year relative survival rate as reported by the American Cancer Society remains only 8% [1, 2].

Only 5–25% of all patients are eligible for surgery, to date the only potential cure [3]. Approximately 40–45% of all patients with pancreatic cancer have metastatic disease at diagnosis and 40% of all patients have locally advanced disease with tumor involvement of surrounding vessels or organs. At the time of surgery, approximately 10–20% of the patients are considered unresectable because of unexpected liver metastasis, peritoneal carcinomatosis or locally advanced disease [4–6].

More than 50% of all liver metastases develop in the first six months postoperatively [7]. These liver metastases are most likely already present at the time of diagnosis and have not been identified pre-operatively, as they are too small to be detected by routine preoperative ultrasound and contrast-enhanced CT (CECT) [8, 9].

CECT is highly accurate in assessing the relationship of the tumor to critical arterial and venous structures, since their involvement can preclude surgical resection. However, CECT has a poor sensitivity (38–76%) for the detection and characterization of liver metastases [7, 10–13], especially for subcentimeter metastases, which are often present in pancreatic cancer [14]. This leads to futile surgical treatment with all the associated morbidity, mortality and costs. Moreover, patients who were explored with curative intent and were found unresectable due to peritoneal or liver metastases had a worse overall survival compared to patients with unexpected locally advanced disease [15].

Nowadays, diffusion-weighted MR imaging (DWI) appears to be valuable in both detection and characterization of focal liver lesions with a high sensitivity (86–97%), even for subcentimeter lesions (60–91%) [16–18]. This technique can be used to detect and characterize liver lesions based on decreased diffusion of water molecules caused by tumoral hypercellularity

and reduced extracellular space. DWI is especially useful for detecting subcentimeter liver metastases, it is more accurate than conventional T2-weighted imaging techniques, because signal suppression of intravascular flow is obtained (black blood effect) while maintaining good residual signal of the liver lesions [19]. It is easy to implement and adds very little time to a standard MRI examination. However, without high-quality evidence of the benefit of MRI, the use of MRI as part of the routine workup is questioned and therefore not implemented. Currently most guidelines advise to use MRI as a problem-solving tool in addition to CECT; e.g. when the primary tumor cannot be visualized, or in case of undefined liver lesions [20–22]. The American Society of Clinical Oncology (ASCO) leaves the choice of imaging modality in the hands of the physician [23]. MRI is advised for all patients according to the Japanese guideline; however, the level of evidence is low (grade C) [24].

Most studies that have been performed for liver metastases of PDAC are retrospective, including our single center study in patients with potentially resectable pancreatic cancer without liver metastases on CECT [25]. In this study Gadolinium (Gd) enhanced MRI with DWI detected synchronous liver metastases in 24% of patients with potentially resectable pancreatic cancer on CECT with a sensitivity of 84%. DWI showed more lesions than Gd-enhanced MRI, most of which were particularly small (< 5 mm). Correspondingly, the only prospective study to our knowledge showed that Gd-enhanced MRI, especially DWI, depicted small liver metastases in approximately 10% of patients with a potentially resectable pancreatic cancer without liver metastases on CECT [26]. The reported sensitivity was 73–80% and the specificity 96–100%. However, due to the relatively low prevalence of patients with liver metastases in their study population, in total only 11 patients with liver metastases were included in this study.

In the DIA-PANC study we will determine the diagnostic accuracy of Gd-enhanced MRI with DWI in the detection of liver metastases in patients with all stages of PDAC.

Methods

Design

The DIA-PANC study is a prospective, international, multicenter, diagnostic cohort study investigating diffusion-weighted, Gd-enhanced MRI for the detection of liver metastases in patients with pancreatic cancer.

This protocol was written and reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Guidance and Checklist [27].

Study population

All patients with (suspected) pancreatic ductal adenocarcinoma are eligible to be included in this study and will be actively recruited at the outpatient clinic by the treating physician. Written informed consent will be obtained by one of the members of the research team. We will include patients until 138 patients with liver metastasis are included, with a maximum total of 465 patients. Exclusion criteria are age below 18 years, previous treatment for pancreatic cancer, concomitant malignancies (except for adequately treated basocellular carcinoma of the skin, subjects with prior malignancies must be disease-free for at least 5 years), contraindications for MRI or CECT (i.e. untreatable contrast allergy, severe renal function impairment, not MRI compatible medical implants), insufficient command of the local language and pregnancy. This study has been approved by the ethical board of our university medical center. Approval of the local medical ethical board is obliged before the start of inclusion in the participating hospitals.

Specific withdrawal of patients

Patients with adenocarcinoma of the distal common bile duct, papilla of Vater or duodenum, patients with a neuro-endocrine tumor or patients with benign tumors will be excluded from analysis and follow-up.

Primary outcome

The sensitivity and specificity of Gd-enhanced MRI with DWI for the detection of liver metastases in patients with pancreatic cancer.

Secondary outcomes

The secondary outcomes of this study are: sensitivity and specificity of CECT for the detection of liver metastases; sensitivity and specificity of MRI

and CECT for the prediction of resectability; and the effect of the MRI on patient management.

Data collection

All patients will be assigned a unique participant code. The key will be stored separately from the data. We plan to collect the following baseline data (age, sex, performance status (WHO performance score), American Society of Anesthesiologists physical status, body mass index, weight loss, decreased appetite, diabetes mellitus, previous liver or pancreatic diseases, smoking and alcohol status and tumor markers (CEA and CA19–9)) using the data management system Castor EDC (Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands). Data on diagnostic procedures (like endoscopic imaging and biopsies), treatment and clinical follow-up will be collected during the entire study period by the local treating physicians or the trial coordinators using Castor EDC. Patients will be asked to fill in validated quality of life questionnaires (EORTC QLQ-C30 and QLQ-PAN26) at baseline and after 3-, 6- and 12-months follow-up.

MRI and CT

MRI scans will be made on a 3 T scanner with T2 weighted imaging, using an intravenous gadolinium-based contrast agent with a T1 weighted pre-contrast, arterial and portal-venous phase, DWI with b-values of 50, 500 and 800 s/mm2 and with a Magnetic Resonance Cholangio-Pancreatography (MRCP). CECT scans are performed with intravenous iodine contrast agent with a pancreatic phase of the upper abdomen, a portal venous phase of the entire abdomen. Additionally, the chest will be staged using chest CT. MRI and CECT will be performed at baseline and after 3-, 6- and 12-months follow-up, the schedule is displayed in a flowchart in Fig. 1.

Interpretation of MRI and CT

All MRI and CECT scans will initially be evaluated by the local radiologist and the findings will be included in the clinical decision making. The MRI and CECT scans will also be independently evaluated by a second radiologist blinded for findings of the first evaluation and the clinical outcome. If the MRI and CECT of one patient is evaluated by the same radiologist a minimum interval of 6 weeks will be used to minimize the risk of recall bias.

The MRI and CECT scans will be analyzed for local resectability and suspicious liver lesions. Number of liver lesions, lesion size, liver segment, presumed diagnosis of suspicious liver lesions (indeterminate or malignant) and imaging characteristics on MRI will be noted.

Reference standard

Indeterminate or malignant liver lesions will be further investigated histopathologically. The first step in obtaining histological proof of suspected liver lesions on CECT and/or MRI is transabdominal ultrasound of the liver. Biopsy will be performed of visible liver lesions and analyzed with routine histological examination. When lesions are not visible or there is no histological proof of the visible lesions, the next step is surgical exploration (laparoscopic or For patients with suspected liver lesions without histopathological proof, follow-up imaging with paired CECT and MRI at 3, 6 and 12 months will serve as an alternative reference standard. Lesions that are growing or increasing in number over time will be considered metastases.

Definitions

On MRI liver lesions are defined as malignant on DWI when they are (moderately) hyperintense at b = 50 s/mm2 and remains hyperintense at b = 800 s/mm2. A lesion is considered benign when it is hyperintense at b = 50 s/mm2 and shows a substantial decrease in signal intensity at higher b values (b = 500 and b = 800 s/mm2). If none of the criteria is met, a lesion is classified as indeterminate.

On CECT liver lesions are defined as malignant if they are hypodense, not showing typical features of a simple cyst (fluid attenuation measurements, round-oval, well-defined borders, no contrast enhancement), hemangioma (localization next to vessels, peripheral nodular enhancement, centripetal fill-in), or focal fatty infiltration (geographic hypodense area, angular margins, typical location). If a lesion is showing signs of simple cyst, hemangioma or focal fatty infiltration it is defined as benign. If a lesion is too small to characterize it is classified as indeterminate.

TNM status is classified according to the American Joint Committee on Cancer (AJCC, 8th edition) [28]. Lymph nodes are defined as suspicious if they are rounded and ≥ 5 mm or if they are not-rounded with the shortest axis ≥ 10 mm.

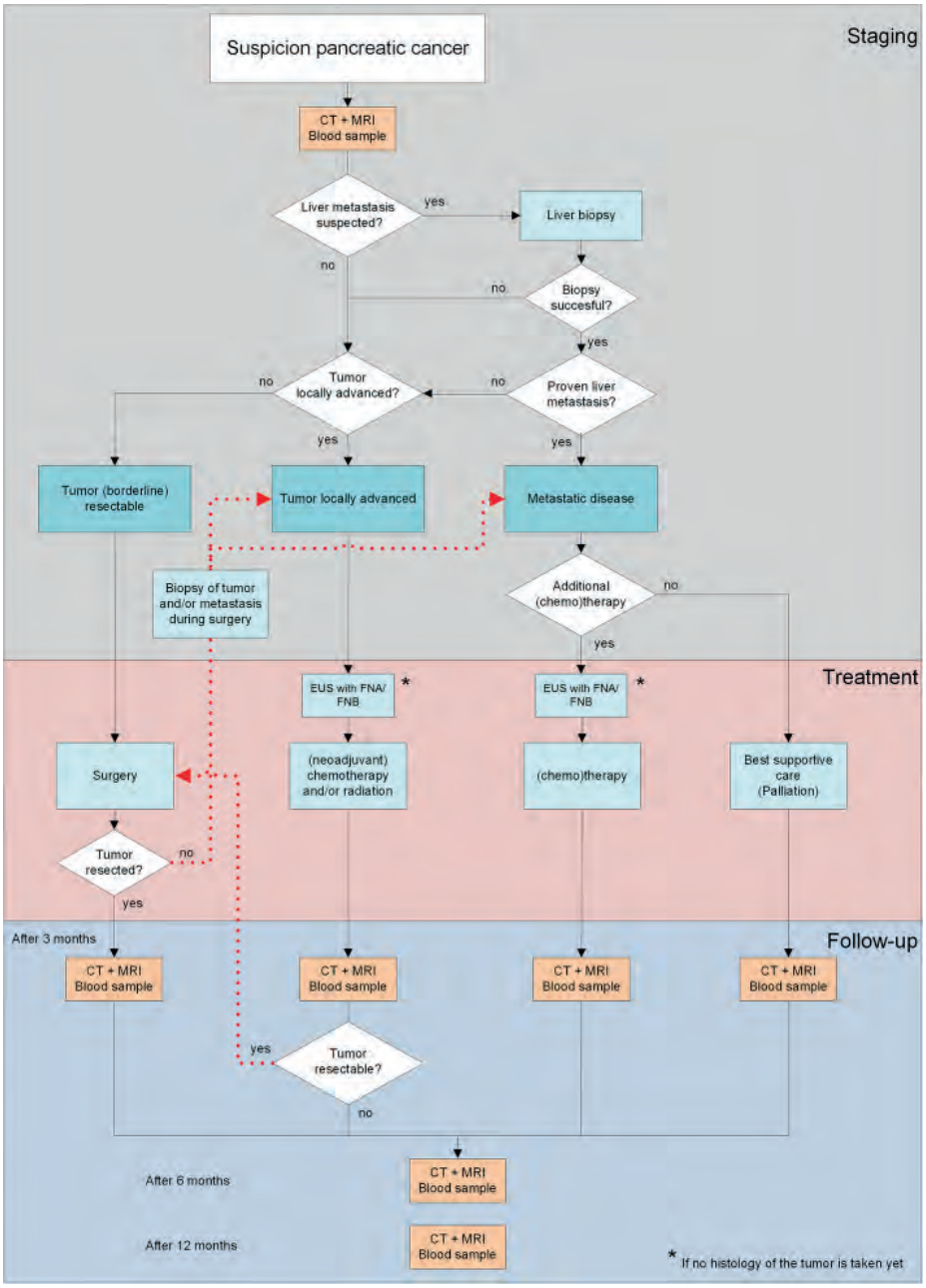

Figure 1. Flowchart of study schedule and proceduresopen) in (borderline) resectable pancreatic cancer. In case liver lesions are identified a frozen section is performed. Hereafter, patients are treated according to standard care protocol.

Safety and ethics

There is a low risk and low burden for patients participating in this study. Patients might benefit from study participation due to possible improvement of detection of liver metastases. The contrast agent used for MRI has few known side effects and rarely leads to a severe allergic reaction [29]. Extra CECT scans might be performed in some study patients with the associated radiation and contrast exposure. Patients diagnosed with pancreatic cancer have a 5-year overall survival of 8%. Radiation-induced cancer has a latency period that substantially exceeds 5 years. Therefore, the health risk for this specific oncologic patient group is almost negligible.

MRI can lead to earlier detection of liver metastases, however in some patients these lesions might be too small to biopsy. Consequently, we cannot always provide the patient certainty about the nature of the liver lesions detected with MRI. Furthermore, in follow-up local recurrence or metastases might be detected before a patient has symptoms. This may be seen as a disadvantage by some individuals.

Statistics

Sample size

The sample size for the study was calculated for the primary endpoint (sensitivity and specificity of MRI for the detection of liver metastases).

The sample size is calculated based on a method for power calculations for diagnostic studies described by Jones et al. [30]. Based on literature and our previously performed retrospective study [9, 25, 31–34] we estimate the sensitivity of MRI will be approximately 90%. In literature the specificity for MRI is usually higher than the sensitivity, therefore we based our sample size calculation on the sensitivity only. With an expected sensitivity of 90%, confidence interval of 95% ($Z = 1.96$) and $\alpha = 0.05$, 138 patients with metastasis are required for analysis. Based on literature the expected percentage of patients with liver metastases is approximately 40% [3, 35]. With an expected inclusion rate of 80% (assuming 20% cannot be analyzed optimally, e.g. because no representative liver biopsies could be acquired, mortality before first follow-up or withdrawal) we need approximately 433 patients. In case the proportion of patients with metastases is not

equal to 40% in our cohort, we will include until we reach 138 patients with liver metastasis or up to a maximum total of 465 patients.

Analysis

Analysis will be done using SPSS (IBM Corp., Armonk, New York, USA). Continuous variables will be summarized with standard descriptive statistics including mean, standard deviation, median, and range. Categorical variables will be summarized with frequencies. A p-value less than 0.05 is considered statistically significant.

For the analysis of the diagnostic accuracy (sensitivity and specificity) a 2×2 cross tabulation will be made comparing MRI and CECT to histopathology and follow up. Performance of CECT and Gd-enhanced MRI with DWI will be compared using McNemar's test. We will report the changes made in patient management in a descriptive manner. Median and 1-year survival will be reported. Survival endpoints (disease free survival and overall survival) will be analyzed using Kaplan-Meier plots. Survival curves are compared using the log rank test. We will compare the results of both readers to determine the inter-observer variability. A Cohen's Kappa (k value) of 0.81–1.00 is interpreted as excellent, 0.61–0.80: substantial agreement, 0.41–0.60: moderate agreement, 0.21–0.40: fair agreement, and 0.00–0.20: poor agreement.

We partly anticipated missing data by introducing the composite reference standard of follow up. Unfortunately, missing data still can occur when, for instance, a patient suspected of having metastatic disease, does not have histopathological confirmation and dies before the composite reference standard follow up could take place. If necessary, additional analysis will be performed to determine the robustness of the results and to deal with missing data.

Trial status

The first patient was included on December 21st 2017. At the time of protocol submission (July 23th 2020) active inclusion of patients has started in six centers; Radboud University Medical Center (Nijmegen, the Netherlands), Konstantopouleio General Hospital (Athens, Greece), Medisch Spectrum Twente (Enschede, The Netherlands) and Jeroen Bosch Hospital (Den Bosch, The Netherlands), University Medical Center Groningen (Groningen, The Netherlands), and University Hospital Ramón y Cajal

(Madrid, Spain) and a total of 190 patients have been included. Four centers are preparing to start with inclusion; Inselspital Universitätsspital Bern (Bern, Switzerland), UCHealth University of Colorado Hospital (Denver, United States of America), Azienda Ospedaliera Universitaria Integrata Verona (Verona, Italy), and Policlinico A Gemelli (Rome, Italy). Inclusion of patients is expected to be finished December 2021.

Discussion

The purpose of the DIA-PANC trial is to investigate the diagnostic accuracy of contrast-enhanced diffusion-weighted MRI in patients with suspected PDAC for the detection of liver metastases. Additionally, we will evaluate whether performing contrast-enhanced diffusion-weighted MRI will improve the detection of liver metastases compared to CECT by determining the sensitivity and specificity of CECT for the detection of liver metastases.

Despite the good diagnostic performance of MRI for liver metastases, the benefits of MRI remain unclear, mostly because of low level of evidence, heterogeneity, and bias in the performed studies. Two recently published meta-analyses have suggested the results should be confirmed by performing a well-designed and sufficiently powered study directly comparing liver CT and MRI in the same cohort [36, 37].

A major difficulty in the interpretation of the current literature is that most studies are retrospective often only reporting on a subset of patients actually undergoing a resection, patients with borderline resectable tumors, or patients with indeterminate liver lesions on CECT. These patients have a higher probability of having liver metastases. However, in an era of neoadjuvant therapy, local ablative therapy for advanced tumors, expensive targeted therapies, and resection of oligometastases, MRI may be beneficial to patients with all stages of PDAC. Therefore, all patients with suspected PDAC are eligible for inclusion in the DIA-PANC.

MRI field strength, 1.5 T versus 3 T, was a significant factor in the heterogeneity between studies that was found in a meta-analysis. 3 T MRI had a higher sensitivity (89%) and a lower specificity (88%) for diagnosing liver metastasis compared to 1.5 T MRI (sensitivity 80% and specificity 100%) [36]. Because the signal-to-noise ratio and the lesion-to-liver

contrast are higher on 3 T MRI than on 1.5 T MRI, it is reasonable that a 3 T MRI permits a higher lesion detection rate [38, 39]. In the DIA-PANC study we plan to perform all MRIs on a 3 T scanner. A potential downside of a multicenter design is the intervendor variability that could occur when comparing the quantitative Apparent Diffusion Coefficient (ADC) value, this variability seems to be more pronounced at 3 T than at 1.5 T [40].

Availability of MRI is not expected to be an issue, as MRI is available in every expert center for pancreatic diseases. However, problems with MRI capacity could arise due to the need for MRI within a short interval after CT. A time interval of two weeks was chosen to provide a feasible time frame for MRI to be performed and no interval lesions are expected within this time interval [4].

The DIA-PANC trial is the first international prospective multicenter cohort study about the diagnostic accuracy of contrast-enhanced diffusion-weighted MRI. On the World Health Organization trial registry website (ICTRP), incorporating all (inter) national trial registries, there are only four other prospective trials registered in this field.

The first trial is a completed French prospective multicenter trial, presumably the only one prospective study that has been published [26]. The study has been performed in 118 patients with potentially resectable pancreatic cancer on a 1,5 T scanner using gadobenate dimeglumine (MultiHance) as contrast agent. The study has been performed to assess the diagnostic performance of diffusion-weighted MRI for the preoperative diagnosis of liver metastasis and the modification of therapeutic strategy as a consequence of the diagnosis of liver metastasis on diffusion-weighted MRI [41].

The second trial is a British single center observational study with a target sample size of 30 patients with confirmed or suspected pancreatic cancer referred for pancreaticoduodenectomy and is completed recently. The primary outcome of this study is the proportion of patients correctly identified by MRI to have lymph node, peritoneal, or liver metastases. To our knowledge, the results have not been published and there is no information on scan parameters and contrast agent available [42].

The third trial from Australia is the only randomized controlled trial. The study has a target sample size of 24 patients and is not yet recruiting.

The aim of the study is to compare the 12-month recurrence rate in patients with locally operable pancreatic adenocarcinoma managed with standard preoperative assessment of liver metastases with CECT, versus preoperative assessment with liver specific contrast MRI [43].

The fourth trial is a Chinese comparative study and is not yet recruiting. The study aims to compare liver specific contrast MRI and CECT in liver metastasis of pancreatic cancer with a target sample size of 60 patients [44].

The DIA-PANC trial hypothesizes a superior value of MRI for the detection of liver metastases compared to CECT. To reliably determine the diagnostic accuracy the gold standard is histopathology of the liver lesions. Considering it is not always possible, and sometimes even unethical, to obtain histopathological proof of every lesion, follow-up is used as a reference standard. Hence, we are able to simultaneously gather information on (early) local recurrence or metastases after resection, disease progression, and therapy response evaluation on MRI and CECT.

In conclusion, the DIA-PANC trial is expected to report high-level evidence of the diagnostic accuracy of MRI for the detection of liver metastases compared to CECT, resulting in significant value for clinical decision making, guideline development and improved stratification for treatment strategies and future trials. Furthermore, DIA-PANC will contribute to our knowledge of liver metastases regarding incidence, imaging characteristics, their number and extent, and their change in time with or without treatment. When our hypothesis is confirmed, it will enhance the worldwide implementation of MRI and consequently improve personalized treatment of patients suspected of PDAC.

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Availability of data and materials

The complete dataset will be property of the Sponsor, all participating institutions will own the dataset of the included patients from their center. Public access to the full trial protocol, trial-related documents, participant-level dataset, and statistical code may be made available on request.

Ethics approval and consent to participate

The DIA-PANC study will be conducted according to the principles of the Declaration of Helsinki (64th version, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The independent ethics review board region Arnhem-Nijmegen (Nijmegen, The Netherlands) has approved the trial protocol (NL60473.091.17). Furthermore, secondary approval for all participating centers from The Netherlands was or will be individually obtained from all local ethics committees. According to Dutch law, ethical approval by the ethics review board of the study sponsor (i.e. initiating center, Radboudumc, Nijmegen, The Netherlands) is appropriate for all Dutch centers. For all participating centers outside of The Netherlands approval from a local independent ethics review board was or will be obtained. The trial is registered in the registry provided by the U.S. National Library of Medicine (clinicaltrials.gov) with identification number NCT03469726. Patients can only participate if written informed consent has been provided.

Protocol modifications will be communicated to all relevant parties (e.g. participating centers, funder) after approval of the ethical committee and will be updated in the trial registry. Possible substudies, like Biobank (samples will be stored at the Radboud Biobank) or artificial intelligence analysis, are included on the informed consent form. Patients must give separate consent to participate in these substudies. The study will be monitored according to the guidelines of The Netherlands Federation of University Medical Centres (NFU) and adverse events related to study procedures will be recorded. There is a study subject insurance for patients that suffer harm from trial participation.

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Chapter 10

General discussion and future perspectives

Preoperative imaging plays a crucial role in pancreatic cancer. The identification of tumor margins, vascular involvement, and proximity to critical structures is pivotal in preoperative planning, preparing surgeons perioperatively. Computed tomography (CT) is the current standard of care for patient selection and preoperative planning, but often underestimates disease severity. Despite tumors appearing technically resectable on preoperative CT, up to 40% of patients experience aborted resections during explorative laparotomy (1), and approximately 40-50% of patients face recurrence within 12 months after resection (2, 3). The TNM system primarily assesses disease burden, guiding cancer surveillance, clinical trial eligibility, and treatment decisions; however, its reliability in predicting survival is still under debate. Unpredictable biological behaviour distinguishes pancreatic cancer from other solid tumors necessitating imaging biomarkers for improved patient selection, beyond current preoperative markers such as tumor diameter and extension, lymph node enlargement, metastases, and serum CA19-9.

Challenges emerge as neoadjuvant treatments redefine standards, questioning the alignment of technical criteria with tumor biology, which impacts the candidacy of patients for surgery. The shift from 'unresectable' to 'locally advanced' prompts a potential redefinition of advanced pancreatic cancer, emphasizing the critical role of precise imaging in treatment planning. Additionally, the expected rapid increase in the adoption of minimally invasive surgery, pending equivalent or improved outcomes compared to traditional surgery, highlights the need for accurate radiological assessments to identify suitable candidates and ensure optimal outcomes. This reflects the evolving landscape in pancreatic cancer management, underlining the importance of precision in diagnosis and treatment decisions.

Minimally invasive surgery

The advent of minimally invasive techniques has brought about a revolutionary transformation in the field of surgery. However, the widespread integration of minimally invasive pancreatic surgery (MIPS) faced significant challenges, primarily attributable to the intricate nature of these procedures. Laparoscopic distal pancreatectomy (LDP) emerged as a relatively straightforward approach due to its involvement of fewer

critical blood vessels and less complex anastomosis than laparoscopic pancreatoduodenectomy (LPD). This thesis aimed to compare the perioperative outcomes of minimally invasive and open surgery for distal pancreatic cancer. The mean length of hospital stay was statistically significantly shorter in the laparoscopic group than in the open group. Reduction in hospital stay may be due to quicker postoperative recovery resulting from the minimally invasive nature of laparoscopic surgery. However, differences in length of hospital stay are important only if laparoscopic distal pancreatectomy provides equivalent cancer clearance as open distal pancreatectomy (ODP) and it was not possible to draw any definite conclusions with respect to cancer clearance. There were no significant differences between laparoscopic and open distal pancreatectomy in terms of short-term mortality. In the absence of RCTs there were worries about selection bias. Those with more extensive cancer underwent OPD, clearly as OPD was associated with greater tumor size, lymph node sampling and the presence of lymph node metastasis and more participants in the open group received neoadjuvant chemotherapy or radiation. Additionally, the decision to perform laparoscopic vs open distal pancreatectomy was based on surgeon or patients' preference.

Recently, the LEOPARD trial, a multicentre RCT, confirmed the time to functional recovery was significantly shorter after minimally invasive distal pancreatectomy (MIDP). Operative blood loss and delayed gastric emptying grade B/C was less after MIDP, whereas operative time was longer. The conversion rate of MIDP was 8%. There were no significant differences in complication rates and postoperative pancreatic fistulas between MIDP and ODP (4).

LDP results in decreased costs and increased QALYs compared to ODP, with a higher net monetary benefit. However, due to lack of data and use of information from observational studies and high risk of systematic error, this thesis could not state whether laparoscopic distal pancreatectomy was cost-effective compared to open distal pancreatectomy for pancreatic cancer in the NHS setting. In the Netherlands, LDP was found to be at least as cost-effective as open distal pancreatectomy in terms of time to functional recovery and quality-adjusted life-years (5).

Resection and reconstruction required for minimally invasive pancreatoduodenectomy (MIPD) are technically challenging, even in the hands

of experienced surgeons. Notably, the pancreatic surgical volume of healthcare institutions assumes paramount importance in ensuring the safety of MIPD. The observed variability in outcomes of MIPD is often ascribed to the protracted learning curve intrinsic to the procedure. This thesis introduces a comprehensive study protocol for a future systematic review and meta-analysis comparing laparoscopic, robotic, and open pancreatoduodenectomy in the context of periampullary malignant and benign tumors. Through this undertaking we aspire to contribute valuable insights to the field of MIPS.

Current opportunities in the diagnostic workup

A considerable proportion of patients undergo unnecessary laparotomy because of underestimation of the local vessel extent of the cancer on CT. This thesis compares the performance of EUS with that of CT for pancreatic cancer staging. When EUS indicates that the pancreatic cancer is not resectable, although CT shows that the tumor is resectable, approximately 13% of people had resectable pancreatic cancer. Therefore, there is no evidence to suggest that EUS should be routinely performed for vascular involvement in people with pancreatic cancer found to have resectable disease on CT. Since pancreatic resection is the only potentially curative option for pancreatic cancer, omission of laparotomy and resection can have a major negative impact on their survival. On the contrary, futile surgery is associated with morbidity and mortality, which results in a delay in the initiation of systemic chemotherapy, as patients need time to recover. Recognizing the pivotal role that EUS plays in pancreatic cancer evaluation, extensive technological advancements have been made in recent years to enhance the quality of EUS imaging and augmented the diagnostic accuracy. EUS has emerged as the preferred imaging technique for screening high-risk populations for pancreatic cancer, as it is the most sensitive imaging tool for the detection of solid pancreatic tumors, especially for lesions under 2 cm in diameter.

The reported diagnostic accuracy of MR imaging has been shown to be equivalent to CT and is comparable in predicting tumor resectability; however, it has an added value in detecting CECT isoattenuating pancreatic cancer and liver metastases. In this thesis we correlate DWI findings with the histopathologic features of pancreatic ductal adenocarcinoma (PDAC). Despite it was impossible to non-invasively grade PDAC with DWI, MRI is an unavoidable tool in the diagnostic work up and staging

of pancreatic cancer. Histopathologic grade plays a less important role in clinical management of PDAC as compared to the stage of the disease. Contrast-enhanced MRI with DWI detected synchronous liver metastases in 24% of patients with potentially resectable pancreatic cancer on CECT. Although our study population included only resectable and borderline resectable tumors, MRI with DWI may also be beneficial for patients with LAPC. Occult systemic disease is more common in LAPC than in primary resectable cases. Critical evaluation of what is technically challenging and what involves aggressive biology becomes increasingly important with the implementation of induction chemotherapy. Without high-quality evidence of the benefit of MRI, the use of MRI as part of the routine workup is questioned and therefore not implemented. In coming years, we will present the results of the DIA-PANC study determining the diagnostic accuracy of Gd-enhanced MRI with DWI in the detection of liver metastases in patients with all stages of PDAC. In an era of neoadjuvant therapy, local ablative therapy for advanced tumors, costly targeted therapies, and treatment of oligometastases, estimation of the metastatic load may become more important. Pancreatic cancer metastases are predominantly small and multiple, with subcentimeter lesions accounting for 95% of all lesions. The inclusion of diffusion-weighted MRI alongside contrast-enhanced MRI has demonstrated a significant improvement in the detection of liver metastases and the estimation of metastatic load. For the time being, histopathological confirmation of suspected liver metastases on Gd-enhanced MRI with DWI remains necessary. DWI detected significantly more liver metastases compared to T2W-HASTE, T1W-VIBE pre-contrast, arterial phase, and portal-venous phase, precluding surgery. MR-guided liver biopsy is a valuable tool for these small subcentimeter lesions that may not be visualized by other imaging modalities. In the pilot feasibility study META-PANC, MR-guided liver biopsies are conducted under local anaesthesia to obtain minimally invasive histopathological proof of liver metastases. Interestingly, in agreement with findings of this thesis, unpublished results reveal some false positive lesions, with biopsy results indicating reactive changes. Emerging evidence suggests that organs predisposed to developing metastases undergo microscopic changes favouring metastatic growth, collectively known as ‘premetastatic niches’ (6). One potential explanation for the occurrence of these false positive results is that DWI allows us to identify changes associated with the premetastatic niche preparation process. This, in turn, may offer the potential to stratify patients at a higher risk for future metastasis at these sites. The follow up results of

the DIAPANC and META-PANC trials may provide valuable insights into the reasons behind these false positives.

Costs need not to be a primary cause for concern when contemplating the implementation of MRI in the routine workup. Combined CECT and contrast-enhanced MRI can be regarded as a cost-effective imaging approach for the staging of pancreatic cancer (7).

Up to now, there are no uniform methods to evaluate diffusion weighted parameters. Technical factors such as vendors, field strength, b-values selection, and placement of region of interest in addition to factors related to the heterogeneous tumor microenvironment of pancreatic cancer influence the ADC values. The errors in the ADC values of a tumor region of interest (ROI) directly affect the usefulness of DWI. In our study population we had to exclude a considerable proportion of patients due to insufficient image quality. The ADC maps of the liver and pancreas particularly contained artifacts and noise. Our primary reliance was on b800 diffusion-weighted images for detecting liver metastases. However, this approach may have led to false positives, as it was not always possible to identify a corresponding low signal on the ADC map. Future research should prioritize standardizing imaging protocols to enhance overall image quality, reduce artifacts, and minimize variability in ADC values. This is beneficial when characterizing, evaluating, and comparing lesions in a multicenter setting, which is necessary to collect enough data in this rare tumor, to identify differences between tumors, tumor behavior and assessing tumor treatment response.

It is clear that the conventional anatomic-morphologic approach for diagnosis, staging and prognostication of pancreatic cancer is insufficient. FDG PET/CT is not able to accurately define tumor extent relative to the surrounding tissues, though it has proved useful in modifying the staging of PDAC for 10% of cases, changing the decision making in about 50% of cases and sparing non-useful surgery in 20% of cases, usually due to the detection of previously undetected metastases (8). Nowadays, PET does not have a role in diagnosis and staging in current guidelines. Nevertheless, literature shows there could be added value of functional imaging in prognostication, evaluation and monitoring of treatment response. Using a combination of tumor metabolism and blood flow with FDG-PET and contrast-enhanced CT, this thesis tried to isolate PDAC with aggressive tumor biology and worse prognostic features. Hypoattenuating PDAC

with high [18F]-FDG-uptake has significantly higher tumor stage, lower curative resection rates and worse overall survival compared to the other flow-metabolic phenotypes. The heterogeneous study population, which included all tumor stages and different treatment strategies, complicated the interpretation of the results. [18F]-FDG-PET is currently not routinely performed for PDAC, yet recent studies illustrated [18F]-FDG-PET could be of value in the diagnostic work-up, treatment assessment and detection of early tumor recurrence (8-12). We found different contrast enhancement patterns and [18F]-FDG uptake patterns that needs further analysis, possibly with the help of machine learning or deep learning. In combination with the discovery of novel molecular subtypes of PDAC, which use different metabolic pathways as their main source of energy, it is not possible to omit the use of [18F]-FDG-PET in PDAC. Molecular subtyping and information on tumor biology, including tumor aggressiveness and chemosensitivity, may aid in treatment planning and patient selection.

Future directions of treatment in pancreatic cancer

Advanced surgery

Further advances in imaging technology and surgical devices will also improve the precision of surgical procedures. Standardization of surgical procedures and widespread educational programs for MIPS may improve outcomes, as demonstrated by a nationwide training program for MIDP in the Netherlands, which reduced blood loss, conversion, margin-positive resection, and the length of hospital stay (13). A similar training program in LPD also indicated that clinical outcomes and safety were not inferior to OPD after training (14). Robotic-assisted pancreatic surgery has the potential to even surpass the outcomes of the open approach after the surgeon has performed a certain number of cases (15). Whether the application of the robotic approach might be superior to laparoscopic surgery is unclear. The robotic-assisted surgical platform provides a magnified 3D visualization, improves the dexterity of instruments, which facilitates the precise stitching required for complex anastomosis. The application of augmented reality for intra-operative guidance may enable surgeons to accurately locate tumors or vessels, overcoming the challenge of the lack of tactile sensation. Additionally, ongoing efforts are focused on reintroducing the sense of touch into MIPS through tactile force sensing of instruments and providing haptic

feedback to the surgeon (16). Another subject for further investigation is the feasibility of MIPS after neoadjuvant therapy. With the introduction of chemotherapy regimens such as FOLFIRINOX the paradigm of indication of surgical challenges has changed. Planned arterial resections are becoming increasingly accepted when performed in highly selected patients with borderline resectable and locally advanced pancreatic cancer, if performed in experienced, high-volume centers (17), but the oncological benefit of arterial resection needs to be further investigated.

Among stage IV pancreatic cancer patients, 58% had liver-only disease, and up to 41% with oligometastatic disease recurrence demonstrated liver-only recurrence (18). While pancreatic cancer's aggressive tumor biology implies it is a systemic disease that cannot be cured with local measures, emerging evidence suggests that oligometastases – defined as having fewer than five metastatic lesions - may require a re-evaluation of current treatment approaches (19). Recent findings suggest that surgical resection of pancreatic cancer with synchronous liver oligometastases can be performed safely and may lead to improved survival outcomes. This approach is particularly promising when patients are selected carefully following primary chemotherapy (20-22). Prospective clinical trials are currently underway to further investigate the efficacy of surgery and ablative techniques in these patients. Interestingly, lung oligometastases in pancreatic cancer appear to have a more favorable prognosis compared to liver and peritoneal metastases. Consequently, surgery for lung metastases may assume a more significant role than surgery for other types of oligometastases (23).

Local ablative treatment

Traditionally, surgical resection has been the only realistic chance of cure. There is no consensus on how to manage those patients who do not have sufficient response to become candidates for resection but also do not have distant progression after weeks or months of systemic therapy. Additionally, with improved systemic control with more aggressive and effective chemotherapeutic regimens, such as FOLFIRINOX and gemcitabine plus nab-paclitaxel, local progression can become a more serious problem in terms of survival and quality of life. Over the past years, remarkable developments in minimally invasive image-guided procedures are changing the management of non-operable or recurrent pancreatic cancer. Ablation treatments, such as radiofrequency ablation (RFA), microwave ablation (MWA), laser ablation,

cryoablation (CA), reversible electrochemotherapy (ECT) and irreversible electroporation (IRE), high intensity focused ultrasound and trans-arterial embolization procedures, have been increasingly applied. Following the initially non-satisfactory results, with unacceptable complication rates while the prognosis remained poor, outcomes of minimally invasive image-guided procedures have significantly improved, mainly due to the cumulative experience, and technological advances of the devices used.

In RFA, one or more electrodes are directly inserted into the core of the tumor. RFA generates heat through the application of a high frequency alternating current, which leads to thermal coagulation and protein denaturation, resulting in tumor destruction. RFA should be avoided when the target tumor is near large vessels due to the heat sink effect, where the proximity of adjacent blood vessels can lead to the dissipation of the heat generated, reducing the effectiveness of the procedure. Furthermore, RFA primarily serves as a means of tumor debulking rather than complete tumor ablation, given the significant risk associated with thermoablative techniques due to the sensitivity of the pancreatic tissue to heat, its rich vascularization and its proximity to arteries and bile ducts. Interestingly, viable residue at the periphery of the treated area, intentionally left untreated to avoid thermal injury to surrounding vital structures, undergoes partial damage. This appears to trigger an intense inflammatory cell response characterized by the infiltration of various immune cells within the transitional zone of ablated tissue. Moreover, this RFA-induced immunomodulation might not solely be a local phenomenon, but a systemic reaction, which could be subject for further research and investigation (24). The combination of RFA with chemo(radio)therapy, has demonstrated promising survival outcomes, sparking interest in further investigating the potential benefits of this combined approach. The Pancreatic Locally Advanced Unresectable Cancer Ablation (PELICAN) trial aims to compare survival in patients with LAPC after a combination of chemotherapy with RFA versus chemotherapy alone (25).

Microwave ablation (MWA) relies on the dielectric effect, which occurs when an imperfect dielectric material is exposed to an alternating electromagnetic field. This effect enables MWA to create a more extensive area of active heating, achieving a greater degree of uniform necrosis within the target zone compared to RFA. Furthermore, MWA offers shorter treatment time, is less susceptible to the protective mechanism of neighboring tissues, minimizing the heat-sink effect, ultimately enhancing the efficacy of MWA (26).

IRE is a primarily nonthermal ablative technique involving the application of high-voltage electrical pulses between needle electrodes, inserted either directly in and around the tumor through a laparotomy or percutaneously. The electrical pulses induce irreversibly damage to the cellular membrane by creating nanopores, ultimately leading to programmed cell death. The PANFIRE-2 study suggests that percutaneous IRE in LAPC and recurrent pancreatic cancer might result in prolonged survival compared to the current standard of care with chemotherapy. As a novel treatment approach, intraoperative IRE could potentially improve negative-margin dissection of the retroperitoneal margins and surrounding perivascular soft tissue, particularly the perineural and mesenteric tissue adjacent to critical vascular structures. However, it is essential to recognize that percutaneous IRE should be considered a high-risk procedure, emphasizing the critical importance of accurate patient selection (27). The ongoing CROSSFIRE trial (NCT02791503) aims to determine the superiority between IRE and stereotactic ablative radiotherapy (SABR/SBRT) in patients with LAPC following induction chemotherapy. Future comparative studies are needed to determine the most effective local ablative treatment in LAPC.

Another interesting development for LAPC is intratumoral injection treatment, such as Holmium. Holmium microspheres (HoMS) were originally developed for selective internal radiation therapy (SIRT) of hepatic tumors. Local tumor therapy with HoMS aims to achieve a positive local tumor response, offering pain relief and enhancing patients' quality of life. However, the effectiveness of intratumoral HoMS injection in prolonging survival for patients with LAPC remains uncertain. Technical limitations such as intratumoral spatial distribution of the HoMS need to be resolved, before larger scale clinical trials can be performed (28).

Stereotactic body radiotherapy

The limited ability of external beam radiotherapy to avoid bowel structures and the need to use large treatment fields to cover the pancreas and surrounding nodal areas result in high toxicity rates. Moreover, conventionally fractionated doses that are based on the tolerability of large-field radiation to the stomach and duodenum, have minimal to no impact on the overall survival of patients.

SBRT can deliver higher doses of radiation to the tumor in fewer treatment fractions, has a better effect and lower toxicity due to reduced volume of

irradiated healthy tissue compared to standard chemoradiotherapy. The combination of SBRT with new chemotherapy regimens has a significant potential to shift patient survival from months to years. Additionally, SBRT may be a permanent treatment option for pain relief and can be well-integrated with other therapeutic options, especially chemotherapy. Further dose escalation to the tumor is limited by poor soft tissue visualization on computed tomography imaging during radiation planning and treatment delivery. The development of stereotactic MR-guided adaptive radiotherapy (SMART), combining X-ray beam delivery, daily adaptive treatment planning, and gating/tracking capability using continuous cine MR images, needs further research to optimize this treatment option (29) . The Dutch ARCADE trial will investigate the value of SBRT in addition to standard of care in patients with isolated local pancreatic cancer recurrence compared to standard of care alone, regarding both survival and quality of life outcomes (30).

Future directions of imaging in pancreatic cancer

Imaging after neoadjuvant chemo

Imaging plays an essential role in the resectability, re-staging, and response evaluation after neoadjuvant therapy. The diagnostic performance of CT after neoadjuvant therapy is not satisfactory due to difficulties in differentiating necrosis, inflammation, fibrosis, and residual vital tumor tissue. The commonly used Response Evaluation Criteria in Solid Tumors (RECIST) criteria prove to be ill-suited for evaluating tumor response following neo-adjuvant therapy (NAT). Accurate assessment of post-NAT response using RECIST1.1 (31) requires precise and reproducible tumor size measurements. Unfortunately, on CECT pre-treatment tumor size is frequently underestimated in comparison to the resection specimen, because of a rim of viable tumor seen as hyperperfused halo, but often not easily depicted from surrounding pancreatic tissue. Accurate tumor size measurement is also limited with PDAC that is isoattenuating to normal pancreatic parenchyma. Tumor size can be overestimated post-NAT due to treatment-related changes, such as necrosis and edema, with limited correlation to achieving tumor-free resection margins (R0). Additionally, only minority of patients show tumor shrinkage after NAT, while most exhibit stable disease. Notably, a significant percentage of cases eventually become resectable, particularly in BRPC. Restaging of arterial involvement

using standard criteria of tumor-vessel contact are not accurate after NAT, primarily due to the persistent visibility of periarterial encasement in a majority of cases showing good response, mainly due to tumor replacement with fibrotic tissue. While complete regression is rare, the only feature indicating objective treatment response is a decrease in tumor-vessel contiguity. Moreover, the 'halo sign' – a thin low-attenuation rim surrounding the vessel- shows promise in predicting pathologic response and R0 resection in patients with arterial involvement. Likewise, the assessment of changes in tumor attenuation presents limitations in predicting resectability, as it cannot effectively differentiate between necrosis, fibro-inflammation, or edema and residual tumor tissue. Concluding, morphological criteria proposed to assess NAT response, encompassing parameters such as tumor size, attenuation, and vascular involvement, do not reliably predict resectability or pathological response. As a result, most patients without apparent tumor progression or metastases undergo exploratory surgery after NAT. Regrettably, it is crucial to acknowledge that a substantial 70% of these surgeries ultimately prove to be futile, primarily due to the presence of local vessel ingrowth. New response evaluation criteria and/or imaging modalities are required to determine resectability more accurately after induction chemotherapy (32).

In CT perfusion pre-treatment blood flow and permeability showed to be a good indicator of histopathological response to chemoradiotherapy. Both responders and non-responders showed an increase in blood flow and blood volume, but only the increase in responders was significant in assessment of the effects after chemoradiation therapy (33, 34)

Among its potential advantages, MRI offers high contrast resolution, leading to improved tumor conspicuity, particularly for tumors that appear isoattenuating on CT. Other than that, MRI and CT have similar performance in assessing tumor size before and after NAT (35). However, studies have shown promising results regarding the performance of DWI for assessment of NAT response. Diffusion weighted imaging markers show better performance than RECIST criteria in evaluating the tumor response to NAT in unresectable PDAC (36). Unified standard criteria for the selection and evaluation of DWI parameters should be developed and verified.

Another direction for future research is metabolic evaluation with the application of PET response criteria (37), which demonstrated greater

accuracy in assessing the effects of NAT when compared to the RECIST criteria, with respective accuracy rates of 72.7% and 36.4%.

CT perfusion

CT perfusion (CTP) consists of the dynamic acquisition after injection of a contrast agent, enabling quantification of tissue vascularization. Using a kinetic model, parameters can be calculated, which reflect intratumoral differences in perfusion and vascular permeability, a potential biomarker for tumor angiogenesis. CTP can accurately distinguish PDAC from non-tumorous pancreatic parenchyma, improve detection of isoattenuating PDAC, and might be helpful as a biomarker for the pathological grade (38), vascular subtypes (39) and predict the histopathologic response to therapy (34). The integration of FDG-PET and perfusion CT holds the potential to generate fully quantitative flow-metabolic phenotype, addressing some of the limitations encountered in our preliminary results using only portal venous phase of CECT. This approach can be instrumental in facilitating tumor classification and advancing precision medicine, while also reducing unnecessary exposure to treatment-related toxicities. Specifically, it can aid in identifying aggressive and angiogenic tumors. Furthermore, if the flow-metabolic phenotype can effectively distinguish molecular subtypes, it can serve as the foundation for more personalized treatment strategies, particularly considering that basal-like tumors exhibit resistance to standard-of-care chemotherapy like FOLFIRINOX, in contrast to classical tumors.

USPIO-MRI

Many primary solid malignancies first metastasize to the lymph nodes, which represents a crucial step in the tumor progression. Nodal involvement often marks the difference between treatment with curative intent and more intensive adjuvant or palliative therapies, underscoring the importance of accurate lymph node staging in therapy planning. Sensitivity of CECT for the detection of lymph node metastases in pancreatic cancer is as low as 50%. The accuracy of MRI for lymph node involvement ranges from 33-75%. With metastases present also in small nodes, and benign nodes that enlarge due to, for example, inflammation, the performance to differentiate between benign and malignant nodes using morphological criteria is poor. Lymph nodes measuring > 10 mm in size are not significantly more common in patients with histopathological lymph node involvement. Interestingly, lymph nodes measuring 4-9 mm in short axis diameter, were equally common in patients with and without lymph node

metastases, resulting in poor discrimination. Instead of relying solely on size as a criterion, specific morphologic criteria, including 'inhomogeneous signal intensity', have demonstrated a degree of specificity in identifying regional nodal metastatic disease. However, it is important to note that substituting size criteria with morphologic indications did not result in an overall improvement in diagnostic accuracy, as sensitivity continued to remain low (40).

Continuously improving opportunities for selective treatment of individual metastatic deposits, knowledge regarding merely the presence (N+) or absence (N0) of nodal metastases is not sufficient anymore, assessment and exact localization of lymph node metastases is crucial. Ultrasmall superparamagnetic particles of iron oxide (USPIO)-enhanced MRI offers a more advanced approach beyond merely assessing the size and shape of the lymph nodes. Normal lymph nodes accumulate the paramagnetic iron oxide particles, administered intravenously 24 to 36 hours before MRI, in macrophages. The presence of these nanoparticles locally disturbs the magnetic field homogeneity, causing MR signal loss on T2*-weighted imaging, providing a contrast between the benign and malignant (part of a) lymph node. The guidance provided by USPIO–enhanced MRI in detecting early nodal metastatic disease holds promise, especially in the context of MR-guided radiotherapy. One limitation that requires attention when applying USPIO-enhanced MRI in pancreatic cancer is the interference of respiratory and cardiac motion, which may potentially obscure signals from small structures, such as lymph nodes, in the upper abdomen. Nevertheless, new schemes have been developed, ensuring high spatial resolution without blurring due to motion (41, 42).

FAPI-PET

Fibroblast activation protein (FAP) is highly expressed in cancer-associated fibroblasts (CAFS) of many epithelial carcinomas, mainly in those characterized by a strong desmoplastic reaction, such as ovarian, digestive, hepatocellular carcinoma and pancreatic cancer. The accuracy of FAPI-PET imaging is higher than FDG and the other conventional imaging for the identification of the metastatic lymph nodes and distant metastases (i.e., liver and peritoneum). Another major advantage over FDG in pancreatic cancer is, that FAPI-PET is independent of glucose activity, leading to the drastic reduction of background signal in the brain, liver, oro- and nasopharyngeal mucosa, and gastrointestinal tract. Moreover, the DOTA

chelator in the molecular structure allows coupling of the FAPI molecules with therapeutic emitters such as Yttrium 90 for theragnostic applications. FAPI-PET might offer ancillary markers to guide clinical decisions after neoadjuvant chemotherapy, as decrease in SUVmax might be associated with histopathological tumor regression and R0 status. Activation of fibroblasts occurs not only in the tumor surrounding tissue but also under benign conditions such as in wound healing, inflammation, or ischemia. This potential limitation could lead to false-positives, and the possible differential uptake kinetics in PDAC and pancreatitis or fibrotic pancreatic tissue need further investigation (43-46).

AI

The use of artificial intelligence (AI) in radiology has rapidly gained attention in recent years. Being a digital image-based specialty, radiology serves as the ideal testing ground for medical applications of AI. Currently, there are two main approaches for image-based AI: radiomics and convolutional neural networks (CNNs). Radiomics employs a feature engineering approach, predicting outcomes by inputting manually defined texture and shape features extracted from a region of interest into machine-learning models. This technique is designed to capture subtle nuances and information within diagnostic images, which may be challenging for the human eye to recognize of quantify. These features, when combined with demographic, histologic, genomic, or proteomic data, offer valuable insights for clinical problem-solving. Conversely, CNNs operate on a fundamentally different principle. They autonomously compute relevant features directly from the imaging data during training. This is achieved through a neural network architecture that comprises a sequence of convolutional and pooling operations. CNNs excel at automatically learning hierarchical representations, allowing them to discern complex patterns and structures within images, making them exceptionally adept at tasks like image classification, segmentation, and object detection. The strength and advantage of employing AI lies in its ability to process vast amounts of data, aiming to reduce misdiagnosis and avoiding both under- and overtreatment, improving the diagnostic performance by combining electronic health data, morphological characteristics and textural features and thereby establishing itself in precision medicine.

In the field of medical imaging, AI has the potential to transform the clinical practice, in an era marked by a growing demand for clinical

imaging with segmentation, lesion detection, and characterization of lesions. AI can significantly contribute to improving patient outcomes through risk stratification, survival prediction, and the ability to predict treatment response.

The PANCAIM project will combine genomics and imaging phenomics using AI to generate ground-breaking knowledge that will enhance our understanding of PDAC biology and improve patient stratification. What sets this project apart is its comprehensive approach, integrating genomics, radiomics, and pathomics, with the goal of facilitating clinical decision-making within multidisciplinary teams.

The integration of AI and human intelligence in clinical medicine is still in its early stages and the potential applications in pancreatic imaging under ongoing investigation, both for non-oncological and oncological purposes. Nonetheless, we are approaching an era where AI will increasingly fulfil its potential and gain widespread adoption in augmenting the capabilities of radiologists, rather than replacing them (47-49).

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Dutch summary / Nederlandse samenvatting

Alvleesklierkanker is een ernstige ziekte die jaarlijks meer dan 2800 mensen in Nederland treft en een van de meest voorkomende oorzaken van kanker gerelateerde sterfte. Het wordt vaak pas laat ontdekt, waardoor de overlevingskansen klein zijn. De meeste mensen met alvleesklierkanker hebben in het begin geen klachten. Als de tumor groeit, kunnen mensen last krijgen van bijvoorbeeld geelzucht, afvallen, pijn of misselijkheid. De precieze oorzaak van alvleesklierkanker is niet bekend. Wel zijn er factoren die de kans groter maken dat je alvleesklierkanker krijgt, zoals roken, chronische alvleesklierontsteking, diabetes, obesitas en genetische mutaties. In ongeveer 10% van de gevallen speelt erfelijke aanleg een rol bij de grotere kans op alvleesklierkanker.

Alvleesklierkanker wordt ingedeeld volgens de TNM-classificatie, waarbij wordt gekeken naar de grootte van de tumor (T), of er lymfeklieruitzaaiingen (N) zijn en of er uitzaaiingen op afstand (M) zijn, bijvoorbeeld naar andere organen. De meest voorkomende plaatsen voor uitzaaiingen zijn de lever, het buikvlies en de longen. De tumoren worden onderscheiden in operabel (resectabel), mogelijk operabel (borderline resectabel), lokaal uitgebreid en uitgezaaid (gemetastaseerd). Het belangrijkste doel van de preoperatieve stadiëring is het identificeren van alle resectabele tumoren en het uitsluiten van uitzaaiingen om onnodige operaties te voorkomen. Dit is van belang omdat 80-85% van de tumoren niet geschikt is voor een operatie vanwege de uitgebreidheid van de ziekte.

Afhankelijk van waar de tumor zich bevindt in de alvleesklier - de kop, of de staart - kan de tumor worden verwijderd door middel van verschillende soorten operaties, zoals een pancreatoduodenectomie (voor tumoren in de kop), distale pancreasresectie (voor tumoren in de staart) of totale pancreatectomie (voor tumoren die de hele alvleesklier omvatten). Op dit moment is chirurgische verwijdering (samen met chemotherapie) de enige manier om te kunnen genezen van alvleesklierkanker. Helaas zijn de overlevingskansen voor alvleesklierkanker de afgelopen decennia nauwelijks verbeterd. Slechts 12% van alle patiënten is vijf jaar na de diagnose nog in leven. Hoge percentages van terugkeer van kanker en uitzaaiingen na een operatie resulteren onvermijdelijk in een sombere langetermijnoverleving. Er is dringend behoefte aan vooruitgang in beeldvormingstechnologieën om de stadiëring van alvleesklierkanker te

verbeteren en zo de juiste behandelingen te kunnen kiezen, met als doel betere resultaten te behalen.

Dit proefschrift hoopt bij te dragen aan het verbeteren van de resultaten voor patiënten met alvleesklierkanker door zich te richten op de ontwikkeling van nieuwe beeldvormingstechnieken en het evalueren van nieuwe behandelopties.

Er worden nieuwe manieren ontwikkeld om operaties veiliger en beter te maken. Een voorbeeld hiervan is minimaal invasieve chirurgie. Maar het gebruik van deze methode voor alvleesklieroperaties is moeilijk vanwege de complexiteit ervan. **Hoofdstuk 2** heeft tot doel de perioperatieve uitkomsten van minimaal invasieve en open distale pancreasresectie te vergelijken. De gemiddelde duur van het ziekenhuisverblijf was significant korter in de laparoscopische (kijkoperatie) groep dan in de open groep. Dit zou te verklaren kunnen zijn door een sneller postoperatief herstel als gevolg van de minder invasieve aard van de kijkoperatie. Verschillen in de duur van het ziekenhuisverblijf zijn echter alleen van belang als laparoscopische distale pancreasresectie hetzelfde oncologische resultaat biedt als open distale pancreasresectie. Middels dit onderzoek was het niet mogelijk om daarover definitieve conclusies te trekken. Er waren geen significante verschillen tussen laparoscopische en open distale pancreasresectie wat betreft korte-termijn sterfte. Doordat er ten tijde van analyse nog geen gerandomiseerde gecontroleerde onderzoeken (randomised controlled trials of RCTs) waren, waren er zorgen over selectiebias. We vonden dat degenen met uitgebreidere kanker vaker open distale pancreasresectie ondergingen. Bovendien werd de beslissing over welke soort operatie uit te voeren gebaseerd op de voorkeur van de chirurg of de patiënten.

Om te begrijpen welke operatie het meest kosteneffectief is en welke gezondheidsvoordelen ze bieden, onderzoekt **Hoofdstuk 3** de kosteneffectiviteit van de laparoscopische en open distale pancreasresectie. Uit dit onderzoek blijkt dat laparoscopische distale pancreasresectie lagere kosten met zich meebrengt en meer gezondheidsvoordelen oplevert in vergelijking met open distale pancreasresectie. Echter, vanwege het gebrek aan gegevens en het gebruik van informatie uit observationele studies, en het risico op fouten in deze studies, kon deze studie niet met zekerheid zeggen of laparoscopische distale pancreasresectie echt kosteneffectiever is dan open distale pancreasresectie voor alvleesklierkanker.

Resectie en reconstructie vereist voor minimaal invasieve pancreato-duodenectomie zijn technisch uitdagend, zelfs in de handen van ervaren chirurgen. Deze complexiteit benadrukt het belang van grondig onderzoek om de beste benaderingen voor deze ingrepen te bepalen. **Hoofdstuk 4** introduceert een onderzoeksprotocol voor een toekomstig uitgebreid literatuuronderzoek dat laparoscopische, robotische en open pancreatoduodenectomie vergelijkt voor kwaadaardige en goedaardige tumoren in en rondom de alvleesklierkop. Dit onderzoek is gericht op het beoordelen van de effectiviteit en veiligheid van verschillende chirurgische benaderingen voor deze tumoren.

Beeldvorming speelt een cruciale rol bij het stellen van de diagnose, het bepalen van het stadium van de ziekte en het nemen van beslissingen over de behandeling. Hoewel echografie vaak als eerste wordt gebruikt om buikpijn of geelzucht te evalueren, heeft het beperkingen bij het duidelijk en volledig in beeld brengen van de alvleesklier, vanwege verschillende factoren zoals lichaamsbouw en darmgassen. Op dit moment is een CT-scan de standaardprocedure om patiënten te diagnosticeren en de behandeling te bepalen. De beoordeling van de tumor uitbreiding, vaatbetrokkenheid, nabijheid van belangrijke structuren en het identificeren van uitzaaiingen is hierin van essentieel belang. Echter, CT-scans kunnen soms de ernst van de ziekte onderschatten. Uitdagingen hierbij zijn het vinden van kleine of niet zichtbare tumoren, het beoordelen van lymfeklierbetrokkenheid, en het identificeren van uitzaaiingen in de lever en het buikvlies. Soms lijken tumoren op de CT-scan verwijderbaar, maar tijdens de operatie blijkt dit niet het geval te zijn. Dit kan ertoe leiden dat de operatie moet worden gestopt. Daarnaast is intra-operatieve detectie van kleine lever- of peritoneale uitzaaiingen een veelvoorkomende reden waarom een operatie wordt gestaakt bij patiënten die voorafgaand aan de operatie een CT-scan hadden waarop de tumor als operabel werd beoordeeld. Bovendien keert de kanker bij ongeveer 50% van de patiënten kort na de operatie terug, wat de effectiviteit van de operatie in twijfel trekt. Onnodige operaties brengen risico's met zich mee en kunnen leiden tot sterfte en complicaties. Ook kan het ervoor zorgen dat patiënten langer moeten wachten voordat ze met chemotherapie kunnen beginnen, omdat ze tijd nodig hebben om te herstellen van de operatie.

In **Hoofdstuk 5** wordt de nauwkeurigheid van endoscopische echografie (EUS) na een CT-scan geëvalueerd om te bepalen of alvleesklierkanker operatief verwijderbaar is. Als EUS aangeeft dat de tumor niet verwijderbaar is, terwijl de CT-scan aangeeft dat dit wel het geval is, had ongeveer 13% van de patiënten eigenlijk wel een operabele tumor. Dit suggereert dat er geen bewijs is om aan te bevelen dat EUS standaard moet worden uitgevoerd om vaat betrokkenheid te beoordelen bij patiënten met alvleesklierkanker die op de CT-scan een operabele tumor hebben.

Het is duidelijk geworden dat de traditionele aanpak voor het diagnosticeren, stadiëren en voorspellen van de prognose van alvleesklierkanker niet voldoende is. Het vinden van nieuwe biomarkers is essentieel om vooruitgang te boeken. Deze nieuwe biomarkers zijn nodig om de selectie van patiënten vóór de operatie te verbeteren en de behandeling meer op maat te maken.

FDG-PET-scans kunnen worden gebruikt om het stadium van de ziekte te beoordelen en de prognose te voorspellen. Hoewel veelbelovend, heeft FDG-PET nog geen vaste rol gekregen in de standaard stadiëring van alvleesklierkanker, omdat het moeilijk is om kleine laesies te detecteren en er mogelijk fout-positieve resultaten zijn. Ook kan FDG-PET de exacte grootte van de tumor ten opzichte van het omliggende weefsel niet nauwkeurig bepalen. Desondanks heeft het wel vaak invloed op de besluitvorming en voorkomt het onderzoek onnodige chirurgie, meestal door eerder onopgemerkte uitzaaiingen te ontdekken. In **Hoofdstuk 6** wordt een potentiële nieuwe biomarker onderzocht die gebruikmaakt van een combinatie van bloedstroom en tumormetabolisme, gemeten met CT en FDG-PET om tumoren te identificeren met een agressieve tumorbiologie en slechtere prognostische kenmerken. Uit het onderzoek blijkt dat op CT minder aankleurende alvleeskliertumoren met hoge opname van [^{18}F]-FDG (radioactief suiker) op FDG-PET een significant hoger tumorstadium hebben, minder vaak geopereerd worden en een lagere overlevingskans hebben in vergelijking met andere combinaties van bloedstroom en metabolisme. De interpretatie van de resultaten werd echter bemoeilijkt door de grote verschillen binnen de studiepopulatie, die alle stadia van tumoren en verschillende behandelstrategieën omvatte.

MRI biedt betere contrasten tussen verschillende soorten weefsel, waardoor het gemakkelijker is om tumoren te herkennen. Het heeft een vergelijkbare diagnostische nauwkeurigheid als CT voor het bepalen of een tumor resectabel is, maar het is beter in het detecteren van tumoren die niet zichtbaar zijn op CT-scans. Een speciale MRI-techniek genaamd diffusie-gewogen beeldvorming (DWI) is ook waardevol voor het opsporen van afwijkingen en het karakteriseren van weefselveranderingen. In **Hoofdstuk 7** proberen we de bevindingen van DWI te koppelen aan de kenmerken die we onder de microscoop zien bij alvleesklierkanker. In dit onderzoek bestuderen we de waarde van MRI en een specifieke meting van DWI genaamd ADC in verband met de totale overleving en de tumorgraad in preparaten van verwijderde tumoren. Ondanks dat het niet mogelijk was om de gradering te vast te stellen met DWI, is MRI toch een waardevol hulpmiddel in de stadiëring van alvleesklierkanker.

In **Hoofdstuk 8** van deze thesis wordt een retrospectieve vergelijking gepresenteerd tussen preoperatieve CT en MRI om te onderzoeken of MRI de detectie van leveruitzaaiingen kan verbeteren. Uit het onderzoek blijkt dat MRI met DWI bij 24% van de patiënten met potentieel resectabele alvleesklierkanker op CT-scan leveruitzaaiingen detecteerde. Bovendien werden met DWI significant meer uitzaaiingen gevonden dan met de standaard MRI. De meeste leveruitzaaiingen bij alvleesklierkanker zijn klein en talrijk, waarbij subcentimeter laesies 95% van alle laesies uitmaken. Door diffusie-gewogen MRI toe te voegen aan de standaard MRI, is er een aanzienlijke verbetering aangetoond in de detectie van levermetastasen en het inschatten van de hoeveelheid uitzaaiingen. Hoewel dit onderzoek alleen patiënten met resectabele en borderline resectabele tumoren omvatte, suggereert het dat MRI met DWI ook nuttig kan zijn voor patiënten met een lokaal uitgebreide tumor. Bij een lokaal uitgebreide tumor komen uitzaaiingen vaker voor dan bij resectabele tumoren.

In het tijdperk van geavanceerde behandelingen zoals neoadjuvante therapieën, lokale ablatie therapieën voor gevorderde tumoren en kostbare doelgerichte therapieën, wordt het inschatten van de mate van uitzaaiingen steeds belangrijker. Het is van cruciaal belang om goed te kunnen beoordelen welke operaties 'slechts' technisch uitdagend zijn en welke tumoren agressieve biologie vertonen.

Hoofdstuk 9 beschrijft het onderzoeksprotocol van een prospectieve studie die de diagnostische nauwkeurigheid van MRI met DWI voor het detecteren van leveruitzaaiingen bij patiënten met alle stadia van alvleesklierkanker onderzoekt. In de komende jaren zullen we de resultaten van deze DIA-PANC studie presenteren.

Tot slot wordt deze thesis afgerond met een algemene discussie in **Hoofdstuk 10**, waarin de resultaten en conclusies van de gepresenteerde studies worden samengevat en toekomstperspectieven worden besproken.

Dankwoord

Dit traject begon 10 jaar geleden als een wetenschappelijke stage en groeide uit tot dit promotietraject. Soms leek het een never ending story, maar zelfs de langste verhalen komen tot een einde, en nu kan dit boekje letterlijk worden gesloten. Ik wil graag mijn waardering uitspreken voor iedereen die heeft bijgedragen aan dit proefschrift, mijn leerproces en persoonlijk groei. Een aantal mensen wil ik in het bijzonder bedanken:

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Prof. van Laarhoven, Beste Kees, dankjewel dat je in me bent blijven geloven. Jouw bemoedigende woorden hielpen me om het vertrouwen vast te houden. Ik waardeer enorm dat je me de kans hebt gegeven om bij de chirurgie te komen werken op het moment dat ik dat het hardst nodig had. Daardoor ben ik nu waar ik altijd heb willen zijn.

Beste leden van de manuscriptcommissie, prof. Verheij, prof. Nagarajah en dr. de Haas, hartelijk dank voor het zorgvuldig beoordelen van mijn werk. Ook wil ik de overige leden van de commissie bedanken voor hun deelname aan de oppositie.

Co-auteurs, veel dank voor jullie waardevolle bijdragen aan een of meerdere hoofdstukken van dit proefschrift.

(Oud)collega's bij de chirurgie en radiologie, ontzettend bedankt voor jullie support wanneer ik even niet wist hoe iets moest, op onderzoeksdagen die anders verliepen dan gehoopt en de momenten waarop we iets mochten vieren. Ik heb zo genoten van de gezellige tijd met jullie en ben trots (en wat was ik stiekem ook een beetje jaloers) op die hele stapel boekjes die ik door de jaren heen van mijn collega-onderzoekers heb mogen ontvangen. Bijzonder veel waardering gaat uit naar Marjan, Germien, Hans en Claudia.

Willem en Sarah, wat geweldig dat we dit nu alle drie hebben afgerond. Jullie hebben een prachtig proefschrift gemaakt, en ik ben blij dat jullie beiden in opleiding tot chirurg zijn gekomen. Ik wens jullie veel succes in jullie verdere carrière.

Geke, wat een werk heb jij gestoken in DIA-PANC. Dat we dit vandaag samen kunnen vieren, ondanks alle uitdagingen die we onderweg tegenkwamen, is een prestatie op trots op te zijn!

AIOS, radiologen en MMB-ers in het Jeroen Bosch Ziekenhuis en het Radboudumc, ik waardeer jullie interesse in mijn promotietraject enorm. Het is eindelijk zo ver! Jullie steun en alles wat ik van jullie heb geleerd, betekenen veel voor mij. Mijn opleiders, Matthieu, Vincent, Liesbeth en Heleen: jullie begeleiding en de tijd die ik kreeg om dit promotietraject tijdens mijn opleiding voor te zetten, hebben een cruciale rol gespeeld in de afronding ervan.

Lieve Stefan, dankjewel voor je positieve energie, je luisterend oor en je interesse in mij. Wat hebben we samen een mooie tijd gehad in Den Bosch! Ik mis je nog elke dag op de werkvloer en geniet van onze telefoontjes om bij te kletsen. Ik hoefde niet lang na te denken over wie ik naast me wilde op deze speciale dag.

Lieve vrienden, jullie zijn ontzettend belangrijk voor me en brengen zoveel positiviteit in mijn leven. Dankzij jullie heb ik mijn zinnen kunnen verzetten, en ik ben dankbaar voor alle mooie herinneringen die we samen hebben gemaakt. Ook de dierbare vriendschappen die in de afgelopen jaren zijn ontstaan, betekenen veel voor mij. Ik kijk ernaar uit om hier meer tijd in te steken en verheug me op nog meer etentjes, festivals, feestjes, en ook op extra uren pompen – een fit lichaam is immers een fit hoofd. Nu ik dit allemaal heb afgerond, hoop ik weer meer tijd op het water door te brengen.

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Youri, ik kijk ernaar uit om de volgende avonturen in mijn leven samen met jou aan te gaan. Ik hou van je.

Curriculum Vitae

Deniece Rivière, born in Curaçao on August 30, 1988, spent her childhood in the Achterhoek with her parents and brothers. She completed her high school education at Almende College Isala in Silvolde in 2006, focusing on arts, humanities, and social sciences. In 2007, driven by her passion for medicine, she obtained qualifications in math, science, and physics at Rijn IJssel in Arnhem. This opened the door for her to start her medical studies at Radboud University Nijmegen in September of the same year.

Throughout her medical education, Deniece participated in various extracurricular activities, including managing the Aesculaaf Café from 2010 to 2011. Her exposure to radiology during clinical rotations sparked a profound interest in the field. Under the mentorship of John Hermans, she laid the groundwork for her PhD thesis during her research internship and master's thesis. Deniece successfully completed her medical degree in November 2014.

In addition to part-time clinical responsibilities as a surgical resident not in training at Radboud University Medical Center, she continued her research in pancreatic cancer. Her hard work paid off when the KWF grant submission for the DIAPANC project was accepted.

In January 2017, Deniece started her radiology training at Jeroen Bosch Hospital in ‘s-Hertogenbosch, under the guidance of Matthieu Rutten and later Vincent Cappendijk. Simultaneously, she worked on her PhD thesis. In March 2023 Deniece became a registered radiologist. Currently, she serves as a radiologist at Radboud University Medical Center, where she continues to expand her expertise in Abdominal Radiology.

Outside of work, Deniece is still loving life in the heart of Nijmegen, soaking up the lively vibes and hanging out with friends. She's all about kite surfing, tending to her urban jungle, and enjoying good food, live music, and festivals.

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Data Management

Ethics and Privacy

This thesis is based on the results of research involving human participants and existing data from published papers, which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct, and Radboudumc policy. The studies described in Chapters 6, 7, and 8 involving human participants were not subject to the Dutch Medical Research Involving Human Subjects Act (WMO) and were approved by the recognized Medical Ethics Review Committee 'METC Oost-Nederland' (file numbers 2014/009 and 2014/183). The need for informed consent was waived. Technical and organizational measures were implemented to safeguard the availability, integrity, and confidentiality of the data (these measures include the use of pseudonymization, access authorization, and secure data storage). The privacy of the participants in these studies was ensured through pseudonymization. The pseudonymization key was stored on a secured network drive that was only accessible to project members who needed access due to their roles within the project, and it was stored separately from the research data.

Data Collection and Storage

Data for Chapters 2, 3, and 5 do not involve human participants and were stored by the responsible co-author, K.S. Gurusamy. The data for Chapter 4 also do not involve human participants and will be stored and analyzed on the department server. Data for Chapters 6, 7, and 8 were extracted from (electronic) health records and medical images into SPSS (SPSS Inc., Chicago, Illinois, USA) and were stored and analyzed on the department server. The folder is accessible only by project members working at Radboudumc. These secure storage options safeguard the availability, integrity, and confidentiality of the data. Paper (hardcopy) data is stored in cabinets in the department. When these studies were developed, the use of digital solutions for data management was not widely available nor affordable for smaller studies without funding.

Availability of Data

All studies are published open access. The dataset itself is under restricted access and anonymized data available from the corresponding author upon reasonable request. The data will be archived for 15 years after the publication of the individual studies.

PhD portfolio of Deniece Rivière

Department: **Department of Medical Imaging & Department of Surgery**
PhD period: **01/07/2015 – 31/10/2024**
PhD Supervisor(s): **Prof. dr. C.J.H.M van Laarhoven**
PhD Co-supervisor(s): **Dr. ir. J.J. Hermans, Dr. E.J.M van Geenen**

Training activities	**Hours**
Courses	
• ESGAR Pancreas Workshop (2015)	24.00
• Cochrane Systematic review course (2015)	28.00
• RIHS - Introduction course for PhD candidates (2017)	15.00
• How to write a medical scientific paper (2017)	6.00
• IDKD Abdomen & Pelvis (2018)	48.00
• Radboudumc - Scientific integrity (2019)	20.00
Seminars	
• Oral presentation Dutch Pancreatic Cancer Meeting (2015)	10.00
• Pancreas Meeting IKNL (2016)	10.00
• Oral presentation Scientific Meeting Jeroen Bosch Hospital (2018)	10.00
• Radboud Research Rounds (2022)	6.00
• Prepare your defence (2024)	3.00
Conferences	
• Oral presentation Radiologendagen (2015)	19.00
• Chirurgendagen (2016)	24.00
• Oral presentation Radiologendagen (2017)	28.00
• Oral presentation (2x) ESGAR Annual Meeting (2017)	62.00
• Radiologendagen 2019 (2019)	24.00
• Radiologendagen 2021 (2021)	18.00
• Radiologendagen 2022 (2022)	24.00
• ESGAR Annual Meeting (2022)	48.00
• ESGAR Annual Meeting (2024)	48.00
Other	
• Preparation poster presentation ISMRM 23rd Annual Meeting & Exhibition (2015)	7.00
• Preparation poster presentation ECR 2016 (2016)	7.00
• Preparation poster presentation European Pancreas Club Meeting (2016)	7.00
• Preparation oral presentation 5th Annual AHPBA HPB Fellows Course (2016)	7.00
• Weekly multidisciplinary meeting PACON (2016)	150.00
• Editor newsletter Tumors of the Digestive Tract (2016)	56.00
• Preparation poster presentation ECR 2017 (2017)	7.00
• Review scientific publications (2022/2023/2024)	14.00
Teaching activities	
Supervision of internships / other	
• Master thesis Annemiek Hogenes (2016)	14.00
• Master thesis Dirk van den Hoven (2016)	28.00
• Junior researcher Barend Mol (2020)	56.00
Total	**828.00**

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