Premalignant Pancreatic Cystic Lesions Management

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Pancreatic cystic lesions are an increasingly common clinical finding. They represent a heterogeneous group of lesions that include two of the three known precursors of pancreatic cancer, intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN). Given that approximately 8% of pancreatic cancers arise from these lesions, careful surveillance and timely surgery offers an opportunity for early curative resection in a disease with a dismal prognosis.

pancreatic cystic lesions pancreatic cancer intraductal papillary mucinous neoplasm mucinous cystic neoplasm endoscopic ultrasonography magnetic resonance imaging computer tomography diagnosis management surveillance

1. Introduction

Globally, pancreatic cancer is the twelfth most common cancer but the seventh most common cause of cancer-related death. In 2018, there were an estimated 459,600 new cases and 432,000 deaths from the disease [1]. The incidence in the Western population is increasing, with the highest being in Europe and North America [1][2][3][4]. It is estimated to become the second leading cause of cancer-related death by 2030 [5]. A study of 3.9 million cancer patients globally found pancreatic cancer to have the lowest five-year survival rates, ranging from 7.9% in the United Kingdom to 14.6% in Australia [6]. Due to the lack of overt symptoms in earlier stages of the disease, most patients are diagnosed at a stage when curative resection is no longer possible, leading to the low survival rate [7]. Patients diagnosed at an early stage have a substantially better prognosis and survival compared to those diagnosed with more advanced stages, as more patients diagnosed in earlier stages are likely to be candidates for surgical resection with improved survival [8]. Even if the tumor is not amendable to surgical resection, a lower tumor burden results in less chemoresistance, therefore making chemoradiotherapy treatments more effective [9][10]. Therefore, early diagnosis in pancreatic cancer has become a recognized healthcare priority [7][11].

Pancreatic cystic lesions (PCL) are an increasingly common incidental finding. They are present in 1.2–2.6% of patients undergoing abdominal computed tomography (CT) [12][13] and in up to 13.5% of patients undergoing abdominal magnetic resonance imaging (MRI) for non-pancreatic indications [14]. The incidence increases further with age, with approximately 10% of individuals over 70 years old undergoing a CT being found to have PCL [15]. PCL have a broad differential diagnosis [16]. Table 1 shows the characteristics of the common PCL. Intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs) are of particular importance because these are considered precursor lesions to pancreatic cancer [17][18][19][20][21][22]. In contrast to the other precursors, such as pancreatic intraepithelial neoplasia (PanIN) which can only be identified on surgical histopathology, IPMNs and MCNs can be easily identified on cross-sectional imaging [23][24][25][26][27] Given that approximately 8% of all pancreatic cancers are believed to arise from these lesions, this offers an opportunity for early cancer detection [28].

Table 1. Key clinical and imaging features of common pancreatic cystic lesions.

	Intraductal Papillary Mucinous Neoplasm (IPMN)	Mucinous Cystic Neoplasm (MCN)	Serous Cystic Adenoma	Pseudocyst	Cystic Pancreatic Neuroendocrine Tumor	Solid Pseudopapillary Neoplasm
Sex	M or F	F	F	M or F	M or F	F
Age	65	40	60	-	50	30
Pancreatic localization	Head	Body/Tail	Throughout	Throughout	Throughout	Body/Tail
Typical imaging features	MD-IPMN: Dilated MPD SB IPMN: Dilated side branch or cyst that connects to the MPD	Unilocular, macrocystic	Microcystic (honeycomb) appearance	Unilocular cyst, sometimes with necrotic debris	Solid cystic lesion, hypervascular	Solid cystic lesion
Communication with the MPD	+	−	−	+ or −	−	−
Solitary/multifocal	Solitary/multifocal	Solitary	Solitary	Solitary	Solitary	Solitary
Malignant potential (surgically resected lesions) *	MD/MT IPMN: 36–100% BD IPMN: 11–30%	10–39%	0%	0%	10%	10–15%

1.1. Classification of IPMNs and MCNs

An IPMN is a mucin producing tumor that arises from the pancreatic duct. They are equally common in men and women. There are three types of IPMNs, which are differentiated based on morphologic differences. Main duct IPMNs (MD-IPMN) are characterized by involvement with the main pancreatic duct (MPD), and identified by a dilated MPD (≥5 mm) without an associated cyst or other cause for ductal obstruction. Branch duct IPMNs (BD-IPMN) arise from a branch off the MPD, and are identified as unilocular or multilocular pancreatic cyst with communication with the MPD, which measures <5 mm. Mixed-type IPMNs (MT-IPMN) meet criteria for both MD and BD IPMNs (Table 1). Furthermore, IPMNs can be histologically classified as gastric, intestinal, pancreaticobiliary or oncocytic based on cellular morphology and mucin (MUC) gene expression and tissue architecture [29]. Studies have suggested that knowing the epithelial subtypes may be of prognostic importance (Table 2) [30].

Table 2. Pathological subtypes of IPMN.

Subtype	Papillae	Mimicker	Typical Level of Atypia	MUC Staining
Gastric	Thick fingerlike or small tubules	Foveolar gland or pyloric gland	LGD	MUC5AC MUC6
Intestinal	Villous	Intestinal villous neoplasm	IGD / HGD	MUC2 MUC5AC
Pancreaticobiliary	Fern like	Cholangiopapillary neoplasm	HGD	MUC1 MUC5AC MUC6
Oncocytic	Pylloid	Oncocytic tumor	HGD	MUC5AC MUC6 (+/− MUC1 or MUC2)

Gastric-type IPMNs have the best prognosis, as they are typically small BD-IPMNs with low-grade dysplasia (LGD), and have a 5-year survival of >90%. Prognosis following resection is good, with 5- and 10-year survival rates of over 90%. Intestinal-type IPMNs are often involving the MPD and are MT or MD-IPMNs with high-grade dysplasia (HGD). Prognosis of intestinal IPMNs are less favorable, with 5- and 10-year survival rates of 70% and 50%, respectively, when associated with pancreatic cancer. Pancreatobiliary-type IPMNs arise from BD, MT or MD-IPMNs but are exclusively high-grade neoplasms, and seen up to 80% of cases associated with invasive pancreatic cancer. Five- and 10-year survival rates are 50% and 0%, respectively. Oncocytic IPMNs are rare but tend to occur in younger patients. They arise in MD-IPMNs with HGD and around 50% are associated with invasive cancer. Patients with oncocytic-type IPMNs with associated cancer have a 5- and 10-year survival of 60% and 40%, respectively [31].

MCNs, on the other hand, are lined by tall columnar mucin producing epithelial cells and in contrast to IPMNs, are surrounded by ovarian-type stroma [16][32]. There is predominance for these lesions to be detected in middle-aged women [33] (Table 1).

1.2. IPMN/ MCN Progression to Invasive Cancer

The natural history and longitudinal risk of malignancy in IPMNs and MCNs are poorly understood. Although these lesions can progress from low-grade to high-grade dysplasia and ultimately pancreatic cancer, not all IPMNs or MCNs progress to cancer within a patient's lifetime. Each type of IPMN is associated with different rates of malignant transformation. In surgically resected BD-IPMN, the risk of malignant transformation has been reported to be between 6 and 51%. MD and MT- IPMNs are recognized to have higher rates of malignant transformation, ranging between 35–100% [23][24][25][26]. The risk of malignant transformation in MCNs have been reported to be between 0–34% [34]. Regardless, the data on the natural history of IPMNs and MCNs have limitations. Natural history studies that rely on surgical specimens include a disproportionate number of high-risk lesions so may overestimate the true cancer risk whereas cohort studies without histologic proven IPMNs and MCNs [35] may underestimate cancer risk.

Pancreatic cancer in IPMN can arise directly from the PCL (an associated cancer) or from the pancreatic parenchyma away from the IPMN (concomitant cancer), which occurs in between 9–44% of cases [36][37]. IPMN-associated and concomitant cancers have a better prognosis than non-IPMN pancreatic cancers. A recent systematic review revealed an improved 5-year survival for IPMN cancers (OR 0.23, 95% CI 0.09–0.56). Median survival ranged from 21 to 58 months in the IPMN cancers compared to 12–23 months in the non-IPMN related cancer group. It was noted that IPMN cancers were frequently found as stage 1 disease (OR 4.40, 95% CI 2.71–7.15) so it is possible that the improved survival is actually due to earlier detection [38].

Whole exome and targeted sequencing of small cohorts of IPMNs and MCNs have identified genetic alterations in oncogenes and tumor suppressor genes, which drive progression to dysplasia and ultimately cancer. Like in pancreatic cancer, one of the earliest genetic alterations in IPMNs are thought to be in KRAS and GNAS [39][40][41]. Over time, mutations in tumor suppressor genes such as RNF43, CDKN2A, TP53 and SMAD4 occur which drives the progression to invasive cancer [40][41]. A targeted analysis of larger cohorts has confirmed that these gene mutations correlate with the grade of dysplasia and histological subtype [42][43]. However, targeted next generation sequencing of IPMNs has suggested there is considerable intratumoral genetic heterogeneity in these lesions and several different molecular alterations are present in different parts of the cyst [44]. It is likely that this combination of genetic alterations drive the transition from a noninvasive precursor lesion to invasive cancer in IPMNs [45][46].

MCNs are lined by columnar mucinous epithelium [16] and like IPMNs, are also now classified pathologically into a three-tiered system with associated LGD, HGD or pancreatic cancer [47]. Like IPMNs, MCNs also harbor genetic changes that lead to tumor progression and ultimately the development of invasive cancer. KRAS mutations are found in 3–100% of MCNs [39][40][48]. The frequency of KRAS alterations also seems to increase with grade of dysplasia [48][49]. GNAS mutations are commonly found in IPMNs but are not found in MCNs; however alterations in RNF43 have been found in 12% of low-grade MCNs and 25% of high-grade MCNs [39]. Loss of CDKN2A/p16 may also play a role in progression to cancer in IPMNs as it is a common finding in MCNs with HGD but is absent in MCNs with LGD. Similarly TP53 is present in 25–56% of MCNs with HGD or cancer, but not in MCNs with LGD [48]. Similar to IPMNs, loss of SMAD4 expression appears predominantly in MCNs with invasive cancer. In one study, which examined 36 MCNs, SMAD4 expression was retained MCNs with LGD or HGD but was lost in 86% of MCNs with invasive cancer [50].

The timeline for progression from IPMN/MCN with LGD to invasive cancer remains poorly understood. Mathematical modelling of the carcinogenesis of PanINs, suggests the progression from PanIN 1 to pancreatic cancer could take up to 35 years, of which 12 years includes the progression from PanIN-3 to pancreatic cancer [51]. Studies classify PCLs as low-risk or high-risk, with high risk having characteristics of high-risk stigmata, defined as presence of obstructive jaundice, enhancing mural nodule ≥5 mm, and main pancreatic duct ≥10 mm or worrisome features, defined as presence of pancreatitis, cyst ≥3 cm, enhancing mural nodule <5 mm, thickened cyst wall, main pancreatic duct of 5–9 mm, abrupt change in caliber of pancreatic duct, lymphadenopathy, increased serum level of carbohydrate antigen 19-9, and a cyst growth rate ≥5 mm/2 years [27]. A systematic review of retrospective surveillance cohorts found that low-risk IPMNs defined as BD-IPMNs without mural nodules, had an approximate 8% chance of progressing to invasive cancer within 10 years while BD-IPMN with worrisome features had 25% chance of progressing to cancer in 10 years [52]. A genetic analysis of the evolutionary timeline of the malignant transformation of IPMNs suggests a window of approximately 3 years to progress from HGD to invasive cancer [53]. These studies suggest progression to cancer occurs over at least several years in IPMNs/MCNs, which supports the utility of surveillance programs that enable the early detection of pancreatic cancer and high-risk lesions.

1.3. Guidelines for the Management of IPMN and MCN

There are currently five major guidelines on the management of IPMN and MCN: the revised International Consensus guidelines [54], the European evidence based guidelines on the management of pancreatic cystic neoplasms [55], the American Gastroenterology Association (AGA) guidelines on the management of asymptomatic PCL [56], the American College of Gastroenterology (ACG) clinical guideline on the diagnosis and management of PCL [57] and the American College of Radiology (ACR) white paper on the management of incidental pancreatic cysts [58]. The similarities and differences between the recommendations are discussed below. The quality of the evidence on which management recommendations are based in IPMN and MCN is often low, so many of the guidelines are formed from expert and consensus opinion (Table 3 and Table 4).

Table 3. Indications for surgical resection in IPMN or MCN as outlined by current guidelines.

Guideline	Cyst Type	Absolute Indications for Surgery	Relative Indications for Surgery
American Gastroenterology Association (2015) [56]	MCN	All MCN	-
	IPMN	• MPD ≥5 mm (on MRI and EUS) and solid component • Cytology positive for malignancy	-
International Consensus Guidelines (2017) [54]	MCN	All MCN	-
	IPMN	• Cytology suspicious or positive for malignancy	• Growth rate ≥5 mm over 2 years • Increased levels of serum CA19-9

Guideline	Cyst Type	Absolute Indications for Surgery	Relative Indications for Surgery
		• Jaundice (tumor-related) • Enhancing mural nodule (≥5 mm) • MPD dilatation ≥10 mm	• PD dilatation between 5 and 9 mm • Cyst diameter ≥30 mm • Acute pancreatitis (caused by IPMN) • Enhancing mural nodule (<5 mm) • Abrupt change in diameter of MPD with distal atrophy • Lymphadenopathy • Thickened or enhancing cyst walls
European (2018) [55]	MCN	• Cyst diameter ≥40 mm • Enhancing mural nodule • Symptoms (jaundice, acute pancreatitis, new- onset diabetes mellitus)	
	IPMN	• Positive cytology for malignancy or HGD • Solid mass • Jaundice (tumor-related) • Enhancing mural nodule (≥5 mm)	• Growth rate ≥5 mm per year • Increased levels of serum CA19-9 (>37 U/mL) • MPD dilatation between 5 and 9.9 mm • Cyst diameter ≥40 mm • New- onset diabetes mellitus • Acute pancreatitis (caused by IPMN)

Guideline	Cyst Type	Absolute Indications for Surgery	Relative Indications for Surgery
		• MPD dilatation ≥10 mm	• Enhancing mural nodule (<5 mm)
American College Gastroenterology (2018) [57]	IPMN or MCN	-	Indication for multidisciplinary review: • Jaundice secondary to the cyst • Acute pancreatitis secondary to the cyst • Significantly elevated serum CA19-9 • Any of the following imaging findings: mural nodule, solid component, dilation of MPD >5 mm, focal dilation of the MPD, mucin-producing cysts ≥3 cm. • The presence of HGD or pancreatic cancer on cytology
		• Jaundice	Indications for EUS-FNA: • High risk features: mural nodules, wall

Guideline	Surveillance Protocol	Indication for EUS	Discharge from Surveillance
American Gastroenterology Association (2015) [56]	Patients with pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct should undergo MRI in 1 year, then every 2 years, for a total of 5 years if there is no change in size or characteristics.	Pancreatic cysts with at least 2 high-risk features, such as size >3 cm, a dilated (or increasingly dilated) main pancreatic duct, or the presence of an associated solid component	Discharge if there has been no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient is no longer a surgical candidate
International Consensus Guidelines (2017) [54]	In cysts without worrisome features: • <1 cm: CT / MRI in 6 months, then every 2 years if no change • 1–2 cm: CT / MRI 6 monthly for 1 year, yearly for 2 years, then every 2 years if no change	If one or more of the following “worrisome features” are present: • Acute Pancreatitis • Cyst >3 cm· Enhancing mural nodule <5 mm • Thickened/enhancing cyst walls • Main duct size 5–9 mm	Continue as long as patients are fit to undergo surgical resection

Guideline	Surveillance Protocol	Indication for EUS	Discharge from Surveillance
	• 2–3 cm: EUS in 3-6 months, then in 1 year if no change, alternating MRI with EUS. Consider surgery in young, fit patients with need for prolonged surveillance. • >3 cm: Alternating MRI with EUS every 3–6 months. Strongly consider surgery in young, fit patients	• Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy • Lymphadenopathy • Increased serum level of CA19-9 • Cyst growth rate > 5 mm/2 years	
European (2018) [55]	• 1st year after diagnosis: Clinical evaluation, serum CA19-9, MRI or EUS every 6 months. • After 1 year + no indications for surgery: Clinical evaluation, serum CA19-9 and MRI or EUS annually	EUS-FNA should only be performed when the results are expected to change clinical management. EUS-FNA should not be performed if the diagnosis is already established by cross-sectional imaging, or where there is a clear indication for surgery	Continue as long as patients are fit to undergo surgical resection
American College Gastroenterology (2018) [57]	In patients with a presumed IPMN/MCN without concerning features or indications for surgery:	EUS-FNA can be considered if the diagnosis is unclear, and results will alter management. Cyst fluid CEA can differentiate IPMN/MCN from other cysts. Cytology can assess for the presence of HGD or pancreatic cancer. Molecular markers can help	Continue as long as patients are fit to undergo surgical resection

Guideline	Surveillance Protocol	Indication for EUS	Discharge from Surveillance
	• <1 cm MRI in 2 years • 1–2cm MRI in 1 year • 2–3 cm MRI or EUS in 6–12 months	identify IPMNs / MCNs in cases where it will change management	
Radiology White paper (2017) [58]	Pancreatic cyst without features of concern: • <2 cm imaging every 1–2 years depending on age and length of size stability • >2 cm imaging every 6 months for 2 years, then annually for 2 years then every 2 years. [59][60]	Increasing cyst size, the presence of “worrisome features” or “high-risk stigmata,” should prompt EUS FNA	Continue as long as patients are fit to undergo surgical resection. Stop surveillance if cyst <1.5 cm and stable over 10 years of surveillance

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The best modality for surveillance of IPMNs and MCNs has not been established, and therefore guidelines vary in their recommendations. For most patients, MRI is preferred method for surveillance as it avoids repeated exposure to ionizing radiation and provides improved delineation of the pancreatic duct and presence of an enhancing mural nodule or internal septations. However, there are ongoing concerns about possible gadolinium deposition in the brain, kidney and bone after repeated use of certain contrast agents in patients with normal renal function [61]. Some patients find MRI scans claustrophobic and they take considerably longer to perform than a CT scan, which only takes a few minutes. EUS or a pancreas protocol CT can therefore be considered as the primary surveillance tools in patients who cannot have or choose not to have MRI with MRCP [54][55][56][57][58].

For IPMNs without high-risk or worrisome features, the cyst size guides the frequency of surveillance in the International Consensus guidelines. In multifocal IPMNs, surveillance intervals are based on the size of the largest IPMN [54]. Size alone correlates imperfectly with malignancy in IPMN as cancers have occasionally been observed in small IPMN (<2 cm) with other worrisome features. The AGA and revised European guidelines do not include size as a basis of their surveillance interval recommendations [55][56] (Table 4). There is limited evidence to support the recommended surveillance intervals in the guidelines. It is likely that this schedule is overly intensive with associated healthcare costs for some patients. For others, this schedule may not be intensive enough and they may develop an interval cancer. All patients should be made aware when entering surveillance programs, that in rare cases, a cancer could develop between surveillance imaging. They should contact their medical team prior to their next imaging study if they develop any new symptoms in the interim period.

Recent studies on MCNs have shown that the risk of cancer in cysts less than 40 mm in size and without worrisome features is exceedingly rare [62][63]; therefore, in contrast to other guidelines, the revised European guidelines recommends surveillance of all MCNs <40 mm, following the same surveillance intervals as for a BD IPMN [55].

2.2. When Can Surveillance Be Stopped?

Although the potential of IPMNs to progress to invasive cancer is clearly recognized, there remains controversy over which guidelines should be followed. The AGA guidelines recommend for the discontinuation of surveillance at 5 years in cysts less 3 cm in the absence of MPD duct dilation and mural nodule. This recommendation was in contrast to the other guidelines [56] and based on a single study of patients with less than 2 cm cysts without worrisome features, in whom none were found to develop invasive cancer after a surveillance period beyond 5 years [64] [Table 4]. Recent studies have varied. Some larger studies of patients with well-characterized IPMNs have disputed this finding by demonstrating a risk of malignant transformation that persists beyond 5 years and which probably increases over time [18][19][22][65][66][67][68]. The largest retrospective study to date of 1404 patients with a clinically defined IPMN found an incidence of malignant transformation of 2.9%, 5.9% and 14% at 5, 10 and 15 years, respectively [36]. As part of secondary analyses, the authors also demonstrated that patients with low risk BD-IPMN <15 mm, had a cumulative incidence rates of pancreatic carcinoma 2.2%, 4.6%, and 7.4% at 5, 10, and 15 years, respectively [36]. In contrast, a recent multicenter study of 806 patients with BD-IPMN ≤15 mm at diagnosis who do not develop worrisome features had an overall risk of malignancy of 1.7% over a 5 year median follow-up, with a cumulative incidence of malignancy of 0.94% at 5 years and 3.37% at 10 years [69]. This is similar to other studies that have suggested cysts can be risk-stratified based on size [22][70][71]. Regardless, the International Consensus and European guidelines recommend continued surveillance in all patients with an IPMN/MCN, as long as they are fit to undergo surgical resection [54][55].

2.3. Surgical Resection in IPMN/MCN

2.3.1. Indications for Surgical Resection

The indications for surgery for patients with IPMN or MCN differ between guidelines but absolute and relative indications for surgery are summarized in Table 3. The International Consensus guidelines define “high risk features” as obstructive jaundice, MPD as greater than 10 mm, positive cytology or an enhancing mural nodule ≥5 mm. If any of these high-risk features are present, they advocate direct surgical referral without further testing. An EUS is advised if any “worrisome features” are present, which includes; cyst growth rate ≥5 mm over 2 years, increased levels of serum CA19-9, MPD dilation between 5 and 9 mm, cyst diameter ≥30 mm, acute pancreatitis (attributable to the IPMN), enhancing mural nodule of <5 mm, an abrupt change in diameter of MPD with distal atrophy, lymphadenopathy or thickened or enhancing cyst walls [54]. The European guidelines, published in 2018, define absolute indications for surgery as positive cytology for malignancy, the presence of a solid mass, obstructive jaundice, an enhancing mural nodule (≥5 mm) or MPD dilatation ≥10 mm. Relative indications for surgery include a growth rate ≥5 mm per year, elevated serum CA19-9 (>37 U/mL), MPD dilatation between 5 and 9.9 mm, cyst diameter ≥40 mm, new-onset diabetes mellitus, acute pancreatitis caused by IPMN or an enhancing mural nodule (<5 mm). If patients have no comorbidity, a lower threshold for surgery is advocated of just one relative indication. In patients with significant comorbidity, more than one relative indication is required to proceed to surgery and if only one relative indication was present, then close surveillance is advised with CA19-9 and MRI with or without an endoscopic ultrasound (EUS) examination [55].

The ACR guidelines define absolute indications for surgery as obstructive jaundice, dilated MPD, positive cytology showing cancer, an enhancing nodule or solid mass. Relative indications included an elevated CA 19-9, new-onset diabetes, acute pancreatitis, cyst growth >5 mm per 2 years, MPD 5–9 mm, cyst >4 cm, or enhancing nodule <5 mm [58]. ACG has set recommendation for referral to surgery which includes obstructive jaundice, acute pancreatitis, solid mass, MPD >5 mm, cyst >3 cm, change in MPD with upstream atrophy, positive cytology showing cancer and presence of a mural nodule but strongly advocates patients are discussed in a multidisciplinary setting prior to surgery [57]. Lastly, the AGA guidelines recommends consideration of surgery if there are two or more of the following features present: dilated MPD, cyst >3 cm, and/or mural nodule. Unlike the other guidelines, the AGA are more conservative and do not recommend resection for MPD dilatation alone, and require the presence of a mural nodule or positive cytology as well [56]. Many of the differences in the recommendations between the guidelines arise because they are based on low or very low quality evidence due to a lack of well characterized prospectively followed cohorts of patients with PCL.

2.3.2. Surgery

High-risk cystic lesions in the head or in the uncinate process of the pancreas typically undergo a pancreatoduodenectomy, whereas a distal pancreatectomy with splenectomy is performed for cysts located in the body or tail of the pancreas. A conventional pancreatoduodenectomy involves removing the pancreatic head, duodenum, part of the jejunum, common bile duct, gallbladder as well as performing a partial gastrectomy, and can be performed open or by minimally invasive laparoscopic or robotic approaches. A distal pancreatectomy involves the removal of the body and tail of the pancreas to the left of the superior mesenteric artery and vein and can also be accomplished using open or minimally invasive approaches. Surgical resection of an IPMN or MCN is associated with a perioperative morbidity of 20–40% and mortality of 1–3% for pancreatoduodenectomy and <1% for distal pancreatectomy [72][73] in high volume centers. Less extensive resections, such as a central pancreatectomy or enucleation, can be performed as a parenchyma-sparing technique. This is a potentially attractive approach because of the potential for improved post-operative pancreatic function. Unfortunately, post-operative morbidity and mortality is similar or higher due to the significant risk of pancreatic fistula. Therefore, this procedure is only performed in select young patients [74].

Although IPMNs can extend along the MPD or be a multifocal disease, none of the current guidelines currently recommend a total pancreatectomy due to the morbidity associated with patient being rendered diabetic and having definite postoperative endocrine insufficiency [54][55]. Despite recommendations, in an international expert survey, around half of the respondents suggested that in certain situations, they would advise total pancreatectomy [75], mainly for IPMN with MPD involvement in order to reduce the risk of recurrence. Indications for surgery in BD-IPMN also differ between the guidelines and are summarized in Table 4.

The International Consensus and AGA guidelines recommend resection of MCN regardless of size whereas the revised European guidelines support surveillance of MCN <40 mm without concerning features, following the same surveillance intervals as for a BD IPMN [54][56].

Several studies have evaluated the accuracy of the different guidelines at predicting advanced neoplasia based on the recommended indications for surgery in IPMN [76][77][78]. These studies recognized that all current guidelines lead to surgical overtreatment of IPMNs. In a comparative study, the AGA guidelines appears to have a significant risk of missing patients with advanced neoplasia (12–45%), although fewer patients would have undergone unnecessary surgery [76][77]. Our center, like many other large hepatopancreaticobiliary centers, broadly follows the International Consensus and European guidelines and discusses each patient with high-risk or worrisome features at a regular multidisciplinary meeting prior to surgical resection [79].

2.3.3. Follow Up after Surgery and Predictors of Recurrence

IPMNs without invasive cancer, recur even after surgery in contrast to MCNs, which do not recur. In a study of 130 patients followed for a median of 38 months, 17% developed imaging evidence of a new or progressive IPMN. Eight percent ultimately underwent a completion pancreatectomy and of those 27% (3 patients) had invasive cancer. In addition, two further patients developed metastatic pancreatic adenocarcinoma and did not undergo resection. All 5 patients (4%) that developed cancer had negative margins after the initial operation. The presence of a negative margin did not significantly affect whether patients developed a recurrence of IPMN. A family history of pancreatic cancer was predictive of developing a new IPMN (23% vs. 7% ($p < 0.05$)). The chances of developing a new IPMN at 1, 5, and 10 years after the initial surgery was 4%, 25%, and 62%, respectively, and the estimated chances of developing invasive cancer at 1, 5, and 10 years after surgery was 0%, 7%, and 38%, respectively [80]. In a multicenter study of 126 patients undergoing resection for a non-invasive IPMN, followed for a median of 9.5 years, a family history of pancreatic cancer (hazard ratio 3.05) and high-grade IPMN (hazard ratio 1.88) were risk factors for recurrence. Again, a positive margin alone was not predictive of recurrence, but the extent and grade of dysplasia at the margin did significantly predict recurrence. Of note, 74% of recurrences occurred after 3 years and 32% after 5 years, supporting long-term surveillance post resection [81].

The European guidelines advocate that patients undergoing a resection of a BD-IPMN with LGD or Intermediate grade dysplasia (IGD) be followed in the same way, as an unresected IPMN and surveillance should be continued as long as patients are fit to undergo a completion pancreatectomy. For patients with HGD, MT IPMN or MD IPMN, follow-up with cross-sectional imaging of the remnant pancreas every 6 months for the first 2 years is recommended, followed by yearly surveillance after that, as long as imaging findings are stable [55]. The International Consensus guidelines advocate enhanced follow- up with at least twice a year imaging in patients with a family history of pancreatic cancer, a surgical resection margin with HGD, and a resected IPMN of a no intestinal subtype. A follow-up every 6 to 12 months in all other patients with resected IPMNs is recommended [54]

An IPMN-associated cancer should be followed up in the same way as follow-up for PDAC after pancreatectomy [55] which involves undertaking cross sectional imaging and measuring CA19-9 every 3–4 months [82].

A systematic review of 13 studies with 773 patients with a MCN, found no risk of recurrence after resection of MCN without pancreatic cancer [34]. Thus, patients with surgically resected MCN whether with LGD or HGD, do not require surveillance. Patients with invasive cancer arising from a surgically resected MCN have a 25% risk of cancer recurrence [62]. Therefore, the International Consensus and European guidelines advocate patients with an MCN- associated cancer should be followed in the same way as those with an IPMN-associated cancer or pancreatic cancer after a partial pancreatectomy [54][55].

2.4. Cyst Ablation

While surgery is the only curative treatment for resectable high-risk IPMNs or MCNs, it is associated with significant morbidity and mortality. In addition, despite current recommendations, approximately 25% of patients who have a presumed IPMN or MCN surgically resected are ultimately found to have a cyst with no malignant potential [83]. This is even more prevalent in resected BD IPMN where up to 78% do not have high-grade dysplasia or invasive cancer [84]. There has therefore been a growing interest in minimally invasive alternative approaches, especially for those patients who are elderly or have high-risk surgical candidates [85][86]. One such method is cystic ablation of the PCL.

Cystic ablation has primarily been undertaken by injecting alcohol or a chemotherapy agent directly into the cyst under EUS-guidance, with the aim of disrupting the epithelial cyst lining leading to cyst resolution [87][88][89][90][91][92][93][94][95]. A recent meta-analysis found the pooled rate of complete resolution of cysts treated with alcohol and paclitaxel was 63.6%, but dropped to 32.8% if ethanol alone was used. Adverse events were reported in approximately 15%, mostly due to acute pancreatitis [96]. An important limitation of many of the single center studies is that follow up was relatively short [87][88][89][90][91][92][93][94][95], but longer-term data is emerging. Choi and colleagues have reported the largest series to date of 164 patients. Patients were followed up for 71 months and complete radiological ablation was achieved in 99% [97]. The highest rate of successful ablation has been in MCNs [96]. This is likely because there are more septations in serous cystic neoplasms and IPMNs, which stop the fluid diffusing through the whole cyst and limiting the ablation of the epithelial lining. Radiofrequency ablation (RFA) causes tissue destruction by the application of a high frequency alternating current, which generates heat leading to a coagulative necrosis. RFA catheters that can be passed through the working channel of a linear echoendoscope have been developed to enable targeted RFA under EUS guidance. Two small prospective studies, with follow up of less than 12 months, evaluated the safety and efficacy of this technique in the management of PCL. Complete ablation was reported between 33–65%, with adverse events occurring in 0–10% [98][99].

Although these initial studies are promising, there continues to be a concern about partial treatment when ablating PCLs. In addition, changes in cyst shape after treatment make it challenging to define complete ablation radiographically. At present, these treatments are only recommended for use within research protocols and formal registries [100]. Further studies are required to determine the long-term efficacy and the clinical benefits of these treatments as well as their place in management protocols [100].

References

1. Arnold, M.; Abnet, C.C.; Neale, R.E.; Vignat, J.; Giovannucci, E.L.; McGlynn, K.A.; Bray, F. Global Burden of 5 Major Types of Gastrointestinal Cancer. Gastroenterology 2020, 159, 335–349.e315.
2. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. Ca A Cancer J. Clin. 2020, 70, 7–30.
3. Huang, J.; Lok, V.; Ngai, C.H.; Zhang, L.; Yuan, J.; Lao, X.Q.; Ng, K.; Chong, C.; Zheng, Z.J.; Wong, M.C.S. Worldwide Burden of, Risk Factors for, and Trends in Pancreatic Cancer. Gastroenterology 2021, 160, 744–754.
4. Lippi, G.; Mattiuzzi, C. The global burden of pancreatic cancer. Arch. Med Sci. AMS 2020, 16, 820–824.
5. Rahib, L.; Smith, B.D.; Aizenberg, R.; Rosenzweig, A.B.; Fleshman, J.M.; Matrisian, L.M. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014, 74, 2913–2921.
6. Arnold, M.; Rutherford, M.J.; Bardot, A.; Ferlay, J.; Andersson, T.M.; Myklebust, T.A.; Tervonen, H.; Thursfield, V.; Ransom, D.; Shack, L.; et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): A population-based study. Lancet Oncol. 2019, 20, 1493–1505.
7. Pereira, S.P.; Oldfield, L.; Ney, A.; Hart, P.A.; Keane, M.G.; Pandol, S.J.; Li, D.; Greenhalf, W.; Jeon, C.Y.; Koay, E.J.; et al. Early detection of pancreatic cancer. Lancet Gastroenterol. Hepatol. 2020, 5, 698–710.
8. Kanno, A.; Masamune, A.; Hanada, K.; Maguchi, H.; Shimizu, Y.; Ueki, T.; Hasebe, O.; Ohtsuka, T.; Nakamura, M.; Takenaka, M.; et al. Multicenter study of early pancreatic cancer in Japan. Pancreatology 2018, 18, 61–67.
9. Neoptolemos, J.P.; Kleeff, J.; Michl, P.; Costello, E.; Greenhalf, W.; Palmer, D.H. Therapeutic developments in pancreatic cancer: Current and future perspectives. Nat. Rev. Gastroenterol. Hepatol. 2018, 15, 333–348.
10. Kamisawa, T.; Wood, L.D.; Itoi, T.; Takaori, K. Pancreatic cancer. Lancet 2016, 388, 73–85.
11. Kenner, B.J.; Chari, S.T.; Cleeter, D.F.; Go, V.L. Early detection of sporadic pancreatic cancer: Strategic map for innovation--a white paper. Pancreas 2015, 44, 686–692.
12. Laffan, T.A.; Horton, K.M.; Klein, A.P.; Berlanstein, B.; Siegelman, S.S.; Kawamoto, S.; Johnson, P.T.; Fishman, E.K.; Hruban, R.H. Prevalence of unsuspected pancreatic cysts on MDCT. Ajr. Am.

J. Roentgenol. 2008, 191, 802–807.

13. Spinelli, K.S.; Fromwiller, T.E.; Daniel, R.A.; Kiely, J.M.; Nakeeb, A.; Komorowski, R.A.; Wilson, S.D.; Pitt, H.A. Cystic pancreatic neoplasms: Observe or operate. Ann. Surg. 2004, 239, 651–657; discussion 657–659.
14. Lee, K.S.; Sekhar, A.; Rofsky, N.M.; Pedrosa, I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am. J. Gastroenterol. 2010, 105, 2079–2084.
15. De Jong, K.; Nio, C.Y.; Mearadji, B.; Phoa, S.S.; Engelbrecht, M.R.; Dijkgraaf, M.G.; Bruno, M.J.; Fockens, P. Disappointing interobserver agreement among radiologists for a classifying diagnosis of pancreatic cysts using magnetic resonance imaging. Pancreas 2012, 41, 278–282.
16. Bosman, F.T.; Carneiro, F.; Hruban, R.H.; Theise, N.D. WHO Classification of Tumours of the Digestive System, 4th ed.; Bosman, F.T., Carneiro, F., Hruban, R.H., Theise, N.D., Eds.; WHO: Paris, France, 2010.
17. Kromrey, M.L.; Bulow, R.; Hubner, J.; Paperlein, C.; Lerch, M.M.; Ittermann, T.; Volzke, H.; Mayerle, J.; Kuhn, J.P. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. Gut 2018, 67, 138–145.
18. Malleo, G.; Marchegiani, G.; Borin, A.; Capelli, P.; Accordini, F.; Butturini, G.; Pederzoli, P.; Bassi, C.; Salvia, R. Observational study of the incidence of pancreatic and extrapancreatic malignancies during surveillance of patients with branch-duct intraductal papillary mucinous neoplasm. Ann. Surg. 2015, 261, 984–990.
19. Kwong, W.T.; Hunt, G.C.; Fehmi, S.M.; Honerkamp-Smith, G.; Xu, R.; Lawson, R.D.; Tang, R.S.; Gonzalez, I.; Krinsky, M.L.; Giap, A.; et al. Low Rates of Malignancy and Mortality in Asymptomatic Patients With Suspected Neoplastic Pancreatic Cysts Beyond 5 Years of Surveillance. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 2016, 14, 865–871.
20. Munigala, S.; Gelrud, A.; Agarwal, B. Risk of pancreatic cancer in patients with pancreatic cyst. Gastrointest. Endosc. 2016, 84, 81–86.
21. Del Chiaro, M.; Ateeb, Z.; Hansson, M.R.; Rangelova, E.; Segersvard, R.; Kartalis, N.; Ansorge, C.; Lohr, M.J.; Arnelo, U.; Verbeke, C. Survival Analysis and Risk for Progression of Intraductal Papillary Mucinous Neoplasia of the Pancreas (IPMN) Under Surveillance: A Single-Institution Experience. Ann. Surg. Oncol. 2017, 24, 1120–1126.
22. Pergolini, I.; Sahora, K.; Ferrone, C.R.; Morales-Oyarvide, V.; Wolpin, B.M.; Mucci, L.A.; Brugge, W.R.; Mino-Kenudson, M.; Patino, M.; Sahani, D.V.; et al. Long-term Risk of Pancreatic Malignancy in Patients With Branch Duct Intraductal Papillary Mucinous Neoplasm in a Referral Center. Gastroenterology 2017, 153, 1284–1294.e1.

23. Nara, S.; Onaya, H.; Hiraoka, N.; Shimada, K.; Sano, T.; Sakamoto, Y.; Esaki, M.; Kosuge, T. Preoperative evaluation of invasive and noninvasive intraductal papillary-mucinous neoplasms of the pancreas: Clinical, radiological, and pathological analysis of 123 cases. Pancreas 2009, 38, 8–16.
24. Hwang, D.W.; Jang, J.Y.; Lee, S.E.; Lim, C.S.; Lee, K.U.; Kim, S.W. Clinicopathologic analysis of surgically proven intraductal papillary mucinous neoplasms of the pancreas in SNUH: A 15-year experience at a single academic institution. Langenbeck's Arch. Surg. Dtsch. Ges. Fur Chir. 2012, 397, 93–102.
25. Kim, S.C.; Park, K.T.; Lee, Y.J.; Lee, S.S.; Seo, D.W.; Lee, S.K.; Kim, M.H.; Jang, S.J.; Byun, J.H.; Han, D.J. Intraductal papillary mucinous neoplasm of the pancreas: Clinical characteristics and treatment outcomes of 118 consecutive patients from a single center. J. Hepato-Biliary-Pancreat. Surg. 2008, 15, 183–188.
26. Nagai, K.; Doi, R.; Kida, A.; Kami, K.; Kawaguchi, Y.; Ito, T.; Sakurai, T.; Uemoto, S. Intraductal papillary mucinous neoplasms of the pancreas: Clinicopathologic characteristics and long-term follow-up after resection. World J. Surg. 2008, 32, 271–278; discussion 279–280.
27. Tanaka, M.; Fernandez-del Castillo, C.; Adsay, V.; Chari, S.; Falconi, M.; Jang, J.Y.; Kimura, W.; Levy, P.; Pitman, M.B.; Schmidt, C.M.; et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 2012, 12, 183–197.
28. Le, H.; Ziogas, A.; Rhee, J.M.; Lee, J.G.; Lipkin, S.M.; Zell, J.A. A population-based, descriptive analysis of malignant intraductal papillary mucinous neoplasms of the pancreas. Cancer Epidemiol. Biomark. Prev. 2008, 17, 2737–2741.
29. Furukawa, T.; Klöppel, G.; Volkan Adsay, N.; Albores-Saavedra, J.; Fukushima, N.; Horii, A.; Hruban, R.H.; Kato, Y.; Klimstra, D.S.; Longnecker, D.S.; et al. Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: A consensus study. Virchows Arch. Int. J. Pathol. 2005, 447, 794–799.
30. Mino-Kenudson, M.; Fernández-del Castillo, C.; Baba, Y.; Valsangkar, N.P.; Liss, A.S.; Hsu, M.; Correa-Gallego, C.; Ingkakul, T.; Perez Johnston, R.; Turner, B.G.; et al. Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. Gut 2011, 60, 1712–1720.
31. Furukawa, T. Subtyping of IPMN. In Pancreatic Cancer: Methods and Protocols; Su, G.H., Ed.; Springer: New York, NY, USA, 2019; pp. 1–8.
32. Hamilton, S.R.; Aaltonen, L.A. WHO Classification of Tumours of the Digestive System; WHO: Lyon, France, 2000.
33. Nilsson, L.; Antila, A.; Millastre Bocos, J.; Marijinissen Van Zanten, M.; Shamali, A.; Verdejo Gil, C.; Keane, M.G.; Laukkarinen, J.; Del Chiaro, M. The current management of mucinous cystic

neoplasms (MCN) of the pancreas. Pancreas 2015, 15, S113.

34. Nilsson, L.N.; Keane, M.G.; Shamali, A.; Millastre Bocos, J.; Marijinissen van Zanten, M.; Antila, A.; Verdejo Gil, C.; Del Chiaro, M.; Laukkarinen, J. Nature and management of pancreatic mucinous cystic neoplasm (MCN): A systematic review of the literature. Pancreatology 2016, 16, 1028–1036.
35. Wu, B.U.; Sampath, K.; Berberian, C.E.; Kwok, K.K.; Lim, B.S.; Kao, K.T.; Giap, A.Q.; Kosco, A.E.; Akmal, Y.M.; Difronzo, A.L.; et al. Prediction of malignancy in cystic neoplasms of the pancreas: A population-based cohort study. Am. J. Gastroenterol. 2014, 109, 121–129, quiz 130.
36. Oyama, H.; Tada, M.; Takagi, K.; Tateishi, K.; Hamada, T.; Nakai, Y.; Hakuta, R.; Ijichi, H.; Ishigaki, K.; Kanai, S.; et al. Long-term Risk of Malignancy in Branch-Duct Intraductal Papillary Mucinous Neoplasms. Gastroenterology 2020, 158, 226–237.e225.
37. Yamaguchi, K.; Ohuchida, J.; Ohtsuka, T.; Nakano, K.; Tanaka, M. Intraductal papillary-mucinous tumor of the pancreas concomitant with ductal carcinoma of the pancreas. Pancreatology 2002, 2, 484–490.
38. Aronsson, L.; Bengtsson, A.; Torén, W.; Andersson, R.; Ansari, D. Intraductal papillary mucinous carcinoma versus pancreatic ductal adenocarcinoma: A systematic review and meta-analysis. Int. J. Surg. 2019, 71, 91–99.
39. Wu, J.; Jiao, Y.; Dal Molin, M.; Maitra, A.; de Wilde, R.F.; Wood, L.D.; Eshleman, J.R.; Goggins, M.G.; Wolfgang, C.L.; Canto, M.I.; et al. Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. Proc. Natl. Acad. Sci. USA 2011, 108, 21188–21193.
40. Wu, J.; Matthaei, H.; Maitra, A.; Dal Molin, M.; Wood, L.D.; Eshleman, J.R.; Goggins, M.; Canto, M.I.; Schulick, R.D.; Edil, B.H.; et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci. Transl. Med. 2011, 3, 92ra66.
41. Furukawa, T.; Kuboki, Y.; Tanji, E.; Yoshida, S.; Hatori, T.; Yamamoto, M.; Shibata, N.; Shimizu, K.; Kamatani, N.; Shiratori, K. Whole-exome sequencing uncovers frequent GNAS mutations in intraductal papillary mucinous neoplasms of the pancreas. Sci. Rep. 2011, 1, 161.
42. Cibulskis, K.; Lawrence, M.S.; Carter, S.L.; Sivachenko, A.; Jaffe, D.; Sougnez, C.; Gabriel, S.; Meyerson, M.; Lander, E.S.; Getz, G. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat. Biotechnol. 2013, 31, 213–219.
43. Fischer, C.G.; Wood, L.D. From somatic mutation to early detection: Insights from molecular characterization of pancreatic cancer precursor lesions. J. Pathol. 2018, 246, 395–404.
44. Amato, E.; Molin, M.D.; Mafficini, A.; Yu, J.; Malleo, G.; Rusev, B.; Fassan, M.; Antonello, D.; Sadakari, Y.; Castelli, P.; et al. Targeted next-generation sequencing of cancer genes dissects the

molecular profiles of intraductal papillary neoplasms of the pancreas. J. Pathol. 2014, 233, 217–227.

45. Fischer, C.G.; Beleva Guthrie, V.; Braxton, A.M.; Zheng, L.; Wang, P.; Song, Q.; Griffin, J.F.; Chianchiano, P.E.; Hosoda, W.; Niknafs, N.; et al. Intraductal Papillary Mucinous Neoplasms Arise From Multiple Independent Clones, Each With Distinct Mutations. Gastroenterology 2019, 157, 1123–1137.e1122.
46. Omori, Y.; Ono, Y.; Tanino, M.; Karasaki, H.; Yamaguchi, H.; Furukawa, T.; Enomoto, K.; Ueda, J.; Sumi, A.; Katayama, J.; et al. Pathways of Progression From Intraductal Papillary Mucinous Neoplasm to Pancreatic Ductal Adenocarcinoma Based on Molecular Features. Gastroenterology 2019, 156, 647–661.e642.
47. Basturk, O.; Hong, S.M.; Wood, L.D.; Adsay, N.V.; Albores-Saavedra, J.; Biankin, A.V.; Brosens, L.A.; Fukushima, N.; Goggins, M.; Hruban, R.H.; et al. A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. Am. J. Surg. Pathol. 2015, 39, 1730–1741.
48. Conner, J.R.; Mariño-Enríquez, A.; Mino-Kenudson, M.; Garcia, E.; Pitman, M.B.; Sholl, L.M.; Srivastava, A.; Doyle, L.A. Genomic Characterization of Low- and High-Grade Pancreatic Mucinous Cystic Neoplasms Reveals Recurrent KRAS Alterations in "High-Risk" Lesions. Pancreas 2017, 46, 665–671.
49. Singhi, A.D.; Nikiforova, M.N.; Fasanella, K.E.; McGrath, K.M.; Pai, R.K.; Ohori, N.P.; Bartholow, T.L.; Brand, R.E.; Chennat, J.S.; Lu, X.; et al. Preoperative GNAS and KRAS testing in the diagnosis of pancreatic mucinous cysts. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2014, 20, 4381–4389.
50. Iacobuzio-Donahue, C.A.; Wilentz, R.E.; Argani, P.; Yeo, C.J.; Cameron, J.L.; Kern, S.E.; Hruban, R.H. Dpc4 protein in mucinous cystic neoplasms of the pancreas: Frequent loss of expression in invasive carcinomas suggests a role in genetic progression. Am. J. Surg. Pathol. 2000, 24, 1544–1548.
51. Peters, M.L.B.; Eckel, A.; Mueller, P.P.; Tramontano, A.C.; Weaver, D.T.; Lietz, A.; Hur, C.; Kong, C.Y.; Pandharipande, P.V. Progression to pancreatic ductal adenocarcinoma from pancreatic intraepithelial neoplasia: Results of a simulation model. Pancreatology 2018, 18, 928–934.
52. Choi, S.H.; Park, S.H.; Kim, K.W.; Lee, J.Y.; Lee, S.S. Progression of Unresected Intraductal Papillary Mucinous Neoplasms of the Pancreas to Cancer: A Systematic Review and Meta-analysis. Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc. 2017, 15, 1509–1520.e1504.
53. Noë, M.; Niknafs, N.; Fischer, C.G.; Hackeng, W.M.; Beleva Guthrie, V.; Hosoda, W.; Debeljak, M.; Papp, E.; Adleff, V.; White, J.R.; et al. Genomic characterization of malignant progression in neoplastic pancreatic cysts. Nat. Commun. 2020, 11, 4085.

54. Tanaka, M.; Fernandez-Del Castillo, C.; Kamisawa, T.; Jang, J.Y.; Levy, P.; Ohtsuka, T.; Salvia, R.; Shimizu, Y.; Tada, M.; Wolfgang, C.L. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 2017, 17, 738–753.
55. European evidence-based guidelines on pancreatic cystic neoplasms. Gut 2018, 67, 789–804.
56. Vege, S.S.; Ziring, B.; Jain, R.; Moayyedi, P. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015, 148, 819–822, quize 812–813.
57. Elta, G.H.; Enestvedt, B.K.; Sauer, B.G.; Lennon, A.M. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. Am. J. Gastroenterol. 2018, 113, 464–479.
58. Megibow, A.J.; Baker, M.E.; Morgan, D.E.; Kamel, I.R.; Sahani, D.V.; Newman, E.; Brugge, W.R.; Berland, L.L.; Pandharipande, P.V. Management of Incidental Pancreatic Cysts: A White Paper of the ACR Incidental Findings Committee. J. Am. Coll. Radiol. 2017, 14, 911–923.
59. Khashab, M.A.; Shin, E.J.; Amateau, S.; Canto, M.I.; Hruban, R.H.; Fishman, E.K.; Cameron, J.L.; Edil, B.H.; Wolfgang, C.L.; Schulick, R.D.; et al. Tumor size and location correlate with behavior of pancreatic serous cystic neoplasms. Am. J. Gastroenterol. 2011, 106, 1521–1526.
60. Keane, M.G.; Dadds, H.R.; El Sayed, G.; Luong, T.V.; Davidson, B.R.; Fusai, G.K.; Thorburn, D.; Pereira, S.P. Clinical and radiological features that predict malignant transformation in cystic lesions of the pancreas: A retrospective case note review. Amrc. Open Res. 2020, 1, 4.
61. Layne, K.A.; Dargan, P.I.; Archer, J.R.H.; Wood, D.M. Gadolinium deposition and the potential for toxicological sequelae—A literature review of issues surrounding gadolinium-based contrast agents. Br. J. Clin. Pharm. 2018, 84, 2522–2534.
62. Postlewait, L.M.; Ethun, C.G.; McInnis, M.R.; Merchant, N.; Parikh, A.; Idrees, K.; Isom, C.A.; Hawkins, W.; Fields, R.C.; Strand, M.; et al. Association of Preoperative Risk Factors With Malignancy in Pancreatic Mucinous Cystic Neoplasms: A Multicenter Study. JAMA Surg. 2017, 152, 19–25.
63. Keane, M.G.; Shamali, A.; Nilsson, L.N.; Antila, A.; Millastre Bocos, J.; Marijinissen Van Zanten, M.; Verdejo Gil, C.; Maisonneuve, P.; Vaalavuo, Y.; Hoskins, T.; et al. Risk of malignancy in resected pancreatic mucinous cystic neoplasms. Br. J. Surg. 2018, 105, 439–446.
64. Handrich, S.J.; Hough, D.M.; Fletcher, J.G.; Sarr, M.G. The natural history of the incidentally discovered small simple pancreatic cyst: Long-term follow-up and clinical implications. Ajr. Am. J. Roentgenol. 2005, 184, 20–23.
65. Cadili, A.; Bazarrelli, A.; Garg, S.; Bailey, R. Survival in cystic neoplasms of the pancreas. Can. J. Gastroenterol. 2009, 23, 537–542.

66. Yoen, H.; Kim, J.H.; Lee, D.H.; Ahn, S.J.; Yoon, J.H.; Han, J.K. Fate of small pancreatic cysts (<3 cm) after long-term follow-up: Analysis of significant radiologic characteristics and proposal of follow-up strategies. Eur. Radiol. 2017, 27, 2591–2599.
67. Khannoussi, W.; Vullierme, M.P.; Rebours, V.; Maire, F.; Hentic, O.; Aubert, A.; Sauvanet, A.; Dokmak, S.; Couvelard, A.; Hammel, P.; et al. The long term risk of malignancy in patients with branch duct intraductal papillary mucinous neoplasms of the pancreas. Pancreatology 2012, 12, 198–202.
68. Kamata, K.; Kitano, M.; Kudo, M.; Sakamoto, H.; Kadosaka, K.; Miyata, T.; Imai, H.; Maekawa, K.; Chikugo, T.; Kumano, M.; et al. Value of EUS in early detection of pancreatic ductal adenocarcinomas in patients with intraductal papillary mucinous neoplasms. Endoscopy 2014, 46, 22–29.
69. Ciprani, D.; Weniger, M.; Qadan, M.; Hank, T.; Horick, N.K.; Harrison, J.M.; Marchegiani, G.; Andrianello, S.; Pandharipande, P.V.; Ferrone, C.R.; et al. Risk of malignancy in small pancreatic cysts decreases over time. Pancreatology 2020, 20, 1213–1217.
70. Marchegiani, G.; Andrianello, S.; Pollini, T.; Caravati, A.; Biancotto, M.; Secchettin, E.; Bonamini, D.; Malleo, G.; Bassi, C.; Salvia, R. “Trivial” Cysts Redefine the Risk of Cancer in Presumed Branch-Duct Intraductal Papillary Mucinous Neoplasms of the Pancreas: A Potential Target for Follow-Up Discontinuation? Am. J. Gastroenterol. 2019, 114, 1678–1684.
71. Lee, B.S.; Nguyen, A.K.; Tekeste, T.F.; Chang, K.; Girgis, A.; Adeyemo, M.; Hanna, M.S.; Yao, J.F.; Kwok, K.K.; Giap, A.Q.; et al. Long-term follow-up of branch-duct intraductal papillary mucinous neoplasms with No change in first 5 Years of diagnosis. Pancreatology 2021, 21, 144–154.
72. Poves, I.; Burdío, F.; Morató, O.; Iglesias, M.; Radosevic, A.; Ilzarbe, L.; Visa, L.; Grande, L. Comparison of Perioperative Outcomes Between Laparoscopic and Open Approach for Pancreatoduodenectomy: The PADULAP Randomized Controlled Trial. Ann. Surg. 2018, 268, 731–739.
73. van Hilst, J.; de Rooij, T.; Bosscha, K.; Brinkman, D.J.; van Dieren, S.; Dijkgraaf, M.G.; Gerhards, M.F.; de Hingh, I.H.; Karsten, T.M.; Lips, D.J.; et al. Laparoscopic versus open pancreatoduodenectomy for pancreatic or periampullary tumours (LEOPARD-2): A multicentre, patient-blinded, randomised controlled phase 2/3 trial. Lancet Gastroenterol. Hepatol. 2019, 4, 199–207.
74. de Rooij, T.; van Hilst, J.; van Santvoort, H.; Boerma, D.; van den Boezem, P.; Daams, F.; van Dam, R.; Dejong, C.; van Duyn, E.; Dijkgraaf, M.; et al. Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD): A Multicenter Patient-blinded Randomized Controlled Trial. Ann. Surg. 2019, 269, 2–9.

75. Scholten, L.; van Huijgevoort, N.C.M.; Bruno, M.J.; Fernandez-Del Castillo, C.; Satoi, S.; Sauvanet, A.; Wolfgang, C.; Fockens, P.; Chari, S.T.; Del Chiaro, M.; et al. Surgical management of intraductal papillary mucinous neoplasm with main duct involvement: An international expert survey and case-vignette study. Surgery 2018, 164, 17–23.

76. Lekkerkerker, S.J.; Besselink, M.G.; Busch, O.R.; Verheij, J.; Engelbrecht, M.R.; Rauws, E.A.; Fockens, P.; van Hooft, J.E. Comparing 3 guidelines on the management of surgically removed pancreatic cysts with regard to pathological outcome. Gastrointest. Endosc. 2017, 85, 1025–1031.

77. Singhi, A.D.; Zeh, H.J.; Brand, R.E.; Nikiforova, M.N.; Chennat, J.S.; Fasanella, K.E.; Khalid, A.; Papachristou, G.I.; Slivka, A.; Hogg, M.; et al. American Gastroenterological Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: A clinicopathologic study of 225 patients with supporting molecular data. Gastrointest. Endosc. 2016, 83, 1107–1117.e1102.

78. Ridtitid, W.; DeWitt, J.M.; Schmidt, C.M.; Roch, A.; Stuart, J.S.; Sherman, S.; Al-Haddad, M.A. Management of branch-duct intraductal papillary mucinous neoplasms: A large single-center study to assess predictors of malignancy and long-term outcomes. Gastrointest. Endosc. 2016, 84, 436–445.

79. Lennon, A.M.; Manos, L.L.; Hruban, R.H.; Ali, S.Z.; Fishman, E.K.; Kamel, I.R.; Raman, S.P.; Zaheer, A.; Hutfless, S.; Salamone, A.; et al. Role of a multidisciplinary clinic in the management of patients with pancreatic cysts: A single-center cohort study. Ann. Surg. Oncol. 2014, 21, 3668–3674.

80. He, J.; Cameron, J.L.; Ahuja, N.; Makary, M.A.; Hirose, K.; Choti, M.A.; Schulick, R.D.; Hruban, R.H.; Pawlik, T.M.; Wolfgang, C.L. Is it necessary to follow patients after resection of a benign pancreatic intraductal papillary mucinous neoplasm? J. Am. Coll. Surg. 2013, 216, 657–665.

81. Pflüger, M.J.; Griffin, J.F.; Hackeng, W.M.; Kawamoto, S.; Yu, J.; Chianchiano, P.; Shin, E.; Lionheart, G.; Tsai, H.L.; Wang, H.; et al. The Impact of Clinical and Pathological Features on Intraductal Papillary Mucinous Neoplasm Recurrence After Surgical Resection: Long-Term Follow-Up Analysis. Ann. Surg. 2020.

82. Balaban, E.P.; Mangu, P.B.; Khorana, A.A.; Shah, M.A.; Mukherjee, S.; Crane, C.H.; Javle, M.M.; Eads, J.R.; Allen, P.; Ko, A.H.; et al. Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2016, 34, 2654–2668.

83. Valsangkar, N.P.; Morales-Oyarvide, V.; Thayer, S.P.; Ferrone, C.R.; Wargo, J.A.; Warshaw, A.L.; Fernandez-del Castillo, C. 851 resected cystic tumors of the pancreas: A 33-year experience at the Massachusetts General Hospital. Surgery 2012, 152, S4–S12.

84. Sahora, K.; Mino-Kenudson, M.; Brugge, W.; Thayer, S.P.; Ferrone, C.R.; Sahani, D.; Pitman, M.B.; Warshaw, A.L.; Lillemoe, K.D.; Fernandez-del Castillo, C.F. Branch duct intraductal papillary mucinous neoplasms: Does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. Ann. Surg. 2013, 258, 466–475.

85. Crippa, S.; Bassi, C.; Salvia, R.; Falconi, M.; Butturini, G.; Pederzoli, P. Enucleation of pancreatic neoplasms. Br. J. Surg. 2007, 94, 1254–1259.

86. Kiely, J.M.; Nakeeb, A.; Komorowski, R.A.; Wilson, S.D.; Pitt, H.A. Cystic pancreatic neoplasms: Enucleate or resect? J. Gastrointest. Surg. Off. J. Soc. Surg. Aliment. Tract 2003, 7, 890–897.

87. Gan, S.I.; Thompson, C.C.; Lauwers, G.Y.; Bounds, B.C.; Brugge, W.R. Ethanol lavage of pancreatic cystic lesions: Initial pilot study. Gastrointest. Endosc. 2005, 61, 746–752.

88. Oh, H.C.; Seo, D.W.; Lee, T.Y.; Kim, J.Y.; Lee, S.S.; Lee, S.K.; Kim, M.H. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. Gastrointest. Endosc. 2008, 67, 636–642.

89. Oh, H.C.; Seo, D.W.; Kim, S.C.; Yu, E.; Kim, K.; Moon, S.H.; Park do, H.; Lee, S.S.; Lee, S.K.; Kim, M.H. Septated cystic tumors of the pancreas: Is it possible to treat them by endoscopic ultrasonography-guided intervention? Scand. J. Gastroenterol. 2009, 44, 242–247.

90. DeWitt, J.; McGreevy, K.; Schmidt, C.M.; Brugge, W.R. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: A randomized, double-blind study. Gastrointest. Endosc. 2009, 70, 710–723.

91. Oh, H.C.; Seo, D.W.; Song, T.J.; Moon, S.H.; Park do, H.; Soo Lee, S.; Lee, S.K.; Kim, M.H.; Kim, J. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. Gastroenterology 2011, 140, 172–179.

92. DeWitt, J.M.; Al-Haddad, M.; Sherman, S.; LeBlanc, J.; Schmidt, C.M.; Sandrasegaran, K.; Finkelstein, S.D. Alterations in cyst fluid genetics following endoscopic ultrasound-guided pancreatic cyst ablation with ethanol and paclitaxel. Endoscopy 2014, 46, 457–464.

93. Moyer, M.T.; Dye, C.E.; Sharzehi, S.; Ancrile, B.; Mathew, A.; McGarrity, T.J.; Gusani, N.; Yee, N.; Wong, J.; Levenick, J.; et al. Is alcohol required for effective pancreatic cyst ablation? The prospective randomized CHARM trial pilot study. Endosc. Int. Open 2016, 4, E603–E607.

94. Kim, K.H.; McGreevy, K.; La Fortune, K.; Cramer, H.; DeWitt, J. Sonographic and cyst fluid cytologic changes after EUS-guided pancreatic cyst ablation. Gastrointest. Endosc. 2017, 85, 1233–1242.

95. Moyer, M.T.; Sharzehi, S.; Mathew, A.; Levenick, J.M.; Headlee, B.D.; Blandford, J.T.; Heisey, H.D.; Birkholz, J.H.; Ancrile, B.B.; Maranki, J.L.; et al. The Safety and Efficacy of an Alcohol-Free Pancreatic Cyst Ablation Protocol. Gastroenterology 2017, 153, 1295–1303.

96. Attila, T.; Adsay, V.; Faigel, D.O. The efficacy and safety of endoscopic ultrasound-guided ablation of pancreatic cysts with alcohol and paclitaxel: A systematic review. Eur. J. Gastroenterol. Hepatol. 2019, 31, 1–9.
97. Choi, J.H.; Seo, D.W.; Song, T.J.; Park, D.H.; Lee, S.S.; Lee, S.K.; Kim, M.H. Long-term outcomes after endoscopic ultrasound-guided ablation of pancreatic cysts. Endoscopy 2017, 49, 866–873.
98. Barthet, M.; Giovannini, M.; Lesavre, N.; Boustiere, C.; Napoleon, B.; Koch, S.; Gasmi, M.; Vanbiervliet, G.; Gonzalez, J.M. Endoscopic ultrasound-guided radiofrequency ablation for pancreatic neuroendocrine tumors and pancreatic cystic neoplasms: A prospective multicenter study. Endoscopy 2019, 51, 836–842.
99. Pai, M.; Habib, N.; Senturk, H.; Lakhtakia, S.; Reddy, N.; Cicinnati, V.R.; Kaba, I.; Beckebaum, S.; Drymousis, P.; Kahaleh, M.; et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J. Gastrointest. Surg. 2015, 7, 52–59.
100. Teoh, A.Y.; Seo, D.W.; Brugge, W.; Dewitt, J.; Kongkam, P.; Linghu, E.; Moyer, M.T.; Ryu, J.K.; Ho, K.Y. Position statement on EUS-guided ablation of pancreatic cystic neoplasms from an international expert panel. Endosc. Int. Open 2019, 7, E1064–E1077.