Universitat Autònoma de Barcelona

Risk Stratification and Natural History of Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Risk Stratification and Natural History of Intraductal Papillary Mucinous Neoplasms of the Pancreas

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HACE CONSTAR

Que la **TESIS DOCTORAL** titulada **"Risk Stratification and Natural History of Intraductal Papillary Mucinous Neoplasms of the Pancreas"** presentada por **María Moris Felgueroso** para optar al grado de Doctor se ha realizado bajo su dirección, y al considerarla concluida, autoriza su presentación para ser juzgada por el Tribunal correspondiente.

Y para que conste a los efectos firma la presente.

Barcelona, Febrero de 2016

Dr. Fernando Azpiroz Vidaur

Director de tesis

To my parents, César y Ana,
all that I ever accomplish I owe it to you

A mis padres, César y Ana,
todos mis logros os los debo a vosotros

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ABREVIATIONS

PCNs: pancreatic cystic neoplasms

PCLs: pancreatic cystic lesions

MRI: magnetic resonance imaging

IPMNs: intraductal papillary mucinous neoplasms

MCAs: mucinous cystadenomas

SCAs: serous cystadenomas

SPNs: solid pseudopapillary neoplasms

CPENs: cystic pancreatic endocrine neoplasms

LGD: low-grade dysplasia

HGD: high-grade dysplasia

MD-IPMN: main duct IPMN

BD-IPMN: brand duct IPMN

EUS: endoscopic ultrasound

CEA: carcynoembriogenic antigen

FNA: fine needle aspiration

RFA: radiofrequency ablation

MRCP: magnetic resonance cholangiography

AUC: Area under the curve

PPV: positive predictive value

NPV: negative predictive value

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1 INTRODUCTION

Pancreatic cancer is the 10th most common cancer in the United States, but it rises to the 4th position when mortality due to cancer is ranked[1]. This is mainly due to its indeterminate presentation that leads to a late diagnosis at an advanced clinical stage.

One of the main aims in the management of pancreatic cancer is to define and identify precursor lesions that allow an early diagnosis, such as pancreatic cystic neoplasms (PCNs), a subtype of pancreatic cysts. It was not until the late 1970s that the first distinction between serous and mucinous cysts was made[2,3]. The publication of these studies increased the interest of the scientific community in the mucin-producing cysts and their potential for malignant transformation.

In recent years, pancreatic cystic lesions (PCLs) are being increasingly diagnosed[4,5]. Despite this, their true prevalence remains uncertain with prevalence ranging from 0.2% to 44.7%[6-11]. It has been postulated that the higher trend of the incident detection rates is due to the widespread use of high-resolution cross sectional images, such as CT scan or magnetic resonance imaging (MRI)[12-14]. Though the majority of these cysts do not contain invasive cancer[15], some do carry a risk of malignant development and, therefore, may require surgical resection.

A common clinical scenario is the finding of an incidental pancreatic cyst on imaging studies performed for non-pancreatic reasons[10,16,17]. This usually initiates a cascade of diagnostic tests that attempt to characterize the lesion to ultimately decide whether surgical resection is needed. However, the line separating cysts that do not need any

surveillance versus those that have a malignant potential is very thin, and the current available methods to discriminate them have limited efficacy.

1.1 CLASSIFICATION OF PANCREATIC CYSTIC NEOPLASMS

Overall, the most common pancreatic cystic neoplasms (PCNs) are intraductal papillary mucinous neoplasms (IPMNs), mucinous cystadenomas (MCAs) and serous cystadenomas (SCAs)[18-20]. The rest of the lesions included in this category, such as solid pseudopapillary neoplasms (SPNs) or cystic pancreatic endocrine neoplasms (CPENs), are rarely seen in daily practice.

Each of these entities has a different prognosis and, consequently, a different management algorithm. Thus, their correct characterization and identification are essential before any clinical decision is taken.

1.1.1 Intraductal papillary mucinous neoplasms

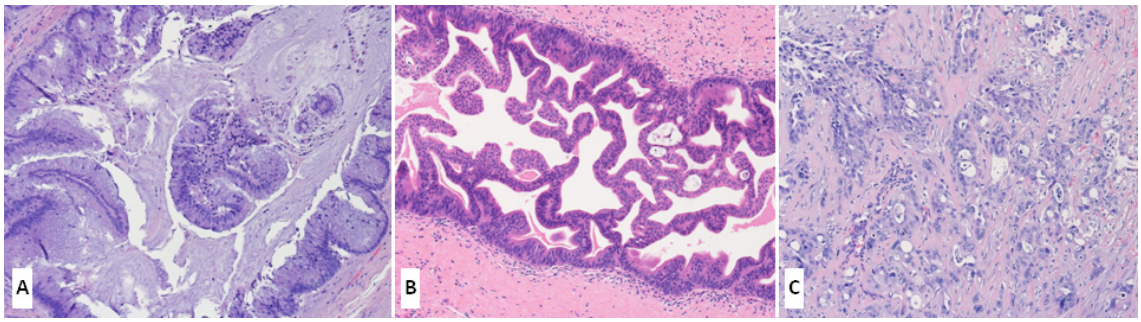
IPMNs are intraductal mucinous cysts that have a potential for malignant transformation[21]. They encompass a spectrum of cystic neoplasms with different malignant potential, following a progressive pathway of low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to invasive pancreatic ductal adenocarcinoma[22-24].

Epidemiology

IPMNs were first considered an independent entity in 1996[25]. Since then, there has been a dramatic increase in their detection rates and, currently, they are the most commonly diagnosed subtype of PCNs[26,27].

IPMNs are equally distributed in gender and are usually diagnosed in the 7th-8th decade of life[28,29]. They may present with a broad spectrum of symptoms ranging from nonspecific abdominal pain to pancreas-related symptoms such as jaundice or acute pancreatitis[30]. Currently, they are the most frequent histological diagnosis in incidentally found pancreatic cysts[27].

Figure 1 Histological pathway from low-grade dysplasia to malignancy in intraductal papillary mucinous neoplasms



A- Low-grade dysplasia
B- High-grade dysplasia
C- IPMN-derived invasive carcinoma with high-grade dysplasia

Imaging features

IPMNs are classified into three types: main duct (MD) IPMN, branch duct (BD) IPMN and mixed type[31,32].

MD-IPMNs are characterized by a segmental or continuous dilation of the main pancreatic duct of ≥ 5 mm, whereas BD-IPMNs include most cysts of > 5 mm that communicate with the main pancreatic duct but do not involve it. The mixed type involves those cysts that have features from both categories. However, they are usually grouped with the MD-IPMNs due to their similar clinical behavior.

MD-IPMNs and Mixed IPMNs carry a higher risk of malignant transformation (62% and 58% of surgically resected cases, respectively[32]), whereas BD-IPMNs have a much more indolent behavior and can be frequently managed nonoperatively[33]. Therefore, the characterization of the IPMN subtype at the time of diagnosis is mandatory to design a tailored management strategy and provide prognosis.

Management

In 2012, the Fukuoka consensus guidelines defined the "high-risk stigmata" and "worrisome features", based on clinical and imaging findings, to establish a management algortihm[32].

Cysts with "high-risk stigmata" such as obstructive jaundice noticed in patients with pancreatic head cysts, enhancing solid intracystic component and/or a dilation of the main pancreatic duct greater than 10mm, should directly undergo surgical resection due to the high probability of underlying malignancy.

On the other hand, those cysts that present with "worrisome features" such as cyst size ≥ 30 mm, thickened/enhancing cyst walls, non-enhancing mural nodules, dilation of the main pancreatic duct between 5 and 9 mm, or abrupt caliber change in the main pancreatic duct associated with distal pancreatic atrophy, should be further evaluated with endoscopic ultrasound (EUS), to characterize the lesion in detail. If any of the following criteria is described in the EUS: confirmation of a mural nodule, main duct involvement or a positive/suspicious cytology report, surgical resection is highly recommended. In contrast, if these criteria are inconclusive, imaging surveillance with CT or MRI is suggested with defined interval times depending on the cyst size.

The current management guidelines provided a valuable framework for diagnosis and treatment of IPMNs. However, these guidelines were based on expert opinion and insufficient long-term clinical data. Therefore, their indications should be taken cautiously and adapted to each patient's circumstances.

Table 1 Main differences between the 2012 International Association of Pancreatology (IAP) guidelines and 2015 American Gastroenterology Association (AGA) guidelines

Indications	2012 IAP	2015 AGA
Targeted population	IPMNs and MCAs	Incidental cysts
Imaging modality	Pancreatic protocol CT or MRI	MRI with MRCP
Threshold for EUS/surgery	One risk factor	Two risk factors
Surveillance indications in non-surgical cysts	Based on cyst size	MRI in 1 year and then every 2 years
Stop surveillance: unresected cysts	Not addressed	After 5 years of stability if no worrisome features are developed
Stop surveillance: resected cysts	After resection of a MCA or SCA without invasive cancer	Select subtypes including BD-IPMNs without HGD or invasive carcinoma

IAP: International Association of Pancreatology, AGA: American Gastroenterology Association
IPMNs: intraductal papillary mucinous neoplasms, MCAs: mucinous cystadenomas,
MRI: magnetic resonance imaging, EUS: endoscopic ultrasound
BD: branch duct, HGD: high-grade dysplasia

Last year, the American Gastroenterology Association published new guidelines for the management of PCLs[34]. One of the main changes, with respect to previous recommendations, addressed the length of surveillance programs if no worrisome features are present. In these new guidelines, they recommend against continuing imaging surveillance if no significant changes are seen in the cyst features after 5 years of follow-up. Despite this novel indication, the lack of good-quality long-term clinical studies continues to limit its generalizability.

Prognosis

One of the main concerns regarding IPMNs is their uncertain natural history. The majority of the initial studies analyzed cohorts of surgically resected patients, which led to an overestimation of their malignant potential secondary to selection bias. Recent publications, based on observational cohorts, have shown noticeable lower estimated risks of malignancy[27,35,36].

Noninvasive IPMN disease is associated with excellent long-term outcomes. However, invasive IPMNs carry a worse prognosis, still better than conventional pancreatic adenocarcinoma[32]. The five-year disease-specific survival after surgical resection for non-invasive IPMN is 95-100% compared to 46-63% in invasive IPMN (carcinoma)[37-39]. Furthermore, recurrence after resection occurs more frequently in invasive IPMNs in variable time between 21 to 28 months post-resection[29,40].

In addition, four main subtypes of the epithelial IPMN component have been described: intestinal, gastric, oncocytic and pancreatobiliary subtype[32]. Differentiating among them is clinically important because of the various grades of malignant potential of each category.

MD-IPMNs mainly have the intestinal subtype. They tend to progress to colloid carcinoma, which has a better prognosis than conventional pancreatic adenocarcinoma. A few cases of MD-IPMNs can have histology compatible with the oncocytic or pancreatobiliary subtypes. In the first case, they can progress to oncocytic carcinoma, which usually behaves indolently. In contrast, the second subtype can progress to an aggressive tubular carcinoma[41,42].

The gastric subtype includes the majority of BD-IPMNs. This category is typically benign, with a minority of cases developing malignancy. However, if a carcinoma arises from the gastric cell lining, it is the tubular subtype, which behaves similarly to conventional pancreatic adenocarcinoma[41,43].

Validation of the international guidelines for the management of BD-IPMNs

Since their publication in 2006 (Sendai guidelines) and 2012 (Fukuoka guidelines), many studies have tried to validate their utility to discern malignancy among IPMNs, especially among the BD-IPMN subtype. To do so, two different approaches can be made.

On one side, surgically resected cohorts can be used to compare the final pathology report with the initial clinical suspicion. However, these studies usually carry an inherent selection bias regarding the study population, ultimately leading to an overestimation of the malignant potential of these lesions.

On the other side, long-term observational cohorts have the advantage of including every clinically suspected BD-IPMN. This way, the natural history can be easily described based on the follow-up imaging techniques performed during the surveillance program. The downside of this approach is the absence of a pathological confirmation. This means that

every BD-IPMN diagnosis is presumed and cannot be confirmed unless the patient has to undergo surgical resection due to progression of the lesion.

Both approaches have been used to verify the accuracy of the old and revised guidelines. The majority of studies have shown a remarkably high sensitivity for the 2006 Sendai guidelines, with a mean of 8.5% of Sendai-negative BD-IPMNs harboring malignancy[35,44-46]. In contrast, these series have also reported a low specificity because only 35% of the patients with Sendai-positive BD-IPMNs had actually HGD or invasive carcinoma in the pathology report[35,47]. Among the worrisome features described in both guidelines, mural nodules have been reported to have the most significant association with malignancy development[47,48].

There are two studies to date that have reported significantly higher rates of malignancy in BD-IPMNs compared to most of the results from current literature[49,50]. These studies showed a 25% and 67% rate of malignancy, respectively, in small BD-IPMNs. However, in one study[50] most of the carcinomas were found in T2 tumors, which by definition are greater than 2 cm in size. Therefore, it is inferred that a solid component was associated with these lesions and, thereby, they cannot be considered Sendai-negative. In the other study[49], the authors specified that the evaluated cysts were Sendai-negative and, moreover, they reported that cyst size was not significantly associated with the rate of malignancy, describing the presence of cancer in cysts as small as 4 mm.

Finally, a large series of BD-IPMNs, either resected or prospectively followed, was recently analyzed using the revised Fukuoka guidelines[36]. Based on their results, the authors concluded that Sendai-negative BD-IPMNs have a remarkably low risk of malignant degeneration (0.9% for HGD and 0.3% for invasive carcinoma). A low positive predictive value was, again, reported with less than 30% of the patients who underwent surgery having indeed

malignancy. On the other hand, those patients who did not meet the criteria for surgical resection were followed for a median of 60 months. 21% of these observational patients had to undergo surgery mainly due to an increase in size that caused secondary symptoms. Of these, the final pathology revealed that 14% did not even have an IPMN. Of those that did have an IPMN, 12% had HGD and 9% invasive cancer.

Current consensus guidelines have limited generalizability. The characterization and staging of small BD-IPMNs remain challenging. Based on current literature findings, the presurgical diagnosis of these lesions remains unsatisfactory with a high proportion of surgically overtreated patients. Despite this, it seems safe to use the revised guidelines because these have proven to accurately identify those lesions that can be followed. However, every management strategy should be individually tailored for each patient and preferably decided in multidisciplinary committees.

1.1.2 Mucinous cystadenomas

MCAs are a different subtype of PCNs that comprises 25% of all of these resected lesions[5]. The main features that differentiate them from IPMNs are the presence of a pathognomonic ovarian-like stroma surrounding the cyst's inner epithelial layer with tall, mucin-producing cells, as well as the absence of communication with the main pancreatic duct. Based on the presence of this ovarian-like stroma, the higher incidence in females, and the typical distal location, it has been postulated that hormones, like human chorionic gonadotropin, might be involved in their pathogenesis[51].

Epidemiology

The vast majority of MCAs (>95%) occurs in females in the 4th-5th decade of life. Most of the cases present incidentally or with undetermined symptoms.

Imaging features

The classical radiologic presentation is a thick-walled solitary cyst, usually septated, located in the body or tail of the pancreas (>95%) that does not communicate with the pancreatic duct[52-54]. Although typically unilocular they can also be multilocular, which has been reported to correlate with malignancy[55,56]. Occasionally, they can have mural nodules and/or calcifications[54].

Management

Apart from different degrees of atypia, the inner epithelium can present areas with pseudopyloric, gastric foveolar, small and colonic intestinal differentiation, with scattered neuroendocrine cells. Based on the highest classification of architectural and cytological atypia, MCAs can be categorized into LGD, moderate dysplasia and HGD. Invasive cancer can also arise from MCAs, resembling conventional pancreatic ductal adenocarcinoma[57].

If a middle-aged woman presents with a solitary cyst with no communication to the pancreatic duct located in the distal pancreas, no further testing needs to be performed due to the high suspicion of a MCA. If the images are indeterminate, however, EUS can help to further characterize the lesion.

The Sendai guidelines[32] highly advise for surgical resection in every suspected MCA due to various reasons: the potential for malignant transformation, the typical presentation in young, otherwise healthy, women, and the less morbid surgical procedure due to their distal location[53,58]. Despite this, if a small MCA with no worrisome features, such as mural nodules, is described, observational management can be advised. However, lifelong surveillance with cross-sectional imaging is mandatory, which would carry greater costs than benefits.

Prognosis

The risk of malignancy development is quite low representing just 17.5% of the cases approximately[32,52]. The prognosis is excellent if no invasive carcinoma with diffuse intracapsular infiltration or extracapsular involvement is detected[52]. However, if invasive carcinoma is found, the post-surgical 5-year overall survival can be as low as 17%[59].

1.1.3 Serous cystadenomas

SCAs have decreased in prevalence in the recent years, currently accounting for around 16% of the resected PCNs[5]. They are non-mucinous cystic lesions that characteristically have an inner epithelium composed by cuboidal cells rich in glycogen. The most important feature of SCAs is their lack of potential for malignant transformation that allows an observational management. Thus, they can be considered apart from most other subtypes of PCNs due to their inherent benign nature.

Epidemiology

SCAs predominantly affect women (80%) with a mean age of 62 years. The majority of patients with symptoms experience abdominal pain, although palpable abdominal mass and jaundice have also been described[60-62].

SCAs occur sporadically in the vast majority of patients. Despite this, at least 2% of the cases are related to von Hipple-Lindau disease, an autosomal dominant genetic disease[63,64].

Imaging features

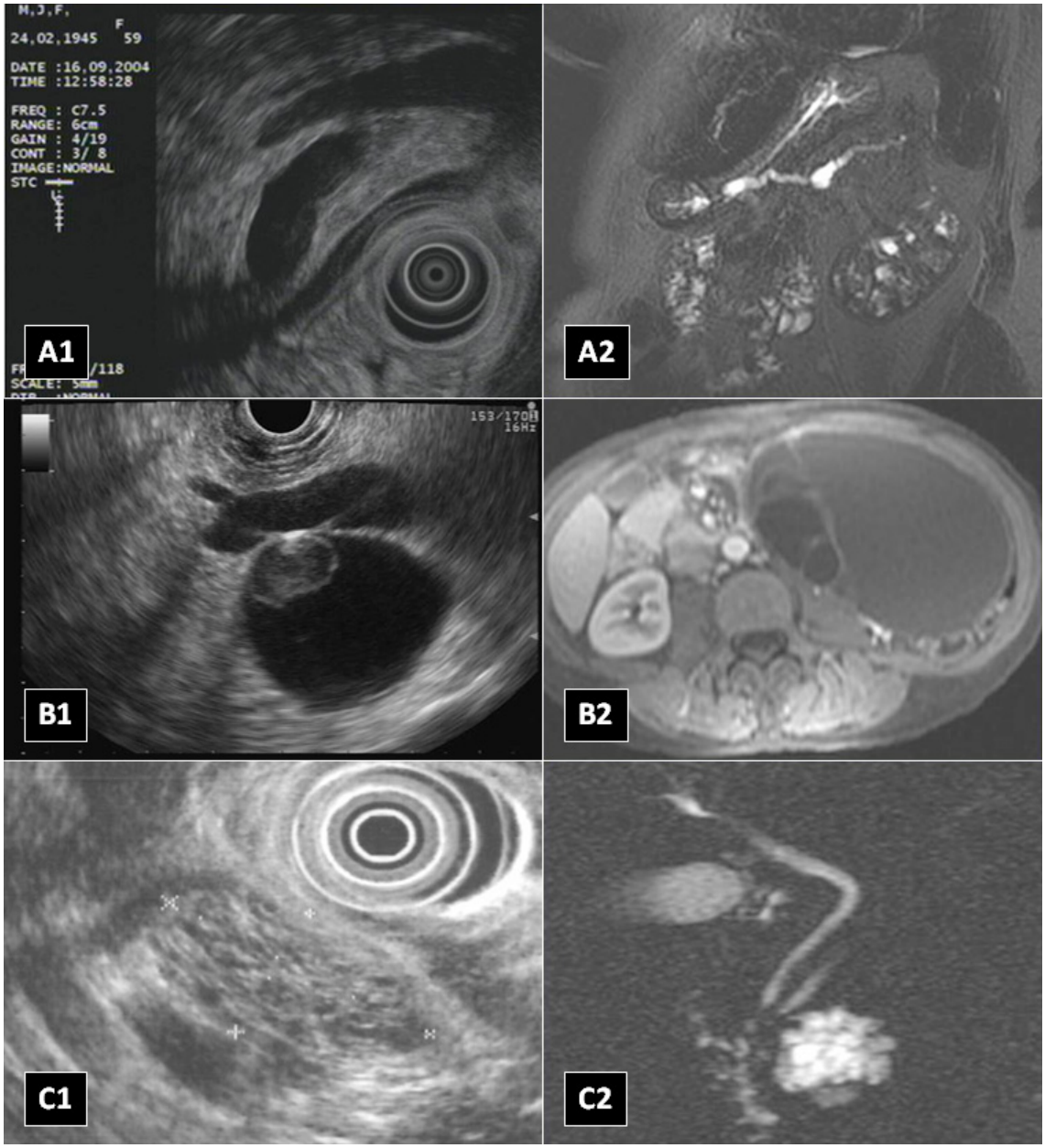
Typical lesions are characterized by various tiny cysts, lined by cuboidal epithelium, that comprise a unifocal, multilobulated lesion with a classical honeycomb appearance. In addition, some other variants, such as oligo or macrocystic types, have also been reported comprising around 10% of the cases[61,65]. Characteristically, SCAs have a central calcified scar, but this is only seen in about 30% of the cases. SCAs can be located anywhere in the pancreas without a clear predominance, and may also involve the entire gland.

Management

Unlike mucinous cysts, such as IPMNs or MCAs, SCAs rarely progress to malignant lesions. Therefore, the management strategy has evolved from unconditional surgical resection to cross-sectional surveillance for asymptomatic lesions if a secure diagnosis is done. Despite this, surgery should still be considered if the lesion causes symptoms (usually size dependent) or the growth rate is fast[66].

For the uncommon oligocystic variant, the differential diagnosis between SCAs and BD-IPMNs can be specially challenging. In those cases in particular, EUS-guided fine needle aspiration (FNA) with analysis of the cyst fluid can identify serous lesions.

Figure 2 EUS and cross-sectional imaging



EUS (left) and cross sectional (right) images of:
A - Main duct intraductal papillary mucinous neoplasm
B - Mucinous cystadenoma
C - Serous cystadenoma

Prognosis

SCAs are a benign, slow-growing tumor, where nonoperative observational strategies of slow-growing asymptomatic lesions are viable. However, due to the drastic differences in prognosis between SCAs and MCAs/IPMNs, an accurate diagnosis is mandatory.

If surgical resection is performed (approximately 16% of the cases[66]), the overall post-surgical survival has been reported to be as high as 100% after 3 to 4 years of follow-up, with recurrence noted in less than 1% of the patients[60,67].

1.1.4 Solid pseudopapillary neoplasms

SPNs are a very rare entity comprising <4% of PCNs. They characteristically have uniform cells forming microadenoid structures, branching, papillary clusters with delicate fibro-vascular cores[68].

Epidemiology

SPNs typically present in young females (> 80%) in the 4th decade of life[69,70] and have also been described in pediatric patients in up to 25% of cases[71]. They can be diagnosed incidentally or secondary to the onset of symptoms (such as abdominal pain, palpable mas or jaundice).

Imaging features

In radiology examinations, SPNs present as encapsulated, well-defined, heterogeneous masses, with both cystic and solid content. Moreover, other features might be rarely seen

such as calcifications or arterially enhancing walls. These lesions can be located anywhere in the pancreas.

Management

SPNs can be diagnosed using EUS-guided FNA or core biopsy analysis. Surgical resection is recommended in all SPNs due to their potential for malignant transformation (<20% of the cases)[69,70].

Prognosis

Despite their potential for malignancy, SPNs have an overall good prognosis even in those patients with invasive disease affecting the lymph nodes or the liver[69,70]. Post-surgical long-term survival is observed in up to 80% of the patients[70] and death caused directly by the tumor is rare.

1.1.5 Cystic pancreatic endocrine neoplasm

CPENs account for 8% of the resected PCNs[5] and 10 to 17% of the resected pancreatic neuroendocrine tumors. They are a rare variant of PCNs that harbor a risk of malignancy.

Epidemiology

CPENs distribute similarly in both genders and are usually diagnosed in the sixth decade[72-74]. The majority of these lesions are incidentally found and nonfunctional, however, they are a frequent finding in patients with multiple endocrine neoplasia type and other genetic diseases such as von Hippel-Lindau syndrome[75].

Imaging features

Typical lesions are unifocal, although multifocal disease has also been previously reported[76]. They present as a cystic lesion, usually with a hypervascular rim (at least 45%) and occasionally with septae or intracystic solid component[26,77]. Despite these features, CPENs are often hard to distinguish from other PCNs, especially MCAs.

Management

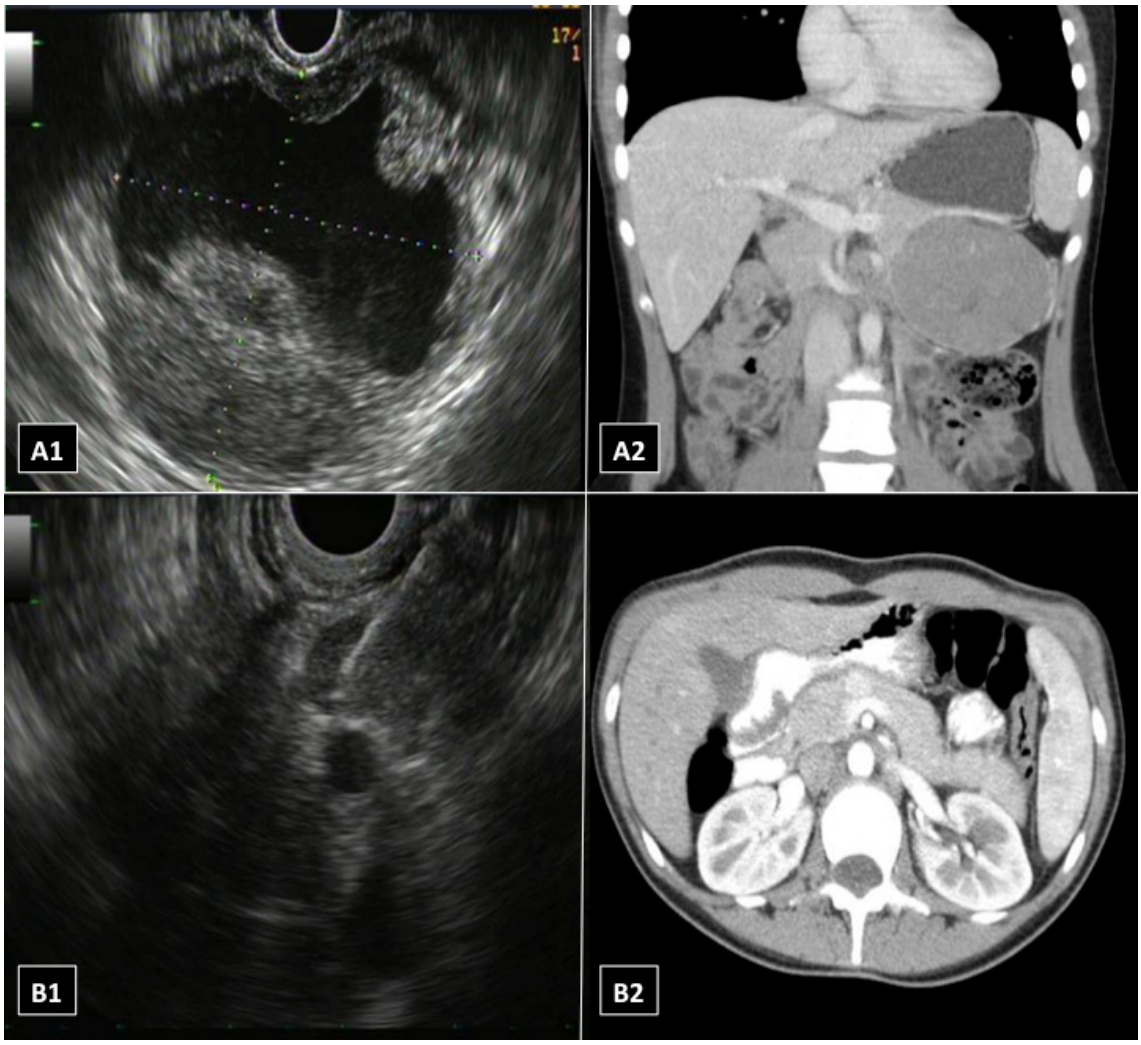
EUS-guided FNA is usually required to establish the final diagnosis due to the insufficient accuracy of cross-sectional techniques such as CT scan or MRI. Even with the biopsy report, malignancy is still difficult to predict. Therefore, once the diagnosis of CPENs is made, surgical resection is recommended.

Prognosis

CPENs have a 14% risk of malignancy. Despite this, compared to the solid neuroendocrine tumors, CPENs are less likely to produce perineural or vascular invasion, lymph node metastasis or distant metastasis[76].

Patients with resected CPENs have an excellent prognosis, with a 5-year overall survival of 87% to 100% and disease-free survival around 95%[75].

Figure 3 EUS and cross-sectional imaging



EUS (left) and cross sectional (right) images of:
A - Solid pseudopapillary neoplasm
B - Cystic pancreatic endocrine neoplasm

Table 2 General characteristics of frequently encountered pancreatic cystic neoplasms of the pancreas

Variable	BD/MD - IPMN	MCA	SCA	SPN	CPEN
Gender predominance	Male (60%) > Female (40%)	Female	Female > Male	Female	Female = Male
Age	6th- 7th	4th- 5th	6th- 7th	2nd - 4th	5th - 6th
Location	Throughout the gland	Distal (body and tail)	Throughout the gland	Distal (body and tail)	Throughout the gland
Loculation	Macrocystic (BD) NA (MD)	Oligo and macrocystic	Microcystic (honeycomb pattern)	Unilocular	NA
Main duct communication	Present (BD) NA (MD)	Absent	Absent	Absent	Absent
Main duct involvement	Absent (BD) Present (MD)	Absent	Absent	Absent	Absent
Malignant potential	Low (BD) High (MD)	Low	Very low	Low	Variable
Imaging predictors of malignancy	Size > 3 cm Main duct > 6 mm Thick irregular walls Septae/Mural nodules	Mural nodules Irregular wall Peripheral calci-fication	NA	Large size Local invasion Enlarged nodes	NA

BD: branch duct, MD: main duct, IPMN: intraductal papilllary mucinous neoplasm, MCA: mucinous cystadenoma, SCA: serous cystadenoma, SPN: solid pseudopapillary neoplasm, CPENs: Cystic pancreatic endocrine neoplasms

1.2. IMAGING OF PANCREATIC CYSTIC NEOPLASMS

1.2.1 Cross-sectional imaging

The two main modalities of high-resolution cross sectional imaging studies currently used in daily practice are CT and MRI.

MRI is considered the best technique for the diagnosis of PCNs because it visualizes in detail the main and secondary pancreatic ducts, as well as intracystic features such as mural nodules or septae. However, recent studies have reported no differences between MRI and multidetector CT for malignant characterization of these lesions[78]. Whereas high resolution CT provides equal high resolution imaging as MRI, the latter has the advantage of providing detailed imaging of the pancreas without the ionizing radiation and lower risk of undesirable contrast-induced effects[79].

Imaging studies can be diagnostic when the classic features of specific PCNs are present. As discussed previously, SCAs can present with a pathognomonic central stellate calcification, or MD-IPMNs can be easily identified if a tortuous, dilated main pancreatic duct is observed. However, most of the times, these features are absent. Thus, a secondary test is often necessary to complete the characterization of the lesion.

Several studies have reported the insufficient accuracy of CT or MRI for the diagnosis of PCNs if used alone. When each of these techniques were compared with post-surgical pathology diagnoses, CT had an accuracy ranging from 24% to 61% and MRI showed a slightly better, not yet sufficient, accuracy of 74%[80,81].

The most challenging scenario is the presence of an isolated single pancreatic cyst especially if no symptoms are present. In most of these cases, CT or MRI cannot accurately determine the nature of the lesion, with the differential including a benign entity like a pseudocyst, a premalignant lesion, such as a BD-IPMN, or a more worrisome lesion such as pancreatic adenocarcinoma or an endocrine neoplasm. This and other findings, like the differential diagnosis between a MCA and a distal macrocystic SCA[82], expose the limitations of CT or MRI for the evaluation of the risk of associated malignancy in PCNs.

1.2.2. EUS imaging

EUS offers various advantages over CT or MRI. It shows high-resolution imaging of ductal communications as well as intracystic features and, more importantly, it allows sampling of cyst contents for cytological and fluid analysis. On the other hand, EUS is a highly operator-dependent technique and an invasive imaging modality as opposed to CT or MRI.

Overall, EUS and MRI are equivalent and much better at detecting small pancreatic cysts than CT, as demonstrated in several studies[83,84]. Despite this, it is frequent that CT or MRI raises concern about involvement of the main pancreatic duct in the PCNs. This is a highly important distinction because it may indicate a mixed or MD-IPMN rather than a more indolent BD-IPMN. It is precisely in these situations that EUS plays an essential role by adding further high-quality information regarding the communications with the ducts.

In addition, a meta-analysis showed that detection of mural nodules by CT, MRI or EUS were associated with a > 9-fold increase in risk for high-grade dysplasia or invasive pathology[85]. However, this risk lowered to a 3-fold increase if these mural nodules were detected only by EUS. Hence, it is very likely that CT and MRI are overdiagnosing mural nodules that actually are non-pathologic intracystic mucin globules[86-88]. In EUS, mucin glo-

bules are shown as hypoechoic images, with smooth edges and hyperechoic rims, and they tend to move if the position of the patient changes or during FNA sampling.

The other major strength of EUS in characterizing PCNs is the possibility of performing cyst fluid aspiration[89] allowing cytological and biomarker determinations. Whereas EUS-guided FNA cytology has an excellent specificity (close to 100%), it has an insufficient sensitivity (30% to 50% for discriminating mucinous cysts). This is mainly due to poor cellularity as well as insufficient amount of fluid in each sample. To improve the efficiency of this technique, a study considered cytological diagnosis "positive" when high-grade epithelial cells (i.e. containing cellular atypia that is quantitatively and qualitatively insufficient for a definite cancer diagnosis) were present. This strategy led to an increased cytology accuracy of 85%[90].

Currently, the role of cyst fluid biomarkers is expanding and its efficiency continues to be evaluated. The CEA is the most commonly used biomarker, however, the real benefit of measuring its level continues to be uncertain. Based on the results from several studies, CEA can discriminate mucinous from non-mucinous cysts. In contrast, its accuracy is clearly insufficient for discriminating malignancy among mucinous cysts[15,91,92]. Despite this, the exact cut-off for pancreatic cyst fluid CEA level for discriminating mucinous from non-mucinous cysts remains unclear.

Other fluid markers, such as amylase, have been proposed to classify and stage PCNs. The role of amylase in mucinous cysts remains uncertain. Theoretically, IPMNs should present higher values of amylase than MCAs due to their communication with the pancreatic ducts, but current data is inconclusive.

DNA in cyst fluid can also be determined using commercially available assays. However, a multicenter prospective study and several retrospective studies were unable to determine the clinical indication[93-96]. Also, studies that detected the presence of a K-ras mutation, allelic imbalance or other genetic features related with cancer, used alone or with assays to measure CEA levels, have shown insufficient accuracy to discriminate between mucinous and non-mucinous cysts or to detect malignancy in PCNs[97,98].

In summary, additional studies of newer biomarkers in cyst fluid, such as variants of GNAS, could help improve the cancer risk estimation and also be used to improve stratification strategies for patients undergoing surveillance programs due to PCNs[99,100].

Table 3 Reported accuracy of currently available cyst fluid tests[101]

Test	Accuracy	Diagnosis
Cytology	63% sensitivity	Mucinous or malignancy
CEA > 192 ng/dl	75% sensitivity 84% specificity	Mucinous
CEA < 5 ng/ml	50% sensitivity 95% specificity	Serous cystadenomas Pseudocysts Cystic endocrine neoplasm
Amylase > 250 U/L	44% sensitivity 98% specificity	Excludes pseudocysts
CEA: carcinoembriogenic antigen		

1.3. NON-SURGICAL TREATMENT OF PANCREATIC CYSTIC NEOPLASMS

Even after extensive evaluation with both cross-sectional imaging techniques, such as CT or MRI, and EUS, the diagnosis and staging of PCNs is challenging. A significant proportion of pancreatic cysts remains indeterminate even after thorough examinations.

Currently, the only accepted method of treatment is surgical resection. Partial or total pancreatectomy is a highly invasive procedure that may carry severe secondary effects and sometimes even death[102,103]. It has been reported that surgical resection of pancreatic cysts is associated with a perioperative morbidity rate up to 40% and a mortality rate of 2%[4,104]. Therefore, a tailored management strategy, evaluating the risk-benefits, is mandatory for every patient.

As a result of this clinical situation, new minimally-invasive treatment strategies are being developed to specifically address these incidentally-found pancreatic cysts. Among these novel techniques, the EUS-guided ethanol and/or paclitaxel injection and the radiofrequency ablation (RFA) have gained increasing importance in the last years due to their promising results.

1.3.1 Proposed indications for cyst ablation

Currently, EUS-guided pancreatic cyst ablation remains an investigational modality. Thereby, the selection of patients should be made carefully. The final aim is to select those cases where high treatment efficacy can be predicted, minimizing at the same time the adverse events related to the procedure.

Presently, the minimally invasive techniques are ideally addressed to those patients with a benign-featured cyst (with no worrisome or high-risk features), with a cyst size less than 3 cm and unilocular morphology, and where no communication with the main pancreatic duct is patent.

Due to the various prognoses of the different PCN subtypes, the selection of patients must also take into consideration which type of cyst has been described in the diagnostic tests performed. Treatment of benign cysts, such as SCAs, is debatable. On one side, SCAs can have a fast growth pattern that may lead to cyst-related symptoms, and, therefore, treatment would be indicated. However, the detractors highlight the existence of treatment-related adverse events, which are not worth the benefits of ablating a benign lesion. If considered, ablation therapy should be indicated only in macrocystic SCAs with demonstrated size increased during follow-up evaluation[61,105]. MCAs, on the other hand, are the perfect candidate due to both their malignant potential and the typical unilocular morphology. On the other hand, despite having a potential for malignant transformation, BD-IPMNs can be challenging to treat due to their characteristic tortuous morphology that usually prevents an even distribution of the ablative agents or radiofrequency energy[106].

1.3.2 EUS-guided ethanol and/or paclitaxel injection

Pancreatic cysts can be punctured using a curvilinear-array scope via a transgastric or transduodenal approach.

Once punctured, the cyst content is optimally evacuated, and an equal volume of ethanol is injected inside the cyst. Then, during 3 to 5 minutes, simple retention of the ethanol or several lavages with alternate filling and emptying of the cavity can be performed. Ethanol

is a low-viscosity agent that can be easily injected through an EUS needle; pure 99% ethanol can be used without dose-related adverse events.

Following the lavages, the ethanol is evacuated (leaving sufficient fluid to outline the cyst surface) and a chemotherapeutic agent, such as paclitaxel, can be injected and left inside the cavity. Paclitaxel is a very commonly used chemotherapeutic agent. It inhibits cell processes that are dependent on microtubules. Thanks to its hydrophobic and viscous nature, it can cause a durable effect on the cyst epithelium avoiding the risk of leakage. Depending on the delivery vehicle, paclitaxel may need dilution with 0.9% normal saline prior to injecting it through the EUS needle.

The entire procedure is performed with real-time imaging, carefully maintaining the tip inside the cyst at all times. This way, pancreatic parenchymal injury or leaks through the cyst wall are avoided. Finally, after completion of the lavage and injection, the needle is removed from the cyst[107].

To date, several studies have reported optimal results with in vivo patients using these ablative agents[108-110]. However, a recent study evaluating the long-term efficacy of this technique, showed that only 9% of the participants achieved complete cyst resolution on follow-up imaging, concluding that ethanol lavage did not appear to be a useful technique for preventing malignancy in PCNs.

1.3.3 Radiofrequency ablation

RFA generally refers to electrosurgical energy in the 350-500 Hz range. It uses high-frequency alternating current to generate thermal energy and ultimately causes a coagulative necrosis to the tissue[111].

This technique has been successfully described for the treatment of several solid malignant lesions[112]. Recently, it has been used to treat pancreatic cancer in non-surgical candidates with promising initial results[111,113], however, the reported high rate of post-procedural morbidities limits its widespread use[114]. These undesirable effects are mainly due to the high susceptibility of the pancreatic tissue to heat. If the energy spreads outside the targeted tissue, parenchymal inflammation is very likely to occur with the corresponding clinical consequences. Massive necrosis of the pancreas following RFA has also been reported, secondarily to sequential ablations performed in close proximity at the same session[115-117].

To address this matter, EUS RFA needle prototypes have been recently developed. As opposed to RFA during laparotomy, EUS-guided ablation allows a less invasive approach with real-time monitoring of the tissue changes. EUS-guided RFA could achieve total ablation of PCNs in non-surgical candidates, thus eliminating the requirements for long-term surveillance in this specific group of patients.

Previous EUS-guided RFA studies performed in in vivo animals have reported some promising results. In one of these studies[118], EUS-RFA of the pancreatic head was performed in 5 pigs using a specific catheter that was introduced through a 19-gauge needle. Overall, the procedure was well tolerated with a low rate of pancreatitis noted.

A recent study reported EUS-guided RFA of PCNs in in vivo patients[119] using a monopolar radiofrequency probe. The results ranged from complete resolution of the cyst to a 50% reduction in the diameter. The patients included in the study were discharged hours after the procedure without any major adverse events. However, the authors acknowledged the existence of potential adverse events secondary to the use of RFA in pancreatic parenchy-

ma, such as acute pancreatitis, pancreatic leak, infection of necrotic pancreatic tissue and bleeding. Also, they recommended using lower energy to allow repeating the ablation process with lower risk of morbidity. Overall, this study demonstrated that this procedure is technically easy and safe.

Despite the promising results, EUS-guided RFA still requires long-term evaluation as well as further multicenter experience before the widespread use of this minimally invasive technique.

1.4. SURGICAL TREATMENT OF PANCREATIC CYSTIC NEOPLASMS

Herein, the different surgical techniques to treat PCNs will not be deeply discussed as they are beyond the purpose of this doctoral thesis. However, a brief introduction to the surgical management of these lesions is summarized below.

The recommendation to resect specific subtypes of PCNs clearly rests on the malignant potential of these lesions. Despite this, any decision to pursue surgical treatment should take into consideration, not only the cysts features, but also the comorbidities of the candidate, as well as other factors directly associated with the surgical procedure.

The challenge regarding surgery remains identifying the predictors of malignancy to allow an early resection in the hope of improving the long-term survival while, at the same time, sparing the morbidity and mortality related to the surgical procedure to those patients with a low-risk lesion.

The final aim of surgery in the treatment of PCNs is the total resection of the tumor, which includes negative margins. Currently, the concept of "negative" margins is being debated.

Whether it means the absence of any grade of dysplasia or it allows the presence of residual moderate to low dysplasia is being discussed[32]. The extent of the disease is usually intraoperatively assessed with frozen sections, or less common techniques such as intraductal ultrasound or irrigation cytology (which has shown a 100% sensitivity and specificity of malignancy)[120-122].

Again, the decision of how much pancreas to resect must take into account the type of lesion and the basal life expectancy of the patient. This is particularly important in patients with a presumed MD-IPMN where total pancreatectomy is indicated. Before proceeding with this highly aggressive technique, consideration of how well the patient will tolerate the unavoidable secondary effects of resecting the entire gland (such as diabetes or exocrine insufficiency) is mandatory.

Pancreatoduodenectomy, partial pancreatectomy or total pancreatectomy, depending on the site and extent of the disease, with lymph node resection remains the standard treatment. Occasionally, focal non-anatomic resections (such as enucleation or excision) may be performed in MCAs or BD-IPMNs that do not have any suspicion of malignancy[123-135]. However, this type of resections may facilitate the generation of leaks[136], pancreatic fistulae and, more importantly, the recurrence of the disease from potential residual neoplasm.

A laparoscopic approach can be feasible in LGD IPMNs or MCAs[137,138]. Despite this, if the intraoperative findings are suspicious of malignancy or the intraoperative pathology reveals HGD or invasive disease, conversion to a standard resection with lymphadenectomy is advised.

1.5 RECURRENCE AFTER TREATMENT

Due to the typical presentation of MCAs as solitary lesions, resection of non-invasive MCAs is almost always curative. Hence, no further surveillance is recommended. However, if invasive carcinoma is present in the surgical specimen, the interval to follow-up imaging is the same as in pancreatic ductal adenocarcinoma. Despite this recommendation, there is no proof that this strategy improves the prognosis compared to a strategy solely based on symptom recurrence[32,139].

IPMNs, on the other hand, may persist as clinically relevant residual lesions after surgical resection due to several reasons: known BD-IPMNs left on the remaining gland, presence of positive margins or newly developed lesions in the remnant pancreas.

Some patients with multifocal BD-IPMNs are left with lesions in the remnant. In these cases, they should be monitored following the same management algorithm as non-resected IPMNs[32]. Regarding the surgical margins, the clinical implications of LGD or moderate dysplasia present in the margin remains unclear. The 2012 guidelines recommend imaging surveillance with magnetic resonance cholangiography (MRCP) performed twice per year in cases of non-invasive IPMN following resection. However, little evidence substantiates these recommendations and the strategy should be redesigned if symptoms or radiological findings dictate a shorter interval of surveillance[140].

Finally, the 5-year postoperative recurrence rate ranges from 0% to 20%[141-143]. Therefore, if no residual lesions are present in the remnant and the margins are negative, surveillance at 2 and 5 years is currently recommended[32]. Despite this, recent studies have reported the development of pancreatic ductal adenocarcinoma in patients previously diag-

nosed with BD-IPMNs. These findings suggest that shorter intervals, for example every 6 months, would be more appropriate for surveillance[144-146].

1.6 HYPOTHESES

Based on the previous background, the following hypotheses were formulated:

- The prevalence of incidental pancreatic cysts has increased in the recent years due to the technical improvements and widespread use of the cross-section imaging technologies.
- The clinical and radiological information that is currently available can predict which of the commonly seen IPMNs are at risk of progress and, therefore, require close surveillance or surgical resection.
- Cytological and biochemical analysis of the cystic fluid can be a useful diagnostic tool to identify and stratify the broad spectrum of PCNs.

2 OBJECTIVES

- To determine whether the prevalence of incidental pancreatic cystic has changed over the past decade.

- To determine whether potential variations in the prevalence trend over the past decade are related to magnetic resonance imaging technical features.

- To identify the risk factors for malignancy in intraductal papillary mucinous neoplasms of the pancreas.

- To determine the accuracy of cytology, carcinoembriogenic antigen concentration and amylase levels in cystic fluid for the differential diagnosis between intraductal papillary mucinous neoplasms and other subtypes of pancreatic cystic neoplasms, as well as for the discrimination of malignancy among intraductal papillary mucinous neoplasms.

3 PUBLICATIONS

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Association Between Advances in High-Resolution Cross-Section Imaging Technologies and Increase in Prevalence of Pancreatic Cysts From 2005 to 2014

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BACKGROUND & AIMS: **Increasingly, pancreatic cysts are discovered incidentally in patients undergoing cross-sectional imaging for nonpancreatic reasons. It is unclear whether this increase is caused by improved detection by progressively more sophisticated cross-sectional imaging techniques or by a true increase in prevalence. We aimed to determine the prevalence of incidental pancreatic cysts in patients undergoing magnetic resonance imaging (MRI) for nonpancreatic indications on successive, increasingly sophisticated MRI systems. Also, we compared prevalence based on the demographic characteristics of the patients.**

METHODS: **We collected data from MRIs performed at the Mayo Clinic in Florida during the sample months of January and February, from 2005 to 2014. Each patient's clinical chart was reviewed in chronological order to include the first 50 MRIs of each year (500 total). Patients were excluded if they had pancreatic disease including cysts, pancreatic surgery, pancreatic symptoms, pancreatic indication for the imaging study, or previous abdominal MRIs. An expert pancreatic MRI radiologist reviewed each image, looking for incidental pancreatic cysts.**

RESULTS: **Of the 500 patients analyzed, 208 patients (41.6%) were found to have an incidental cyst. A significant relationship was observed between pancreatic cysts and patient age ($P < .0001$), diabetes mellitus ($P = .001$), and nonpancreatic cancer ($P = .01$), specifically nonmelanoma skin cancer ($P = .03$) or hepatocellular carcinoma ($P = .02$). The multivariable model showed a strong association between hardware and software versions and detection of cysts ($P < .0001$); the old hardware detected pancreatic cysts in 30.3% of patients, whereas the newest hardware detected cysts in 56.3% of patients.**

CONCLUSIONS: **Based on an analysis of data collected from 2005 through 2014, newer versions of MRI hardware and software corresponded with higher numbers of pancreatic cysts detected. Older age, diabetes, and the presence of nonpancreatic cancer (specifically nonmelanoma skin cancer and hepatocarcinoma) were also associated with the presence of cysts.**

Keywords: Pancreatic Cystic Neoplasm; Intraductal Papillary Mucinous Neoplasm; Magnetic Resonance Imaging Pancreatic Cancer.

Pancreatic canceris the 10th most common cancer in the United States but the 4th most common cause of cancer death, largely because of its late presentation and high lethality.[1] The only known precursors of these lesions, apart from rare inherited genetic disorders, are pancreatic cystic neoplasms,[2–5] a subtype of the broad spectrum of pancreatic cystic lesions (PCLs).

A common scenario in clinical practice is the finding of an incidental small pancreatic cyst on imaging done for other reasons.[6,7] Several studies[8–11] have reported an increased trend in the diagnosis of these incidental cysts in recent years. It has been suggested that this increase is a direct result of the development and widespread use of new imaging techniques that improve detection of these

Abbreviations used in this paper: DM, diabetes mellitus; HCC, hepatocellular carcinoma; IPMNs, intraductal papillary mucinous neoplasms; MRI, magnetic resonance imaging; PCL, pancreatic cystic lesion.

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lesions,[12–14] but only limited data are available on the real prevalence of PCLs in the population.

To address this matter, this study aims to determine the prevalence of incidental PCLs in patients undergoing magnetic resonance imaging (MRI) for nonpancreatic indications, according to their technical features. The secondary aim is to compare prevalence based on the demographic characteristics and relevant comorbidities of the patients.

Methods

The study was approved by the Mayo Clinic Institutional Review Board.

Study Design and Population

This is a retrospective descriptive study. All consecutive abdominal MRIs performed at Mayo Clinic in Jacksonville, Florida, during January and February from 2005 to 2014 were listed. The clinical chart of each patient was manually and chronologically reviewed to identify the first 50 suitable candidates in each calendar year. Patients were excluded if there was a known history of symptomatic or asymptomatic pancreatitis (acute or chronic), pancreatic masses, or pancreatic cysts. Also, they were excluded if there was a history of pancreatic surgery, pancreatic symptoms (including isolated abdominal pain), or if the MRI indication was pancreas-related. Moreover, to avoid selection bias, only those patients who had had no previous MRI performed in this institution were included. If there had been more than 1 MRI during the study decade, only the earliest examination was included in the study.

The secondary exclusion criteria was applied after the radiologist's review and included significantly motion-degraded scans, obscuring metal artifact, incomplete examinations, or modified anatomy that prevented visualization of the entire pancreas. Whenever an exclusion criterion arose and the associated MRI was excluded, a new candidate was added to the study, following a strict chronological order.

Epidemiologic and Clinical Information

Demographic information regarding sex, age, race, body mass index, and smoking history was extracted from the clinical records corresponding to the visit when the imaging study was performed. Other data, such as family history of pancreatic cancer or pancreatitis and personal history of any extrapancreatic cancer or organ transplantation, were collected from the clinical information available at this institution, independently of the time when it was recorded.

Magnetic Resonance Imaging Protocol and Technical Features

Over the 10-year period of this study, scanner hardware (platform) and software were updated at our site as new technology became available. Each major platform upgrade received a new model name from the vendor (Siemens Medical Solutions USA Inc, Malvern, PA). Besides the strength of the static magnetic field (1.5 T or 3 T), other major differences in scanner hardware include improvements in scanning speed (maximum gradient amplitude and rate), scanning flexibility (increasing numbers of surface coil elements), and image signal-to-noise ratio (eg, more efficient radiofrequency

Table 1. Technical MRI Features

Field strength						
n	1.5 T	3 T				
500	468 (93.6%)	32 (6.4%)				
Hardware						
n	Symphony	Sonata	Espree	Avanto	Aera	Skyra
500	155 (31.0%)	39 (7.8%)	64 (12.8%)	206 (41.2%)	4 (0.8%)	32 (6.4%)
Software						
n	VA	VB	VD			
500	190 (38.0%)	273 (54.6%)	32 (6.4%)			
Intravenous contrast						
n	No	Yes				
500	12 (2.4%)	488 (97.6%)				
Dedicated MRCP sequences						
n	No	Yes				
500	405 (81.0%)	95 (19.0%)				
T1 pancreas signal intensity						
n	Hyperintense to liver	Hypointense to liver	Isointense to liver			
500	206 (41.2%)	33 (6.6%)	261 (52.2%)			

MRCP, magnetic resonance cholangiopancreatography.

coils). Signal-to-noise ratio is also nearly doubled on the higher magnetic field strength 3-T systems when compared with 1.5 T, allowing for higher resolution imaging, but 3 T is also more susceptible to image degradation by metal and air-tissue interface artifacts.

As hardware improved, scanner software likewise improved to take advantage of the new hardware technology. Thus major software versions (VA, VB, VD) correspond to major hardware improvements (Symphony/Sonata, Espree/Avanto, Aera/Skyra, respectively). In addition, for each major software version there were incremental improvements in scanner software (eg, VA21, VA25, VA30), allowing, for example, new types of scan sequences, new software options, or new software postprocessing capabilities (Supplementary Table 1). In summary, the data in this study were acquired on 20 different combinations of MRI hardware and software.

Regardless of MRI platform, each examination included an axial and a coronal T2-weighted single-shot (HASTE) pulse sequence. Basic scan parameters were TR 1400–1500 ms, TE 82–99 ms, and slice thickness 5–7 mm (gap, 0.5–0.7 mm). The HASTE sequences were acquired during an expiratory breathhold. Motion insensitive and fluid sensitive, these are optimal for cyst detection and analysis. T1-weighted and contrast-enhanced sequences were used secondarily to exclude solid elements and abnormal enhancement (eg, of septations).

Table 2. Imaging Features

Cyst morphology							
n	Unilocular	Multilocular					
208	177 (85.1%)	31 (14.9%)					
Cyst location							
n	Head	Uncinate	Body	Tail	Multiple		
208	60 (28.9%)	20 (9.6%)	64 (30.8%)	49 (23.6%)	15 (7.2%)		
Long axis (*mm*)							
n	Median	Standard deviation	Minimum	Maximum			
208	4	4.3	2	31			
Short axis (*mm*)							
n	Median	Standard deviation	Minimum	Maximum			
208	3	2.4	1.5	16			
MPD size (*mm*)							
n	Median	Standard deviation	Minimum	Maximum			
500	2	0.7	1	6			
MPD aspect							
n	Irregular	Smooth					
500	19 (3.8%)	481 (96.2%)					
Connection to main duct							
n	No	Yes					
500	419 (83.8%)	81 (16.2%)					
Septae							
n	No	Yes					
500	497 (99.4%)	3 (0.6%)					
Atrophic pancreas							
n	None	Mild-moderate	Severe				
500	390 (78.0%)	99 (19.8%)	11 (2.2%)				
Pancreatic fat infiltration							
n	None	Mild-moderate	Severe				
500	417 (83.4%)	77 (15.4%)	6 (1.2%)				
Presence of extrapancreatic cysts							
n	No	Yes					
500	150 (30.0%)	350 (70.0%)					
Kidney cysts							
n	0	1	2	3	4	5	>5
349	50 (14.3%)	67 (19.2%)	37 (10.6%)	43 (12.3%)	35 (10.0%)	12 (3.4%)	105 (30.1%)
Liver cysts							
n	0	1	2	3	4	5	>5
343	186 (54.2%)	63 (18.4%)	24 (7.0%)	22 (6.4%)	12 (3.5%)	4 (1.2%)	32 (9.3%)
Other organ cysts							
n	0	1	2	3	4	5	>5
325	307 (94.5%)	13 (4.0%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0

MPD, main pancreatic duct.

Magnetic Resonance Imaging Interpretation

After the clinical charts and the MRI report of each patient were reviewed to ensure the application of the inclusion criteria, all the images from each study were downloaded and examined by an expert pancreatic MRI radiologist. Cysts were identified as closed sac-like structures with a fluid or semi-fluid content. If seen, their size, the number, the location, and the morphology were recorded. When more than 1 cyst was seen, the features of the largest 1 were reported. Also, the presence of high-risk features, such as mural nodules, septae, or masses, was reported. The main pancreatic duct was measured in every examination in its widest segment, and duct margination (smooth or irregular) was also determined. The overall imaging appearance of the pancreas and the presence of extrapancreatic cysts, if seen, were also entered in the database. Regarding the technical features, the field strength (1.5 T/3 T), the hardware platform (Symphony, Sonata, Espree, Avanto, Skyra, or Aera), and the software version (VA: 21, 25, 30, 35; VB: 12, 13, 15, 17, 19; or VD: 11, 13) were recorded for each examination.

Statistical Analysis

Study data were collected and managed using a Research Electronic Data Capture hosted at Mayo Clinic database. The Stata 13 software for Mac OS X Lion (Stata Inc, College Station, TX) was used for the analysis.

A single-variable logistic regression was used to compare baseline characteristics of patients with and without a pancreatic cyst. A multivariate logistic analysis was performed to describe the presence of any association between the technical variables of the MRI and the presence of pancreatic cysts. The multivariable models were adjusted for all baseline patient characteristics that were associated with the presence of a pancreatic cyst with a P value of .20 or lower. A $P < .05$ was considered significant.

Only those variables with more than 10 patients were included in the univariate analysis. The continuous variables "age" and "body mass index" were categorized to allow an easier interpretation of the data. Also, because of the asymmetrical distribution of the variables "race," "hardware," and "software," some of their categories were merged to avoid the loss of data; specifically, the categories "Asian" and "others" for race, "Avanto" and "Aera" (following the similarities between these 2 versions) for hardware, and the software categories of VA, VB, and VD.

Results

A total of 1962 patients from 2005 to 2014 were reviewed for the study. Of these, 1462 patients were excluded for various reasons (Supplementary Figure 1), leaving a final study sample of 500 patients (50 patients per year). The study cohort (n = 500) had a nearly equal distribution of sexes, with an overall median age of 60 years and a predominance of white race (85%). The percentage of patients with a positive smoking history was slightly higher (53%). No family history of pancreatitis was reported, but 4% of the cohort had a family history of pancreatic cancer, and 12% (n = 60) had a personal history of solid organ transplantation, liver

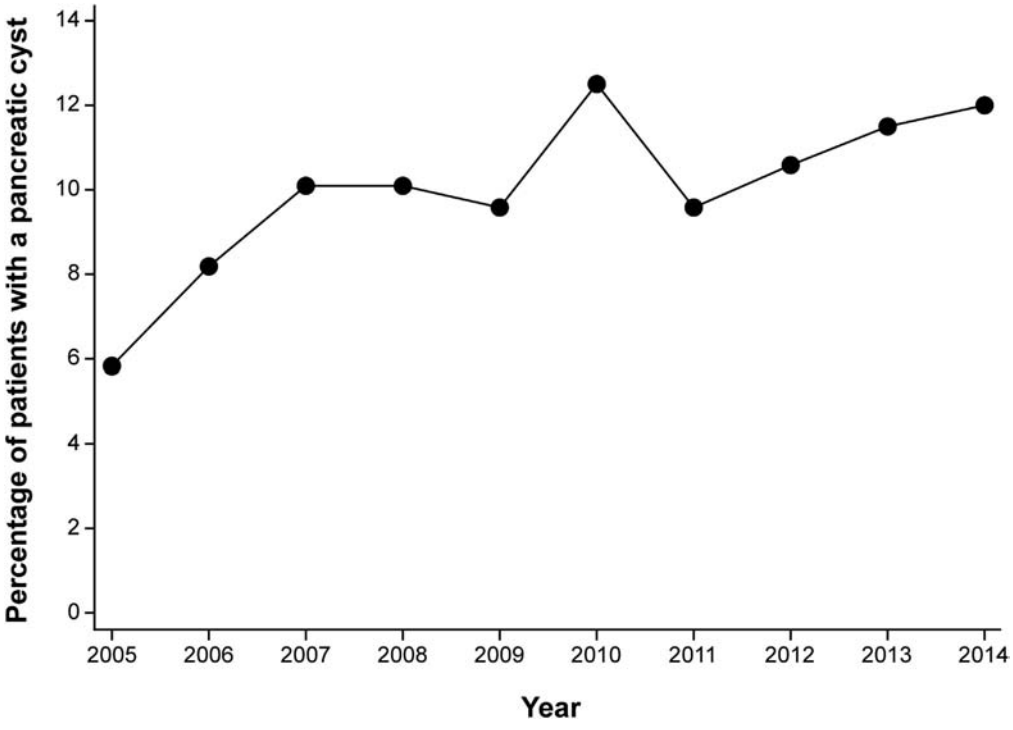

Figure 1. Increased trend of incident pancreatic cysts (n = 208).

being the most common (11%). The demographics of the whole cohort are summarized in Supplementary Table 2. Overall, 186 patients (37%) had a positive history of nonpancreatic cancers, with hepatocellular carcinoma (HCC) (9%) and nonmelanoma skin cancer (8%) representing the predominant types (Supplementary Table 3). Extrapancreatic cysts were found in 70% of the patients, kidney being the most frequent organ. The univariate analysis showed a strong association between the presence of extrapancreatic and pancreatic cysts (Supplementary Table 4).

Overall, 208 patients (41.6%) had an incidental cyst but only 44 cases had the cyst described in the original MRI report. Most of the cysts were small (median, 4 mm) and almost half of patients with cysts (48%) had only 1 cyst described. The proposed diagnosis was uncertain in 128 cases (62%), followed by an intraductal papillary mucinous neoplasms (IPMN) in 72 patients (35%). The technical and imaging features are shown in Tables 1 and 2. No mural nodules, masses, central scars, calcifications, or contrast enhancement were seen. Only 1 patient had a radiologic image compatible with subacute pancreatitis. An increased trend of pancreatic cysts was seen over the 10 years (Figure 1) with no statistically significant differences seen in the demographic variables among groups.

The demographics and comorbidities of the patients with an incidental PCL (n = 208) were compared with the rest of the cohort (n = 292) (Tables 3 and 4). The single-variable logistic regression model showed a significant association between the presence of cysts and the variables age ($P < .0001$), with cysts diagnosed in older aged patients; diabetes mellitus (DM; $P = .001$), with more DM in patients with a PCL; and the personal history of any type of cancer ($P = .01$). If analyzed separately, nonmelanoma skin cancer ($P = .03$) and HCC ($P = .02$) were the only types of cancer with a significant relationship with incidentally found PCLs.

The multivariable models showed a very strong association between the type of hardware and software and the presence of cysts. Newer versions of both variables corresponded with an increased number of PCLs seen in the MRIs. The field strength (3 T vs 1.5 T) was not significantly associated with these incidentally found lesions (Table 5).

Table 3. Baseline Characteristics

Variable	Pancreatic cysts (%)	Noncyst (%)
Age (n)	208	292
Mean ± SD	63.8 ± 11.2	54.5 ± 14.0
Body mass index (n)	203	272
Mean ± SD	28.5 ± 6.4	28.3 ± 5.3
Gender (n)	208	292
Male	109 (52.4)	143 (49.0)
Race (n)	208	292
White	181 (87.0)	243 (83.2)
African American	10 (4.8)	25 (8.6)
Other	17 (8.2)	24 (8.2)
Latin (n)	208	292
Yes	11 (5.3)	17 (5.0)
Smoking history (n)	208	292
Never	96 (46.6)	137 (47.0)
Previous	209 (41.8)	117 (40.1)
Current	58 (11.6)	38 (13.0)
Diabetes mellitus (n)	208	292
Yes	57 (27.4)	44 (15.1)
Family history of pancreatic cancer (n)	208	292
Yes	7 (3.4)	12 (4.1)
Colorectal-anal cancer (n)	208	292
Yes	12 (4.1)	12 (5.8)
Breast cancer (n)	208	292
Yes	6 (2.9)	10 (3.4)
Nonmelanoma skin cancer (n)	208	292
Yes	23 (11.1)	16 (5.5)
Renourethral cancer (n)	208	292
Yes	11 (5.3)	10 (3.4)
Hepatocarcinoma (n)	208	292
Yes	25 (12.0)	18 (6.2)
Solid organ transplantation (n)	208	292
Yes	22 (10.6)	38 (13.0)
Liver transplant (n)	208	292
Yes	20 (9.6)	36 (12.3)

SD, standard deviation.

Discussion

Our study demonstrates the relationship between the higher trend of incidental pancreatic cysts observed in the recent years and the improvements in the technical features of MRIs. These findings suggest that the changes in imaging capabilities are a contributing factor for the observed rise of PCLs detection rates. This study also shows the significant relationship between age, DM, and a previous nonpancreatic cancer (specifically, nonmelanoma skin cancer and HCC) with the presence of PCLs.

The real prevalence of the PCLs remains uncertain with prevalence ranging from 0.2% to 44.7%.[15–20] Despite this, a growing body of evidence suggests that there is an increased trend of incidentally found PCLs. It has been postulated that this trend is correlated to the technical improvements of the imaging diagnostic tests, and their widespread use,[21] but to our knowledge this has not yet been addressed by any study.

Despite the fact that the diagnostic criteria for PCLs are well established,[22,23] many studies have exposed the limitations of the currently available imaging modalities to characterize and diagnose the cyst subtypes.[24–27] MRI is considered the best technique for cyst diagnosis because it visualizes intracystic features and pancreatic duct communications. However, a study by Lee et al[28] showed no differences between MRI and multidetector computed tomography for malignant characterization of these lesions. Even if the diagnostic accuracy is the same, MRI still offers more advantages in terms of lack of radiation and lower risk of undesirable contrast-induced effects.[29]

Table 4. Univariate Analysis

Variable	Categories	Percentage with a pancreatic cyst	Odds ratio (*95% CI*)	*P* value
Age			Overall test of difference <0.0001	
	<50	20	1.0 (reference)	N/A
	50.01–60	32.4	1.9 (1.1–3.4)	0.026
	60.01–70	54.9	4.86 (2.8–8.5)	<.0001
	>70	61.5	6.4 (3.5–11.8)	<.0001
Sex				
	Male	43.3	1.0 (reference)	N/A
	Female	39.9	0.87 (0.6–1.2)	.45
Race			Overall test of difference 0.28	
	White	42.7	1.0 (reference)	N/A
	African American	28.6	0.5 (0.3–1.2)	.11
	Other	41.5	1.0 (0.5–1.8)	.88
BMI			Overall test of difference 0.19	
	<25	43.6	1.0 (reference)	N/A
	25–29.99	43.4	1.0 (0.6–1.6)	.97
	30–34.99	35.2	0.7 (0.4–1.2)	.19
	≥35	52.6	1.4 (0.8–2.7)	.25
Smoking history			Overall test of difference 0.42	
	Never	41.2	1.0 (reference)	N/A
	Previous	44.0	1.1 (0.8–1.6)	.55
	Current	34.5	0.8 (0.4–1.4)	.35
Diabetes				
	No	37.8	1.0 (reference)	N/A
	Yes	56.4	2.1 (1.4–3.3)	.001
Family history of pancreatic Ca				
	No	41.8	1.0 (reference)	N/A
	Yes	36.8	0.8 (0.3–2.1)	.67
Personal history of any nonpancreatic Ca				
	No	36.9	1.0 (reference)	N/A
	Yes	49.5	1.7 (1.2–2.4)	.006
Colorectal-anal Ca				
	No	41.2	1.0 (reference)	N/A
	Yes	50.0	1.4 (0.6–3.3)	.39
Breast Ca				
	No	40.1	1.0 (reference)	N/A
	Yes	37.5	0.9 (0.3–2.6)	.84
Nonmelanoma skin Ca				
	No	40.1	1.0 (reference)	N/A
	Yes	59.0	2.2 (1.1–4.2)	.025
Renourethral Ca				
	No	41.1	1.0 (reference)	N/A
	Yes	52.4	1.6 (0.7–3.8)	.31
Hepatocarcinoma				
	No	40.0	1.0 (reference)	N/A
	Yes	58.1	2.1 (1.1–3.9)	.024
Solid organ transplantation				
	No	42.3	1.0 (reference)	N/A
	Yes	36.7	0.8 (0.5–1.4)	.41
Liver transplantation				
	No	42.6	1.0 (reference)	N/A
	Yes	33.3	0.7 (0.4–1.2)	.19

BMI, body mass index; Ca, cancer; CI, confidence interval; N/A, no answer.

An incidental PCL prevalence of 42% was found in the study cohort. This is a high number compared with similar recent publications. Lee et al[30] carried out a study under similar conditions, finding a prevalence of 14%. Also, Matsubara et al[31] performed another study including a control group without pancreatic disease that showed a prevalence of 10%. However, in this last study, only cysts greater than 5 mm were included, whereas in ours there was no size limit. If this criterion is taken into consideration, the prevalence of our study drops to 21% (77 cysts >5 mm), which is still higher than Matsubara's study. No clear explanation can be given for this disparity. Moreover, we believe that we may have even underestimated the real prevalence because of the absence of magnetic

Table 5. Multivariate Analysis

Variable	Percentage with a pancreatic cyst	Univariate analysis		Multivariate analysis[a]	
		Odds ratio (*95% CI*)	*P* value	Odds ratio (*95% CI*)	*P* value
Field strength					
1.5 T	40.6	1.00 (reference)	N/A	1.00 (reference)	N/A
3 T	56.3	1.9 (0.9–3.9)	.086	2.0 (0.9–4.3)	.095
Hardware platform		Overall test of difference 0.0002		Overall test of difference <0.0001	
Symphony	30.3	1.00 (reference)	N/A	1.00 (reference)	N/A
Sonata	23.1	0.7 (0.3–1.6)	.37	1.0 (0.4–2.5)	.98
Espree	48.4	2.2 (1.2–3.9)	.012	2.7 (1.3–5.4)	.005
Avanto/Aera	49.0	2.2 (1.4–3.4)	.0004	3.0 (1.8–5.0)	<.0001
Skyra	56.3	3.0 (1.4–6.4)	.006	3.9 (1.6–9.2)	.002
Software		Overall test of difference <0.0001		Overall test of difference <0.0001	
VA	29.0	1.00 (reference)	N/A	1.00 (reference)	N/A
VB	49.1	2.4 (1.6–3.5)	<.0001	3.0 (1.9–4.7)	<.0001
VD	51.4	2.6 (1.3–5.3)	.009	3.1 (1.4–6.8)	.006

CI, confidence interval; N/A, no answer.
[a]Adjusted for age; body mass index; and history of any nonpancreatic cancer, nonmelanoma, HCC, liver transplantation, and DM.

resonance cholangiopancreatography sequences[20,32] (only 19% of the examinations), and the lack of 3-T studies (6% of the MRIs).

Thirty-five percent of the MRIs had a proposed diagnosis of IPMN. Although it seems to be a high proportion of patients, a recent study by Girometti et al[20] showed a much higher percentage of cysts with an IPMN-like pattern (71%). However, Del Chiaro et al[33] studied a high-risk population for pancreatic cancer finding 35% of patients with an IPMN. However, in this study, the mean age was younger (59 years) and the median cyst size was higher (11 mm). Also, 5 of their 14 IPMN patients had a mixed or main duct type, whereas in our cohort all the IPMNs were presumably branch duct type.

Overall, the median size of the PCLs was 4 mm, a low value compared with those published in previous studies, which ranged from 8 to 20 mm.[5,26,27,29] This smaller size was unexpected because, as a result of the exclusion criteria applied, the technical features of the MRIs were not the most specific for PCLs visualization. Thus, the most suitable explanation for this lower threshold is the wide experience in this field of the radiologist involved in the study.

No mural nodules or masses were seen in any of the examinations, and only 1% of the cohort showed internal septae. This benign appearance of the PCLs is similar to outcomes from previous studies[5] and also supports actual trends toward a more conservative approach of these incidentally found lesions.

No significant relationship was seen between sex (substantiating previous studies[30]), race, positive smoking history, or body mass index. The variable age and DM, however, were strongly related with incidental pancreatic cysts, concurring with actual literature findings.[2,16,20,34] However, in the DM outcomes, we acknowledge the potential confusion factor caused by age (64 years in the PCL group vs 55 years in the noncyst group), because it seems improbable that such small cysts like the ones described here cause pancreatic endocrine malfunction.

Regarding the presence of nonpancreatic neoplasms, there is not a clear position based on current publications. In accordance with a study carried out by Sugiyama and Atomi,[35] extrapancreatic neoplasms are more often diagnosed in patients with IPMNs. In contrast, a different study[20] suggested that there was no correlation between these neoplasms and the presence of PCLs.

These contradictory findings may respond to the different outcome of both studies; the first one focused only in IPMNs and the second one in all PCLs. However, in our study (where only 38% of the patients were suspected IPMNs), we found a significant relationship between a positive history of any cancer and PCLs. When studied in detail, only nonmelanoma skin cancer and HCC were significantly associated. Despite this, we acknowledge that nonmelanoma skin cancer may be acting as a possible confounder, because this entity is typically diagnosed in older ages. However, in the case of the HCC, previous studies have shown a significant relationship between liver-transplanted patients and pancreatic cysts.[20,36] We also recorded the variables of history of solid organ transplantation and history of liver transplantation. None of them showed a significant relationship with PCLs, despite HCC being a frequent indication for liver transplant.

A strong association was observed between the presence of PCLs and extrapancreatic cysts. Although some studies have postulated the existence of an association between the presence of PCLs and renal cysts,[37,38] a recent case-control study showed the opposite results.[39] Based on these contradictory findings, further specific studies are needed, because this matter is beyond the purpose of our study.

The adjusted multivariate analysis showed a very strong relationship between the presence of PCLs and both the hardware and software MRI versions. These

versions were analyzed in chronological order, showing an increased trend in the number of PCLs seen in the examinations. This confirmed what had been postulated in many previous studies but had not yet been studied: the development and improvement of the imaging techniques play an important role in the dramatic increased number of PCLs diagnosed in the recent years.

However, the variable "field strength" (1.5 T vs 3 T) was not significantly related with the presence of PCLs. We believe this may be secondary to the lack of power of the analysis, because only 6% of the examinations were 3-T studies. Therefore, we speculate that this relationship may be confirmed if the number of 3-T studies increased.

We acknowledge several limitations in this study. The study cohort was extracted from the clinical records of a tertiary referral center. Hence, there could be a potential selection bias in the selected population. However, to minimize it, we applied very strict exclusion criteria to include a representative sample of the general population. Because the patients in our study underwent MRI examinations for nonpancreatic indications (involving a wide spectrum of clinical diseases), there is not a homogenous abdominal MRI protocol that applies to all the examinations. Also, a consequence of the nonpancreatic indication of the studies is the low percentage of magnetic resonance cholangiopancreatography sequences (<20%), which may have led to an underestimation of the real prevalence of PCLs. In addition, this underestimation may have also been influenced by the low number of 3-T examinations. However, in this case, this limitation was inherent to the design of the study because the 3-T MRIs were not available in the initial years of the decade.

In summary, to our knowledge this is the first study to analyze the relationship between the technical improvements in imaging techniques (specifically, MRI) and the presence of incidentally found PCLs. The results showed a strong association between newer versions of hardware and software and the increased trend of PCLs detected in the recent years. Also, we confirmed previous findings regarding the association between older age, DM, and the presence of pancreatic cysts, and we postulate the influence of a positive history of nonpancreatic neoplasms and extrapancreatic cysts in the presence of PCLs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2015.08.038.

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Conflicts of interest
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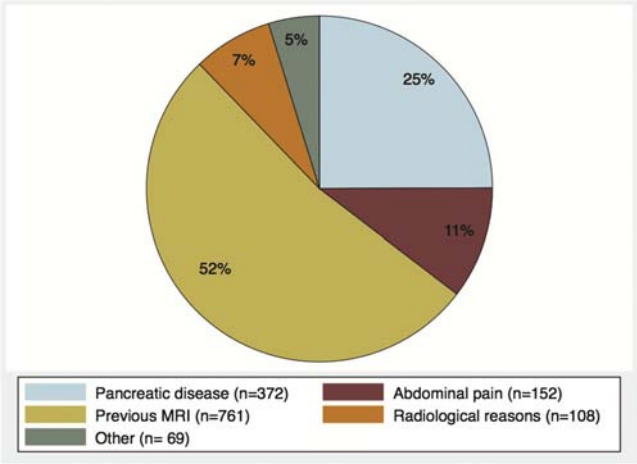

Supplementary Figure 1. Patients excluded from the study.

Supplementary Table 1. Technical Features of the MRIs Included in the Study

Model	Field strength (*T*)	Software versions	Installation date (month/year)
Symphony	1.5	VA21, VA25, VA30, VA35	9/2001
Sonata	1.5	VA21, VA25	9/2001
Espree	1.5	VB12, VB13, VB15, VB17, VB19	9/2004
Avanto	1.5	VB12, VB13, VB15, VB17, VB19	6/2006
Skyra	3	VD11, VD13	2/2010
Aera	1.5	VD11, VD13	2/2013

Supplementary Table 2. Demographic Characteristics of the Study Cohort

Sex					
n	Male	Female			
500	252 (50.4%)	248 (49.6%)			
Age					
n	Median	Standard deviation	Minimum	Maximum	
500	59.5	13.7	17.2	91.1	
Race					
n	White	African American	Asian	Other	Unknown
500	424 (84.8%)	35 (7.0%)	9 (1.8%)	24 (4.8%)	8 (1.6%)
Latin origin					
n	Yes	No			
500	28 (5.6%)	472 (94.4%)			
Smoking history					
n	Never	Previous smoker	Current smoker		
500	233 (46.6%)	209 (41.8%)	58 (11.6%)		
Years smoked					
n	Median	Standard deviation	Minimum	Maximum	
461	1.0	14.4	0	70	
Height (*cm*)					
n	Median	Standard deviation	Minimum	Maximum	
475	169.6	10.0	142.5	198.0	
Weight (*kg*)					
n	Median	Standard deviation	Minimum	Maximum	
489	81.8	18.8	40.0	149.7	
Body mass index					
n	Median	Standard deviation	Minimum	Maximum	
475	28.4	5.8	13.4	55.1	
Diabetes mellitus					
n	Yes	No			
500	101 (20.2%)	399 (79.8%)			
Family history of pancreatic cancer					
n	Yes	No			
500	19 (3.8%)	481 (96.2%)			
Personal history of nonpancreatic cancer					
n	Yes	No			
500	186 (37.2%)	314 (62.8%)			
Personal history of solid organ transplantation					
n	Liver	Kidney	Kidney + liver	Lung	None
500	54 (10.8%)	2 (0.4%)	2 (0.4%)	2 (0.4%)	440 (88.0%)

Supplementary Table 3. Personal History of Nonpancreatic Cancer

Type of cancer	Yes (%)
Hepatocellular carcinoma	43 (8.6)
Nonmelanoma skin	39 (7.8)
Colorectoanal	24 (4.8)
Renourethral	21 (4.2)
Breast	16 (3.2)
Prostate	9 (1.8)
Uterus	8 (1.6)
Melanoma	7 (1.4)
Lung	7 (1.4)
Bladder	5 (1)
Lymphoma non-Hodgkin	5 (1.0)
Thyroid	5 (1.0)
Leukemia	3 (0.6)
Ovary	2 (0.4)
Esophagus	2 (0.4)
Gastric	1 (0.2)

Supplementary Table 4. Association Between the Presence of Pancreatic and Extrapancreatic Cysts

Variable	Categories	Percentage with a pancreatic cyst	Odds ratio (*95% CI*)	*P* value
Extrapancreatic cysts				
	No	28.0	1.0 (reference)	N/A
	Yes	47.4	2.3 (1.5–3.5)	<.0001
Kidney cysts				
	No	32.3	1.0 (reference)	N/A
	Yes	47.8	1.9 (1.3–2.8)	.001
Liver cysts				
	No	38.8	1.0 (reference)	N/A
	Yes	47.8	1.4 (1.0–2.1)	.06
Other cysts				
	No	40.5	1.0 (reference)	N/A
	Yes	72.2	3.8 (1.3–10.9)	.012

CI, confidence interval; N/A, no answer.

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Liver, Pancreas and Biliary Tract

Risk factors for malignant progression of intraductal papillary mucinous neoplasms

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ABSTRACT

Background: Intraductal papillary mucinous neoplasms of the pancreas are increasingly diagnosed. Due to their malignant potential, greater understanding of their nature is required.
Aims: Define risk factors for malignancy in intraductal papillary mucinous neoplasms.
Methods: An international, multicentre study was performed in Europe and the United States. Clinical databases were reviewed for patients with intraductal papillary mucinous neoplasms diagnosis.
Results: Of 1126 patients, 84 were diagnosed with invasive carcinoma/high-grade dysplasia and were compared to the rest of the cohort. Multivariate logistic analysis showed a statistically significant association between cancer/high-grade dysplasia and the variables smoking history (OR 1.9, 95% CI [1.1–3.1]), body mass index (OR 1.1, 95% CI [1–1.1]), symptoms (OR 3.4, 95% CI [1.9–6]), jaundice (OR 0.1, 95% CI [0–0.3]), and steatorrhea (OR 0.3, 95% CI [0.1–0.8]). Univariate analysis showed no association between malignancy and the cyst number/location ($p = 0.3$ and $p = 0.5$, respectively) although a strong association was shown for cyst size ($p < 0.001$). The presence and size of nodules ($p < 0.01$) and main duct involvement ($p < 0.001$) were also strongly related with malignancy.
Conclusion: The presence of jaundice and steatorrhea, smoking, high body mass index, and imaging features such as cyst size, main duct involvement, and the presence and size of mural nodules are associated with high-grade neoplasia in intraductal papillary mucinous neoplasms.

1. Introduction

Since its first consideration as an independent entity in 1996 [1], intraductal papillary mucinous neoplasms (IPMN) of the pancreas have been diagnosed with increasing frequency [2]. Detection and resection of IPMN offer a unique opportunity to cure and prevent adenocarcinoma of the pancreas, an otherwise highly lethal disease. The main clinical concern related to IPMN is its wide-ranging potential for malignancy from low-risk indolent lesions to those with high incidence of malignant degeneration. It is well-established that this malignant progression varies based on the morphological subtypes [3–6]. The current methods of predicting malignant potential are limited to clinical, morphological, and cyst fluid cytology and biomarker data.

To address these limitations, the aim of the present study is to identify and define the risk factors for malignancy progression in IPMN.

2. Materials and methods

The ethics committee at each of the participating centres approved collection of the registry data.

2.1. Study design and population

This was an international, multicentre study that included four centres. One centre in the USA (Mayo Clinic [Jacksonville, FL]) and

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three in Italy (San Rafaelle Scientific Institute [Milano], Azienda Universitario-Ospedaliera San Giovanni Battista [Torino], and University of Bologna/Hospital of Imola [Bologna]).

We conducted a retrospective descriptive study. Every patient with a clinical suspicion of an IPMN following the actual guidelines criteria [7–10], who also had a high resolution imaging technique (MRI, CT scan, or endoscopic ultrasound [EUS]) performed as a baseline examination, was included in the study. Once in the registry, each patient was prospectively updated with the corresponding follow-up visits until August 2014.

2.2. Epidemiological variables

One demographic standardised data form was completed per patient. All variables were filled with the information available at the time of the diagnosis.

Two environmental factors were also included in this data form: smoking history and alcohol consumption. To assure the absence of bias when comparing smoker groups, the amount and duration of smoking were also collected. These two variables were afterwards merged into one called "pack-years" that was defined as the product of packs smoked per day and the years smoking.

Due to the size difference between the Mayo Clinic and the Italian group cohorts, demographic characteristics were also analysed separately to evaluate possible confounding by centre.

2.3. Visit information

A second, different standardised data form was also filled with the information regarding symptoms, cyst features, imaging tests, and surgery if present. These data was extracted from the clinical charts of each of the follow-up visits performed. For the analysis results presented here, we collected only the information contained in the initial visit, i.e., when the cyst was first diagnosed. This way, a homogeneous criterion was used independently of the final outcome.

For the cyst features, a suspicious diagnosis of IPMN was made when a dilated main pancreatic duct ([MPD] ≥5 mm) or a cystically dilated branch duct (≥5 mm) was recognised. If there was involvement of both main and branch ducts, these patients were placed in the main duct group for the analysis. In case of multiple cysts, the features of the biggest cyst were reported. The cyst size was determined by the maximum dimensions measured in both the major and the minor axes. Mural nodules were considered present if described in the final imaging report. As patients with main duct involvement are almost always referred for surgery, we also performed a secondary analysis of the cyst features to look separately at those patients with isolated side branch involvement. The imaging technique used for the data collection (MRI, CT scan, or EUS) depended on which one was performed in the initial visit. If more than one was performed in the same visit, the order of preference was firstly EUS (as other variables EUS-dependent were also registered in the questionnaire), then MRI, and finally CT scan.

2.4. Criteria for consolidation of groups

Once the whole data was entered in the registry, the final sample was divided into two groups. The first group comprised patients who underwent surgery and had a pathological confirmation of malignancy in the surgical specimen. We included in this group patients with both high-grade dysplasia ([HGD] formerly carcinoma *in situ*) and invasive carcinoma.

On the other hand, the control group included those patients who either underwent surgical resection and the pathological report was consistent with intermediate-grade dysplasia (IGD) or low-grade dysplasia (LGD), or those who had a high clinical suspicion of a non-malignant lesion and, therefore, were included in an observational follow-up programme.

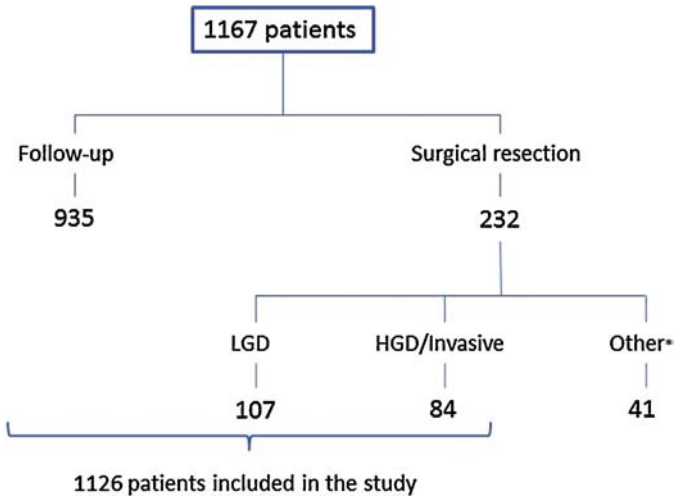

Fig. 1. Patients selected for the final analysis. **Other*: 7 Serous cystadenoma, 9 benign cysts, 1 chronic pancreatitis, 3 neuroendocrine tumours, 12 mucinous cystic neoplasms, 2 other malignant tumours, 7 unknown. LGD, low-grade dysplasia intraductal papillary mucinous neoplasms; HGD, high-grade dysplasia intraductal papillary mucinous neoplasms.

2.5. Statistical analysis

Study data were collected and managed using REDCap (Research electronic Data Capture hosted at Mayo Clinic) database. The Stata 13 software for Mac OS X Lion (Stata Inc., College Station, TX) was used for the analysis. Categorical variables were compared using a χ^2 test or Fischer's exact test and continuous variables were analysed with a two-tailed Student's *t* test or a Wilcoxon rank-sum test when appropriate. Multivariate logistic analysis was performed with the demographical and clinical variables. Imaging variables were not included in the analysis as it would have eliminated a large proportion of patients with missing values and significant loss of power. All variables that had a *p* value of <0.20 in the univariate analysis were considered candidates for the initial model. A backward elimination procedure was used to obtain the final optimal model. Due to the different biological behaviour between BD-IPMNs and MD-/mixed-IPMNs, we also performed two different subanalyses in these populations.

All statistical tests were two-sided and considered significant when *p* values were less than 0.05. Bonferroni correction was not used for variables *a priori*.

3. Results

A total of 1167 patients with a clinical suspicion of an IPMN were included from October 1997 until November 2013. This included 972 patients from Mayo Clinic, 95 from San Raffaele Hospital, 87 from San Giovanni Battista Hospital, and 13 from Imola Hospital.

From this cohort, 41 patients were finally excluded from the analysis due to a pathological diagnosis different from IPMN after surgical resection, leading to a final study sample of 1126 patients (Fig. 1). Overall, the median age was 70.6 years, the median BMI was 25.9, and females were slightly predominant (61%). Eighty-one percent of the study cohort had a EUS performed in their initial visit, followed by MRI (5%) and CT (3%). Two hundred fifty-four patients (23%) had a FNA-based IPMN diagnosis in their first visit. A total of 84 patients (7.5%) were diagnosed with either HGD or IPMN-derived invasive carcinoma (29 cases [2.5%] and 55 cases [4.7%], respectively). The mean time of the incidental cases (>3 months

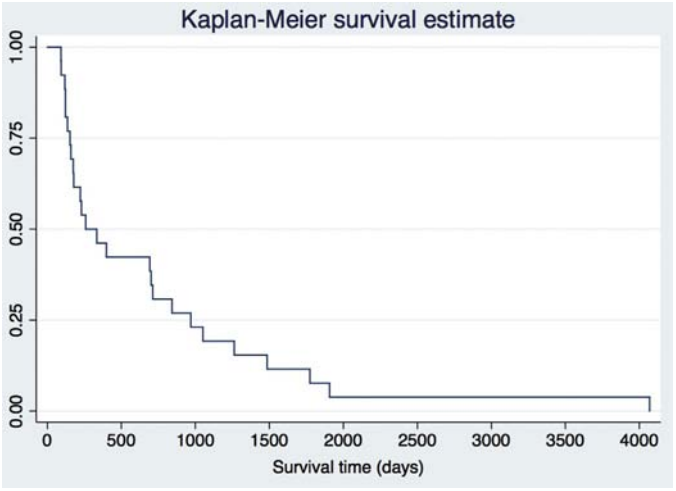

Fig. 2. Kaplan–Meier curve of the incidental malignant cases ($n = 26$).

since diagnosis) between the first visit and the surgical resection was 702 days (interquartile range of 816 days; Fig. 2).

3.1. Demographic factors

Demographic characteristics depending on the site of service are shown in Table 1. Statistically significant differences were shown between age, BMI, race and smoking history. However, the outcome was not associated with the enrolling centre.

3.1.1. Univariate analysis

Final comparisons were made between the malignant and the control group, showing no statistically significant differences between gender, age, BMI, race, or alcohol consumption (Table 2).

However, regarding the smoking history, former or current smoking was significantly associated with malignancy in IPMN compared to never having smoked (relative risk of 1.3 [95% CI of 1.1–1.6]).

3.2. Cyst features

The number of cysts was not associated with malignancy. When describing their location, the head and the body of the pancreas were overall the most frequently reported, with similar percentages noted in both groups. Regarding the cyst size, the long and the short axis were independently considered for the analysis. Both variables were related with malignancy. Larger cysts were strongly related with higher risk of developing neoplasia. The presence of nodules was also strongly associated with malignancy with risk increasing as the size of the nodule increased (Table 2). The same results were seen after excluding the patients with a high, but non-confirmed, malignant suspicion ($n = 47$) from the control group (Supplementary Tables 1 and 2).

Finally, main duct type and the mixed type were more frequently described in the malignant group. Also, the relative risk value resulted after comparing the main duct involvement, (pure main duct IPMN [MD-IPMN] and mixed type), *versus* branch duct IPMN (BD-IPMN) was 3.3 (95% CI of 2.6–4.0).

In the secondary analysis performed in isolated branch duct involvement ($n = 856$), we obtained the same conclusions: larger cyst size, presence of nodules, and larger nodules were risk factors for malignancy (Table 3).

3.3. Clinical factors

Overall, the presence of pancreas-specific signs or symptoms (steatorrhea, jaundice, acute pancreatitis, and diabetes mellitus), as well as weight loss, were significantly more frequent in the malignant disease group (Table 2).

3.4. Multivariate analysis

In the multivariate analysis of the epidemiological and clinical variables, a total of 269 patients were excluded due to the presence of at least one missing value in any of the groups. Therefore, a final sample of 857 patients (76% of the study cohort) was included.

Overall, the presence of symptoms and, more specifically, jaundice were strongly related with malignancy. However, when the same analysis was performed in the two subgroups depending on the duct involvement, the presence of symptoms was the only risk factor in BD-IPMNs (Table 4).

4. Discussion

Our study suggests that imaging features, such as main duct involvement, mural nodules, and specific pancreatic symptoms such as steatorrhea or jaundice, are associated with malignancy in IPMN. It further adds that higher BMI and any tobacco exposure are significant risk factors.

The current IPMN guidelines [7–10] have provided a valuable framework for management, but were largely based on limited clinical data and expert opinion. Despite the recent progress in the diagnostic techniques for pancreatic cystic neoplasms (PCNs), the reported agreement between the preoperative diagnosis and the histology (68–78%) [11,12] continues to be insufficient.

The current consensus guidelines, strongly recommend surgical resection when a MD-IPMN is identified, especially if there is a duct dilation of more than 9 mm. In contrast, when a BD-IPMN is diagnosed, the management strategy remains uncertain.

In the Fukuoka consensus guidelines, the incidence of malignancy in surgically resected BD-IPMN cases was noted in 24.4% [10]. This led to the conclusion that, although the risk of malignancy progression is still present, many of these lesions may be treated conservatively.

In these same guidelines, cyst characteristics grouped in "high-risk stigmata" and "worrisome" features were defined to stratify the risk of malignancy. Globally, the presence of mural nodules, cyst size $\geq$3 cm, thickened cyst walls, and enhanced solid component within the cyst were considered risk factors for neoplasia.

Many studies have evaluated the utility of these features with different outcomes. A meta-analysis published by Anand et al. that included 41 articles (3304 surgically resected BD-IPMN) [13] concluded that a cyst size greater than 3 cm was the most associated risk factor for malignancy (OR 62.4), followed by the presence of mural nodules (OR 9.3). However, another meta-analysis performed by Kim et al. that included 23 studies based on surgical IPMN cohorts [14] showed that the most suggestive imaging finding for malignant BD-IPMN was the presence of mural nodules (Diagnostic Odds Ratio [DOR] 6.0) followed by MPD dilation $\geq$5 mm (DOR 4.4). Cyst size over 3 cm had a weak diagnostic value as an indicator of malignancy. These last results were mostly validated by Jang et al. in a recent retrospective study that included 350 patients who underwent BD-IPMN resection [15]. In their study, both presence of nodules and MD dilation above 5 mm, were predictors of malignancy. In accordance with their results, cyst size was not even related with malignancy progression.

Regarding the overall utility of the Sendai consensus guidelines in the management of BD-IPMNs, Goh et al. recently published a

Table 1
Demographic characteristics based on the site of service.

Demographic factors	Mayo Clinic in Jacksonville, FL	Italian Centers	*p* value
Gender (*n*)	936	190	0.61[b]
Male	356 (38.0%)	76 (40.0%)	
Age (*n*)	936	186	<0.001[a]
Mean (years) ± SD	69.9 ± 10.5	66.9 ± 9.5	
BMI (*n*)	835	65	0.004[a]
Mean ± SD	26.9 ± 5.6	24.8 ± 3.9	
Race (*n*)	936	190	<0.001[c]
White	851 (90.9%)	189 (99.5%	
Black/African American	54 (5.8%)	0 (0%)	
Asian	9 (1.0%)	0 (0%)	
Native American	1 (0.1%)	0 (0%)	
Other	5 (0.5%)	0 (0%)	
Unknown	16 (1.7%)	1 (0.5%)	
Family history of pancreatic cancer (*n*)	930	183	0.002[c]
Yes	67 (7.2%)	3 (1.6%)	
Smoking history (*n*)	934	178	<0.001[b]
Never smoked	470 (50.4%)	126 (70.8%)	
Previous smoker	401 (43.0%)	38 (21.3%)	
Current smoker	62 (6.6%)	14 (7.9%)	
Pack/Year (*n*)	796	52	0.002[a]
Mean ± SD	13.2 ± 23.6	23.7 ± 20.4	
Outcome (*n*)	936	190	0.21[a]
Invasive/HGD	74 (7.9%)	10 (5.3%)	
Control group	862 (92.1%)	180 (94.7%)	

BMI, body mass index; HGD, high grade dysplasia; *n*, number; SD, standard deviation.
[a] Two-tailed *T* test.
[b] Chi-squared test.
[c] Fisher's exact test.

systematic review that included twelve studies of IPMN surgical cohorts [16]. Overall, the positive predictive value ranged between 11% and 52% while the negative predictive value was between 71% and 100%. These results mean that at least 70% of the resected cases were IGD or LGD and 10% of the benign-considered lesions were actually malignant.

In the current study, we have addressed these matters studying a large, IPMN-focused cohort. Overall, the prevalence of malignancy is slightly higher with that recently reported by Wu et al., where a percentage of 2.9% was noted [17].

The increased malignancy found in our cohort is probably due to our aim of focusing only on IPMN lesions, whereas in the Wu et al. study all PCNs were analysed (including serous cysts that have lower rates of malignancy).

When analysing the whole cohort in terms of gender, the predominance of females (61.63%) is remarkable due to the traditionally described equality of genders in the distribution of IPMNs [18]. However, when observed separately, both genders are almost equally described in the malignancy group. Therefore, this difference between genders may represent a selection bias in the control group, where the suspicion of IPMN is only clinical and other PCNs may also have been included in the analysis. The median age (70.6 years) corroborates literature findings that consider age as a risk factor for developing IPMN [19].

When the whole cohort was analysed separately depending on the site of service, (Mayo Clinic *versus* Italian centres), a significant difference was shown in race. This was an expected outcome due to the characteristic Caucasian predominance of the Italian population. Also, the variable age showed differences between the two groups. However, both mean values were comprised between the decade of 60–70 years old, when IPMNs are mostly described. Despite these differences noted in the risk factors, no association was shown between the centre and the outcome. Both groups had very similar proportions of malignancy lesions, showing, therefore, no evidence of confounding.

Regarding the environmental factors, the alcohol consumption was not a risk factor for malignancy development. In contrast, a strong relationship with neoplastic outcomes was found in the case of patients with a positive smoking history. A recent study by Capurso et al. analysed risk factors for development of IPMN [20]. In this study, 390 patients with certain or highly probable diagnosis of IPMN were compared with control patients (patients followed in the Gastroenterology Department for other disorders). When comparing both groups, neither alcohol consumption nor smoking history was considered a risk factor for IPMN development. Based on these contradictory findings, further studies are needed to confirm if a positive smoking history alone has a role in the malignant progression of IPMN.

Neither the number nor location of cysts was a risk factor for malignancy. Cyst size, however, is one of the most controversial predictors of malignancy. Sadakari et al. conducted a study with BD-IPMN to elucidate the role of cyst size as a malignant predictor independent of other variables, such as mural nodules [21]. In their study, they included 73 patients with flat BD-IPMN, concluding that cysts of more than 30 mm in size, were more likely to be malignant than the smaller ones. Herein we corroborate these results. Malignant cysts were clearly correlated with larger size (mean long axis of 29.9 mm and mean short axis of 23.6 mm in the neoplastic group *versus* 17.5 mm and 13.3 mm respectively, in the control group). However, a growing body of evidence suggests that, if present alone without other "worrisome features", such as mural nodules or MPD dilation, cysts of more than 30 mm can be managed conservatively under a strict programme of surveillance [10,22].

In the malignant group, there was a higher prevalence of main duct involvement. This was an expected result as the contribution of the MPD dilation as a risk factor in the development of malignancy is a common point of agreement in the current literature [10,23–27].

Recently, many articles have corroborated mural nodules as a risk factor for malignancy [13,14,28,29], including our study. In

Table 2
Demographic, imaging, and clinical factors.

Variables	Invasive/HGD	Control group	*p* value	Relative risk [CI 95%]
Gender (*n*)	84	1042	0.07[b]	
Male	40 (47.6%)	392 (37.6%)		
Age (*n*)	84	1038	0.87[a]	
Mean (years) ± SD	69.6 ± 8.4	69.4 ± 10.6		
BMI (*n*)	57	883	0.37[a]	
Mean ± SD	27.3 ± 5.1	26.7 ± 5.5		
Race (*n*)	84	1042	0.25[c]	
White	77 (91.7%)	963 (92.4%)		
Black/African American	3 (3.6%)	51 (4.9%)		
Asian	0 (0%)	9 (0.9%)		
Native American	0 (0%)	1 (0.10%)		
Other	0 (0%)	5 (0.5%)		
Unknown	4 (4.7%)	13 (1.2%)		
Family history of pancreatic cancer (*n*)	83	1030		
Yes	7 (8.4%)	63 (6.1%)	0.40[b]	
Smoking history (*n*)	83	1028	0.03[b]	
Never smoked	33 (39.8%)	536 (54.8%)		
Previous smoker	42 (50.6%)	397 (38.6%)		
Current smoker	8 (9.6%)	68 (6.6%)		
Pack/Year (*n*)	69	779	0.70[a]	
Mean ± SD	14.9 ± 14.5	13.7 ± 24.0		
Alcohol consumption (*n*)	75	931		
Mean (glass/day) ± SD	0.6 ± 1.0	0.8 ± 1.9	0.27[a]	
Cyst number (*n*)	72	993	0.26[a]	
Mean ± SD	2.7 ± 5.4	3.5 ± 5.8		
Cyst long axis (*n*)	59	963	<0.001[a]	
Mean (mm) ± SD	29.9 ± 16.5	17.5 ± 11.8		
Cyst short axis (*n*)	43	659	<0.001[a]	
Mean (mm) ± SD	23.6 ± 12.5	13.3 ± 10.1		
Cyst location (*n*)	73	987	0.53[b]	
Head	32 (43.8%)	351 (35.6%)		
Uncinate	8 (11.0%)	106 (10.7%)		
Body	23 (31.5%)	365 (37.0%)		
Tail	10 (13.7%)	165 (16.7%)		
Presence of nodules (*n*)	83	1030	<0.001[b]	4.5 [3.3–6.1]
Yes	35 (42.2%)	97 (9.4%)		
Nodule size (*n*)	28	61	0.004[d]	
Mean (mm) ± SD	21.3 ± 12.1	14.5 ± 14.4		
Duct involved (*n*)	82	1020	<0.001[b]	3.3 [2.6–4.0]
Main duct	22 (26.8%)	60 (5.9%)		
Branch duct	31 (37.8%)	825 (80.9%)		
Both	29 (35.4%)	135 (13.2%)		
Presence of symptoms (*n*)	84	1036	<0.001[b]	1.8 [1.6–2.1]
Yes	61 (72.6%)	413 (39.9%)		
Steatorrhea (*n*)	84	1042	0.01[c]	4.8 [1.7–13.1]
Yes	5 (6.0%)	13 (1.2%)		
Jaundice (*n*)	84	1042	<0.001[b]	10.5 [4.9–22.7]
Yes	11 (13.1%)	13 (1.2%)		
Weight loss (*n*)	84	1042	0.001[b]	2.0 [1.3–2.9]
Yes	22 (26.2%)	138 (13.2%)		
Abdominal pain (*n*)	84	1042	0.09[b]	1.3 [1.0–1.7]
Yes	34 (40.5%)	329 (31.6%)		
Acute pancreatitis (*n*)	83	1030	<0.001[b]	11.4 [9.0–14.5]
Yes	68 (18.1%)	74 (7.2%)		
Diabetes mellitus (*n*)	84	1042	0.01[b]	1.7 [1.2–2.6]
Yes	22 (26.2%)	157 (15.1%)		

BMI, body mass index; CI, confidence interval; HGD, high grade dysplasia; *n*, number; SD, standard deviation.
[a] Two-tailed *T* test.
[b] Chi-squared test.
[c] Fisher's exact test.
[d] Wilcoxon rank-sum test (Mann–Whitney).

Table 3
Cyst features in branch duct intraductal papillary mucinous neoplasms.

Variable	Invasive/HGD	Control group	P value	Relative Risk [CI 95%]
BD-IPMN (*n*)	31	825		
Cyst number (*n*)	27	804	0.39[c]	
Mean ± SD	4.0 ± 6.9	3.4 ± 5.5		
Cyst long axis (*n*)	28	803	<0.001[c]	
Mean (mm) ± SD	27.4 ± 16.3	16.8 ± 11.2		
Cyst short axis (*n*)	21	542	<0.001[c]	
Mean (mm) ± SD	21.1 ± 12.4	12.6 ± 9.5		
Cyst location (*n*)	30	810	0.78[a]	
Head	9 (30.0%)	275 (34.0%)		
Uncinate	3 (10.0%)	97 (12.0%)		
Body	11 (36.7%)	305 (37.6%)		
Tail	7 (23.3%)	133 (16.4%)		
Presence of nodules (*n*)	31	819	<0.001[b]	5.1 [3.1–8.5]
Yes	12 (38.7%)	62 (7.6%)		
Nodule size (*n*)	8	43	0.01[c]	
Mean (mm) ± SD	26.0 ± 13.4	13.0 ±13.9		

BD-IPMN, branch duct intraductal papillary mucinous neoplasms; CI, confidence interval; HGD, high grade dysplasia; *n*, number; SD, standard deviation.
[a] Fisher's exact test.
[b] Chi-squared test.
[c] Wilcoxon rank-sum test (Mann–Whitney).

our results, both the presence and the size of the mural nodules were strongly related with neoplasia. However, a recent publication by Kobayashi et al., showed data supporting observation instead of immediate resection in BD-IPMN with mural nodules less than 10 mm in height [30].

The presence of symptoms has already been contemplated as an important risk factor. However, apart from the presence of obstructive jaundice, no differentiation between specific symptoms has been reported to our knowledge.

It has been postulated that not all symptoms harbour the same malignant potential, but few studies have specifically addressed this issue. In the meta-analysis carried out by Anand et al., the presence of symptoms appeared to be the least significant marker of malignancy [13]. However, the authors already discussed about the bias that the absence of the description of each symptom may have produced in their results. Herein, an *ad hoc* stratified analysis was performed to address this matter. We confirm that the presence of symptoms in general is an important risk factor for malignancy, but when analysed separately, not all symptoms had the same relevance.

As expected, pancreas-related symptoms, such as steatorrhea, jaundice, diagnosed acute pancreatitis, or diabetes mellitus, were more frequently seen in patients with malignant disease. However, only steatorrhea and jaundice were good predictors of malignancy in the multivariate analysis. On the other hand, abdominal pain did not seem to be useful to discriminate malignant cases albeit with diverging results depending on whether we excluded cases with highly suspicious but not pathologically confirmed cancer. This is a remarkable fact as this symptom, is a quite nonspecific and common clinical complaint in daily practice. If misinterpreted, it could lead to the performance of unnecessary tests or even surgical procedures, with the subsequent economical expenses and comorbidities. Given the uncertainty of this issue even within our own study, we suggest that abdominal pain should continue to be considered a possible risk factor for malignancy.

There are several limitations in this study. The most significant one is inherent to the study design. In the control group, we included patients with a high clinical suspicion of an IPMN lesion based on the imaging findings. But, as mentioned previously, the concordance between the imaging findings and the histological

Table 4
Demographical and clinical risk factors on univariate and multivariate analysis.

Risk factor	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Whole cohort (*n* = 857)				
BMI	1.0 (1.0–1.1)	0.07	1.1 (1.0–1.1)	0.01
Smoking history	1.7 (1.1–2.8)	0.03	1.9 (1.1–3.1)	0.02
Symptoms	3.8 (2.2–6.6)	<0.001	3.4 (1.9–6.0)	<0.001
Jaundice	0.1 (0–0.2)	<0.001	0.1 (0–0.3)	<0.001
Steatorrhea	0.2 (0.1–0.6)	0.003	0.3 (0.1–0.8)	0.02
BD-IPMN subcohort (*n* = 655)				
Symptoms	3.8 (2.2–6.6)	<0.001		
MD/mixed IPMN subcohort (*n* = 185)				
Age	1.0 (0.9–1.0)	0.04	1.0 (0.9–1.0)	0.05
BMI	1.1 (1.0–1.2)	0.01	1.1 (1.0–1.2)	0.002
Symptoms	2.8 (1.3–6.2)	0.01	2.7 (1.1–6.2)	0.02
Jaundice	0.2 (0.1–0.6)	0.01	0.2 (0.1–0.7)	0.01
Steatorrhea	0.1 (0.0–0.8)	0.03	0.1 (0.0–0.7)	0.02

BD-IPMN, branch-duct intraductal papillary mucinous neoplasms; BMI, body mass index; CI, confidence interval; MD IPMN, Main duct intraductal papillary mucinous neoplasms; *n*, number.

report is still insufficient. Therefore, we cannot assure that all PCNs included in this group are IPMN lesions. On the other hand, the weakest point of this study is also one of its main strengths, as in the current literature most of the IPMN cohorts studied are surgical cohorts which may be overestimating their malignant potential due to a selection bias. Hence, it is crucial to expand our knowledge in the benign-appearing IPMN lesions, which are the majority seen in daily practice, to avoid over-treating. Also, in order to be as specific as possible, we only included patients with a pathological confirmation of malignancy. This means that some patients with high-risk lesions who did not undergo surgery may have been included in the control group. To address this matter, we performed a secondary analysis excluding these patients ($n=47$) that showed the same results except for the variables abdominal pain and steatorrhea.

As this was a retrospective study, the imaging techniques used to define the cyst features differed between patients. Despite this, we tried to be as homogenous as possible, following a specific order of preference when not all techniques were available. In addition, we could not include all patients in the multivariate analysis due to missing data on some important variables. The results of the univariate analysis (which included cyst size, main/side branch involvement and mural nodules, and found these to be associated with malignancy) could not be confirmed or excluded in the multivariate analysis.

Major strengths of the current study are its large size, multicentre involvement in both the US and Europe, and rigorous focus on IPMN. It is also one of the longest cohort studies of suspected IPMN.

In summary, in this large, international registry we considered only cases with a proven pathological diagnosis or a high clinical suspicion of IPMN, comparing the malignancy group (HGD lesions and invasive carcinoma) to the control group.

Herein, we confirm that the presence of pancreas-related symptoms (especially jaundice and steatorrhea), a high BMI and a positive smoking history are significantly associated with malignancy in IPMN. Moreover, we corroborate current IPMN consensus guidelines regarding the risk factors for cyst features, such as cyst size, main duct involvement, and presence and size of mural nodules.

Conflict of interest

MBW receives grant funding from Olympus, Boston Scientific, and Cosmo Pharmaceuticals. None of the other authors have conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.03.007.

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Diagnostic Accuracy of Endoscopic Ultrasound-Guided Fine-Needle Aspiration Cytology, Carcinoembryonic Antigen, and Amylase in Intraductal Papillary Mucinous Neoplasm

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Objectives: The aim of this study was to determine the accuracy of cytology, carcinoembryonic antigen (CEA), and amylase levels in the preoperative diagnosis of intraductal papillary mucinous neoplasms (IPMNs).

Methods: An international registry was started in 2005 and included patients with clinically suspected IPMNs. Those who underwent surgery and had preoperative endoscopic ultrasonography fine-needle aspiration were selected for the study.

Results: One hundred eighty patients were included. Cytological analysis for neoplastic cells in IPMNs showed high specificity (87.8%) but low sensitivity (39.4%). The median CEA level was 525.5 ng/mL (n = 78) in IPMNs versus 9.7 ng/mL in nonmucinous cysts (n = 6), showing an area under the receiver operating characteristic curve (AUC) of 0.87. The optimal cutoff CEA value for distinguishing IPMN from nonmucinous cysts was 129 ng/mL. At this level, the sensitivity was 76.9%, and specificity was 83.3%, yielding a positive predictive value of 95.9% and a negative predictive value of 41.9%. Carcinoembryonic antigen was a poor predictor of neoplasia in IPMNs (AUC = 0.55). Amylase did not distinguish IPMNs from mucinous cystic adenomas (MCAs) (median, 3759 U/L [n = 28 IPMNs] and 497 U/L [n = 3 MCAs], AUC = 0.65).

Conclusions: Cytology has a limited role because of its lack of sensitivity. Carcinoembryonic antigen modestly differentiated between mucinous and nonmucinous lesions. Amylase did not distinguish IPMNs versus MCAs.

Key Words: cyst, EUS, IPMN, sensitivity, specificity

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Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are a recently described entity that has considerable clinical importance because of its malignant potential. Intraductal papillary mucinous neoplasms can be classified into low-grade dysplasia (LGD), intermediate-grade dysplasia, high-grade dysplasia (HGD), or invasive carcinoma.[1] At present, the only accepted method of treatment is surgical resection. Such an aggressive approach presents a clinical dilemma because only a small proportion of IPMNs are malignant, and most are diagnosed in asymptomatic patients.[2] Therefore, the main challenge regarding IPMNs is to correctly diagnose and risk stratify these lesions before any management decision is taken.

Publication of the consensus guidelines in 2006,[3] which were updated in 2012,[4] provided a valuable management algorithm based on the imaging and clinical findings. Although this consensus guideline advanced IPMN knowledge, the studies that have followed that publication have highlighted the limitations of the guidelines.[5] Overall, the preoperative diagnostic accuracy, which is based on conventional imaging and endoscopic ultrasonography (EUS), is still not optimal (80.7% in both main-duct [MD-IPMN] and mixed-type IPMN, 72% in branch-duct IPMN [BD-IPMN][6]). Endoscopic ultrasonography–guided fine-needle aspiration (FNA) has been shown to be a useful tool that complements the imaging techniques,[7,8] but in the current guidelines, its role is still limited.[4] Elevated cyst fluid amylase has been proposed to identify lesions directly connected to the pancreatic duct, including IPMNs, and distinguish those from mucinous cystic adenomas (MCAs). This is a clinically important distinction because surgery is generally recommended for all MCAs, whereas it is recommended only for high-risk IPMNs.[4,9]

Following the hypothesis that cyst fluid analysis can provide essential information to characterize IPMN lesions, the aim of this study was to determine the accuracy of cytology, carcinoembryonic antigen (CEA), and amylase levels as preoperative tests for the differential diagnosis between IPMNs and non-IPMN cysts, as well as distinguish malignancy among IPMNs.

MATERIALS AND METHODS

The study was approved by the Mayo Clinic Institutional Review Board as well as the Human Safety Committee of each participating center.

Study Design and Population

This was a retrospective, descriptive study using an international IPMN registry that was started in 2005. This registry involved a total of 4 centers: 3 in Italy (San Raffaele Scientific Institute [Milan], Azienda Universitario-Ospedaliera San Giovanni Battista [Torino], University of Bologna/Hospital of Imola [Imola]) and 1 in the United States (Mayo Clinic, Jacksonville, Fla).

A manual review of the electronic medical records of each center was performed to build the registry. To narrow the search, the terms "pancreatic cyst" and "IPMN" were used to select the potential candidates. All patients who were clinically suspected to have an IPMN, which was defined as the presence of a dilated

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main pancreatic duct (≥5 mm) or a cystically dilated branch duct (≥5 mm), were entered in the registry. From these patients, those who underwent surgical resection were identified, and only the patients who had an EUS-guided FNA of the pancreatic cyst performed before the surgery were included in the analysis.

Study Variables

For the cyst features, the imaging technique (magnetic resonance imaging, computed tomography scan, or EUS) performed during the initial visit was included. If more than 1 imaging technique was done in the same visit, we first reviewed EUS data (as other EUS-dependent variables were also registered in the data form), then the magnetic resonance imaging scans, and finally computed tomography scan. If there was involvement of both the main and branch ducts, then these patients were categorized into the main duct group for analysis. In case of multiple cysts, the features of the largest cyst were reported. The cyst size was determined by the maximum dimensions measured on both the major and the minor axes. Mural nodules were considered present if they were described in the final imaging report.

Immediate processing and interpretation were not routinely requested for cyst-fluid cytology. The standard procedure in the cytology laboratories involved consisted of centrifugation of the standard specimens to prepare cellblocks and staining with the Papanicolaou stain for cytologic assessment. Cell blocks were also prepared with harvested tissue fragments. In addition, tissue sections were obtained and stained with hematoxylin-eosin for histological assessment. Histological sections were evaluated by a pathologist who was not blinded to the results. They were confirmed by a second pathologist if an HGD lesion or a carcinoma was suspected. For this study, the final reviewed reports were classified as either negative or positive following guidelines' recommendation.[10] Only those reports with a conclusive interpretation were considered as diagnostic. Pancreatic cyst fluid was also sent for measurements of CEA and amylase concentrations in those cases where enough cyst fluid was still available after cytological analysis. If the values were present in the clinical charts, they were collected and added to the registry.

Statistical Analysis

Study data were collected and managed using REDCap database (Research Electronic Data Capture, Nashville, Tenn; hosted by Mayo Clinic). The Stata 13 software for Mac OS X Lion (Stata Inc, College Station, Tex) was used for the analysis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for each test separately and in combination. In the case of the CEA concentrations, an optimal cutoff value based for the study cohort was used to calculate the sensitivity and specificity. The receiver operating characteristic curve was calculated, and the area under the curve (AUC) was noted for both CEA concentrations and amylase levels.

RESULTS

A total of 1167 patients from October 1997 until September 2014 were entered in the registry. This included 972 patients from the Mayo Clinic, 95 from San Raffaele Hospital, 87 from San Giovanni Battista Hospital, and 13 from Imola Hospital.

Two hundred thirty-seven patients underwent pancreatic surgical resection due to a suspicion of malignancy. From this surgical subgroup, 180 patients (168 from Mayo Clinic, 7 from Milan, 3 from Torino, and 2 from Imola) had a previous EUS-FNA of the pancreatic cyst and were included in the analysis.

Demographic and clinical characteristics of the study population are shown in Table 1. Overall, there was a higher prevalence of white female patients, and the mean age was 68 years. The proportion of patients with a positive smoking history was also slightly higher than the proportion of never smokers (58% vs 42%, respectively). Regarding the cyst features, a mean of 3 pancreatic cysts per patient were described in the preoperative imaging reports. The mean size was 2.5 cm, and the most common location was the pancreatic body followed by the head. Branch-duct IPMNs were more numerous (59%) than both MD-IPMNs and mixed-type IPMNs (16% and 25%, respectively). For the clinical factors, the proportion of symptomatic patients was only slightly higher than the asymptomatic patients. When analyzed separately, abdominal pain was the most common symptom followed almost equally by the presence of diabetes mellitus and weight loss. Other symptoms, especially steatorrhea and jaundice, were rare.

The surgical procedure was recorded in 139 patients (77% of the cohort). Distal pancreatectomy and pylorus-preserving pancreaticoduodenectomy were the most common procedures (23%

TABLE 1. Demographic and Clinical Variables

Variable (n)	Study Cohort, n (%) or Mean (SD)	
Sex (141)	Male	58 (41.1)
	Female	83 (58.9)
Age (y) (180)	Mean (SD)	67.6 (9.2)
Race (180)	White	165 (91.7)
	African American	8 (4.4)
	Asian	2 (1.1)
	Unknown	5 (2.8)
Body mass index (kg/m^2) (164)	Mean (SD)	27.7 (5.6)
Smoking history (177)	Never smoked	75 (42.3)
	Previous smoker	86 (48.6)
	Current smoker	16 (9.0)
No. of cysts (171)	Mean (SD)	3.2 (5.8)
Location of largest lesion (167)	Head	54 (32.3)
	Uncinate	10 (6.0)
	Body	68 (40.7)
	Tail	35 (21.0)
Cyst long axis (mm) (154)	Mean (SD)	24.7 (14.3)
Nodules described (178)	No	121 (68.0)
	Yes	57 (32.0)
Nodule size (mm) (39)	Mean (SD)	18.2 (11.7)
Duct involved (174)	Main duct	28 (16.1)
	Branch duct	103 (59.2)
	Both	43 (24.7)
Presence of symptoms (180)	No	80 (44.4)
	Yes	100 (55.6)
Steatorrhea (180)	No	176 (97.8)
	Yes	4 (2.2)
Jaundice (180)	No	168 (93.3)
	Yes	12 (6.7)
Weight loss (180)	No	147 (81.7)
	Yes	33 (18.3)
Abdominal pain (180)	No	112 (62.2)
	Yes	68 (37.8)
Acute pancreatitis (177)	No	153 (86.4)
	Yes	24 (13.6)
Diabetes (180)	No	144 (80.0)
	Yes	36 (20.0)

and 22% of the cases, respectively) followed by subtotal pancreatectomy (13%) and Whipple procedure (12%). The majority of the surgical resections (91%) were carried out in less than 6 months from the initial visit, which included all the invasive IPMNs and HGD lesions of this cohort. The pathological report of the surgical specimens revealed that 83% of the resected lesions were IPMNs (44% LGD and 39% malignant lesions [14% HGD and 25% invasive IPMNs, respectively]) (Fig. 1).

When only IPMN-confirmed lesions were considered, the cytology of the cyst fluid had a sensitivity of 39%, specificity of 88%, PPV of 76%, and NPV of 60% for the diagnosis of malignancy (HGD/invasive IPMN). Overall, the accuracy of the test was 64% (Table 2). Carcinoembryonic antigen and amylase values were analyzed separately depending on the surgical pathology (details are shown in Table 3). Overall, CEA showed an AUC of 0.88 when discriminating between IPMNs and nonmucinous lesions (Fig. 2). Carcinoembryonic antigen also showed good diagnostic accuracy for differentiating between mucinous lesions (both IPMNs and MCAs) and nonmucinous lesions (AUC = 0.87). The optimal cutoff value for CEA when diagnosing IPMNs versus nonmucinous lesions was 129 ng/mL. At this value, the sensitivity was 77%, and the specificity was 83%, which yielded a PPV of 96% and NPV of 42%. The PPV and NPV obtained with these sensitivity and specificity values in the clinically suspected IPMN cohort (n = 1126) are shown in Supplemental Table 1, http://links.lww.com/MPA/A468. The same CEA cutoff value was seen if all mucinous cysts were analyzed, including MCAs (n = 7). The accuracy of the widely used standard of 192 ng/mL was also evaluated; the closest evaluable cutoff in our cohort was 194 ng/mL, and it showed a slightly lower sensitivity (72%) and the same specificity (83%). Because of the multicenter nature of the study and the fact that different laboratories performed CEA analysis, we also did a subanalysis that included only the Mayo Clinic patients, and it showed the same optimal CEA cutoff value of 129 ng/mL (sensitivity of 76% and specificity of 83%). Carcinoembryonic antigen was poor for predicting the grade of malignancy for IPMNs and had an AUC of 0.55. Despite the differences noted in the median amylase levels between IPMN and MCAs (3759 vs 497 U/L, respectively), this test did not distinguish between these 2 types of lesions, showing an AUC of 0.65. The results for amylase concentrations to discriminate mucinous and nonmucinous lesions were also unsatisfactory (AUC = 0.27).

TABLE 2. Cytology Results in Surgically Resected IPMNs

	Surgical Pathology		
Cytology	**LGD**	**HGD/Invasive IPMN**	**Total**
Positive	9	28	37
Negative	65	43	108
Total	74	71	145

Finally, we performed several analyses to show the combined accuracy of cytology, CEA concentrations, and amylase levels, depending on the nature of the cysts. When IPMNs were compared with the whole cohort, CEA concentrations showed good sensitivity (77%) but low specificity (57%). As expected, if the tests were combined, the specificity increased at the expense of the sensitivity (Table 4). The results of the other cyst subtypes are shown in Supplemental Tables 2 to 4, http://links.lww.com/MPA/A468.

DISCUSSION

We confirm the limited diagnostic role of cytology for IPMNs because of its lack of sensitivity. We also report the modest accuracy of CEA concentrations for differentiating between IPMNs and nonmucinous lesions, specifically in benign-appearing pancreatic cysts. In contrast, amylase levels yielded no diagnostic contribution to differentiating IPMNs from MCAs.

Pancreatic cysts are being discovered in asymptomatic patients with increasing frequency. Proper characterization of these lesions is vital to designing tailored management strategies. Although imaging techniques can be diagnostic of the cyst etiology,[11] their reported accuracies vary greatly depending on the study,[12,13] and this is mainly due to the morphological overlap

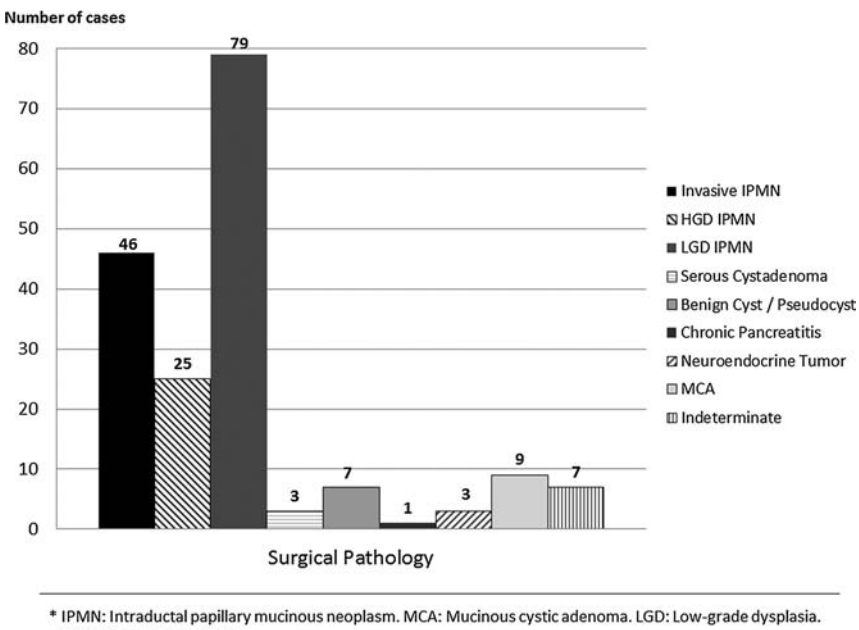

FIGURE 1. Pathology outcomes.

TABLE 3. CEA and Amylase Values

Surgical Pathology	n	Median
CEA, ng/mL		
All IPMNs	78	525.5
Invasive IPMN/HGD IPMN	33	653.0
Invasive IPMN	17	653
HGD IPMN	16	632.0
LGD IPMN	45	404.0
Mucinous cystic adenomas	7	544.7
Nonmucinous lesions	6	9.7
Amylase, U/L		
All IPMNs	28	3759
Invasive IPMN/HGD IPMN	9	1813
Invasive IPMN	5	1813
HGD IPMN	4	2183
LGD IPMN	19	4400
Mucinous cystic adenomas	3	497
Nonmucinous lesions	3	25830

with nonneoplastic cysts. In contrast, EUS has shown an advantage in distinguishing pancreatic cysts,[14] although it is still suboptimal if based only on the appearance of the lesion.[15] Hence, the main strength of EUS is the ability to perform FNA and collect cyst fluid for cytological and biochemical analysis.

In our study cohort, we found some variances from other pure IPMN studies. We found a predominance of female patients with clinically suspected IPMNs. Although IPMNs have been equally described in both genders,[16] the discrepancy in our cohort could be partly explained by the inclusion of serous cystadenomas and MCAs that were ultimately confirmed by surgical histology, even though the preoperative diagnosis was an IPMN. Both lesions have a female predominance. The mean age concurs with what has been previously described in the literature for IPMNs.[17]

TABLE 4. Accuracy of Fluid Tests for the Diagnosis of IPMNs in the Study Cohort

Test	Sensitivity, %	Specificity, %	PPV, %	NPV, %
CEA^+	76.9	57.1	90.9	30.8
CEA^+ $amylase^+$	46.4	83.3	92.9	25.0
$Cytology^+$ $amylase^+$	21.4	87.5	85.7	24.1
CEA^+ $cytology^+$ $amylase^+$	21.4	83.3	85.7	18.5

CEA^+: CEA value 129 ng/mL or greater; $cytology^+$: intracellular mucin present; $amylase^+$: amylase value 1326 U/L or greater (optimal cutoff value for IPMN).

Overall, the cyst features of the cohort vary somewhat from what is now considered a high-risk cyst. The mean size was less than 3 cm, a high proportion of cysts did not show any mural nodules (68%), and BD-IPMNs were more numerous than MD-IPMNs and mixed-type IPMNs. Although these findings may now seem quite surprising in an IPMN surgical cohort, our population comprises a period that begins in 1997 when IPMNs were first described,[18] and surgical resection was the main management option. On the other hand, the overall low-risk appearance of these cysts provides added strength to our study because it may reduce the selection bias associated with a series where surgery was performed only on the highest-risk lesions. The main management dilemma lies precisely in those lesions that do not show any high-risk feature.

Our cohort included nearly equal proportions of patients who were symptomatic or asymptomatic, allowing a robust analysis of the predictive value of symptoms. The presence of symptoms is a well-established risk factor of malignancy and has been discussed in the Sendai Guidelines. However, not all symptoms harbor the same grade of malignancy. In a recent study performed by our group on the entire cohort of patients with suspected IPMN (n = 1126), abdominal pain was not significantly associated with

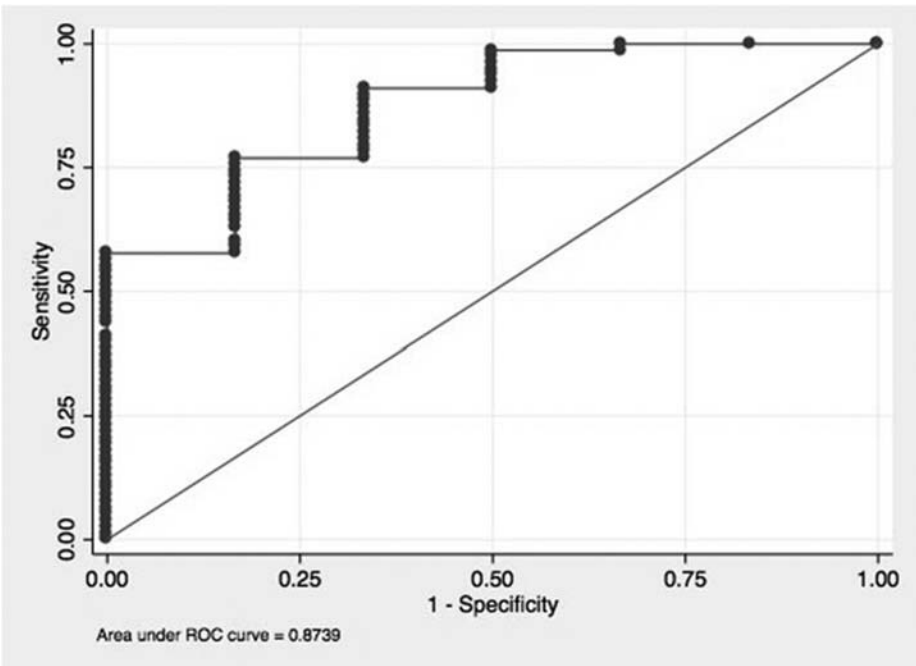

FIGURE 2. Receiver operating characteristic curve for CEA values discriminating IPMN versus nonmucinous lesions.

malignancy, whereas pancreatic-related symptoms were associated with it.[19]

Our study also provides insight into the limitations of clinical diagnostic and prognostic accuracy. The overall clinical diagnosis of IPMNs had only modest accuracy because only 83% of patients were confirmed to have IPMN by the final histology. Assuming that a suspicion of advanced neoplasia led to the choice of surgery, only 39% were found to harbor HGD or invasive IPMN. This highlights the limitations of our clinical and cyst fluid selection criteria, even among a highly experienced group of pancreatologists. Del Chiaro et al[20] determined the accuracy of a pancreatic multidisciplinary conference that was based on a clinical evaluation, imaging modalities, and the concerted opinion of the team members in diagnosing pancreatic cystic neoplasms and found that when IPMNs were analyzed independently the accuracy of the clinical diagnosis was 78.1%. No further classification regarding the grade of IPMN dysplasia was shown, but the authors stated that all IPMNs fulfilled the criteria for resection. Recent studies[21–23] have highlighted that even strict application of the consensus criteria to select patients for surgery has very modest accuracy.

The cytological accuracy in our study was also very modest. Pitman et al[24] reported a sensitivity of 72% and a specificity of 85% to predict HGD or invasive carcinoma in mucinous cysts, which was a better result than the sensitivity of 40% found in our study. This may be due to differences in definition and subjectivity of a positive FNA cytology. Pitman and colleagues'[24] study defines positive FNA cytology as "the identification of high-grade atypical epithelial cells," and our study has defined it as "the presence of sufficient quantity and quality of atypia to diagnose a malignant neoplasm." Genevay et al[25] found a sensitivity of 77% and a specificity of 80% when only IPMNs were analyzed. However, if only small (<30 mm) BD-IPMNs were studied, the sensitivity dropped to 67% with a specificity slightly increased to 88%. Our cohort, which mostly included small cysts, also had a high specificity (88%) and a lower sensitivity value (40%).

Cyst-fluid CEA has proven to be a valuable tool for discriminating mucinous cysts from nonmucinous ones.[26,27] We confirmed these findings after testing this biomarker in both IPMNs only and in all mucinous cysts and compared the results to those of nonmucinous cysts (AUC = 0.87 in both cases). The optimal cutoff CEA value was 129 ng/mL (sensitivity of 77% and specificity of 83%). Brugge et al[7] reported similar results, showing a cutoff value of 192 ng/mL (sensitivity of 75% and specificity of 84%). In our cohort, the closest value to this threshold was 194 ng/mL, and it showed a slightly lower sensitivity (72%) than the values reported by Brugge et al, and our specificity (83%) was almost the same as what was reported by Brugge et al.[7] Despite the recent publications, there is still no consensus regarding the optimal cutoff CEA value.[28–30]

We conclude that CEA should not be solely considered to guide the management strategy because of its lack of discrimination between malignant and benign IPMNs (AUC = 0.55) and particularly its low NPV. To correct a possible underestimation of the NPV due to a selection bias in this study, we calculated the NPV and the PPV for the whole registry cohort of clinically suspected IPMNs under different theoretical prevalence. The results confirmed an insufficient NPV if the IPMN prevalence was higher than 60%. A recent meta-analysis by Ngamruengphong et al[31] showed that the sensitivity and specificity of CEA concentrations were 65% and 66%, respectively, when only mucinous cysts were considered, discouraging the use of CEA concentrations as a unique diagnostic test.

The role of amylase in mucinous pancreatic cysts remains uncertain Theoretically, IPMNs should present higher values of amylase than MCAs because of their communication with the pancreatic ducts. We performed an analysis confronting the amylase values of the IPMNs and the MCAs of our cohort. The results showed an insufficient AUC (0.65), suggesting that amylase was unable to accurately differentiate between IPMNs and MCAs. Park et al[30] reported a significantly lower amylase level in malignant mucinous cysts versus benign mucinous cysts (including both MCAs and IPMNs). We compared the malignant group of IPMNs (HGD and invasive IPMNs) versus the benign group (LGD), and amylase did not show any advantage to discriminating malignancy (AUC = 0.38). Lastly, we performed a receiver operating characteristic analysis for mucinous cysts versus nonmucinous cysts, and the results were also unsatisfactory.

The main limitation to our study is inherent to its retrospective design. As a result, some of the data, especially the symptom-related data, are limited to what was reported in the clinical charts. Therefore, the results may have been underestimated. However, to the best of our knowledge, this is one of the few reported surgical cohorts that focused exclusively on clinically suspected IPMNs. Thus, the majority of the surgical outcomes (83%) were histologically confirmed IPMNs, which validates the results toward a thorough description of the efficacy of the tests for diagnostic purposes. Moreover, this cohort mainly involves lower-risk cysts that are the ones that present the greatest clinical challenges. This analysis allows a more realistic and unbiased approach regarding the cysts seen in daily practice.

In conclusion, cytology was a limited diagnostic tool for IPMNs because of its lack of sensitivity. We were able to use CEA levels to discriminate IPMNs versus nonmucinous lesions with moderate accuracy, and therefore, its use is recommended when the clinical and imaging features are inconclusive. However, CEA should not be used to establish the grade of malignancy among IPMN-suspected lesions. On the contrary, amylase did not show any utility for the diagnosis of IPMN, and it did not provide a benefit for differentiating between MCAs and IPMNs or recognizing malignancy. Considering that the amount of the cystic fluid obtained by EUS-guided FNA is usually quite scarce, the avoidance of this test may provide an opportunity for expanded biomarker discovery in cyst fluid biobanks. Overall, this study emphasized the limited potential of our current diagnostic capabilities for pancreatic cysts and clearly indicated the need for improved diagnostic and prognostic biomarkers to better choose which patient benefits from surgical resection.

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4 DISCUSSION

This work addresses several important aspects regarding PCLs, and more specifically, IPMNs, such as the real prevalence of incidentally found PCLs, the risk factors for malignant progression in IPMNs and the accuracy of routinely performed tests such as cyst fluid cytology, CEA and amylase.

First of all, the study entitled "Association between advances in high-resolution cross section imaging technologies and increase prevalence of pancreatic cysts from 2005 to 2014" aimed to determine the real prevalence of incidental pancreatic cysts in patients undergoing MRI for non-pancreatic indications on increasingly sophisticated MRI systems.

To do so, every MRI performed at the Mayo Clinic in Jacksonville during the months of January and February from 2005 to 2014 were listed. Both the MRI indication and the clinical information from the corresponding patients were chronologically reviewed to select the first 50 suitable candidates in each calendar year. Strict exclusion criteria were applied to eliminate those patients with a positive personal history or/and a current clinical suspicion of pancreatic disease. Once a potential cohort was identified, an expert MRI Radiologist reviewed each study looking for PCLs. At this time, secondary exclusion criteria were applied to eliminate low-quality studies. Whenever an exclusion criterion arose and the corresponding MRI was excluded, a new candidate was added to the study following a strict chronological order.

Of the 500 patients included in the study, 208 patients (which correspond with 42% of the cohort) were fount to have an incidental PCL. However, of these, only 21% of the cases were described in the original report. The most common diagnosis was uncertain (62% of

the cases) followed by a BD-IPMN (35% of the MRIs). No worrisome or high-risk features were described in any cyst. When the demographical variables of the patients with cysts were compared with the rest of the study cohort, a statistically significant association between the presence of cysts and age, diabetes mellitus and the personal history of a pancreatic cancer was observed. Finally, the multivariable analysis showed a strong association between the technical MRI features, such as the hardware platform and the software version, and the presence of cysts. Newer versions corresponded with an increased number of PCLs described in the imaging studies.

This study demonstrates the association between the higher trend of incidentally found pancreatic cysts in the recent years and the development of more sophisticated MRIs. Although we cannot state that this higher trend is solely due to the improvements in the MRI technical features, we can conclude that this factor plays an important role on it, which to our knowledge had not yet been addressed by any study.

The prevalence found in our cohort is significantly high compared to previous publications. Similar recent studies showed prevalence values around 10-14%. One of the factors that may have influenced this variability is the absence of a cyst size limit in our study. Thereby, if a size limit of 5 mm is applied, our prevalence drops to 21% (still higher than previously reported values). Despite the high proportion of patients with an incidental cyst in our study, we believe we may have underestimated the results due to the lack of 3 T MRIs (which correspond with the highest strength of the static magnetic field) and magnetic resonance cholangiopancreatography sequences (which are specifically designed to visualize the pancreatic parenchima).

The adjusted multivariate analysis showed a very strong association between the presence of PCLs and both the hardware platform and software version. These two varia-

bles were analyzed following a chronological order, showing an increased trend in the number of PCLs seen in the MRIs. This confirmed what had been previously postulated but had not yet been studied: the development of newer imaging techniques plays an important role in the dramatic increased number of PCLs diagnosed in the recent years.

Another important point of this study is the high proportion (35% of the MRIs) of presumed BD-IPMNs described in a non-pancreatic population. This finding supports current publications that define this entity as the most commonly diagnosed subtype of PCN. The main challenge regarding these lesions is to identify whether they can be followed with observational programs or require surgical resection due to their malignant potential instead. The current guidelines are based on expert consensus and, therefore, lack of sufficient accuracy to allow its generalizability.

To address these limitations, the studies "Risk factors for malignant progression of IPMNs" and "Diagnostic accuracy of EUS-guided FNA cytology, CEA and amylase in IPMNs" were designed and performed. These retrospective, descriptive studies were carried out using an international IPMN registry that involves a total of 4 centers in Europe and the United States. Every patient with a clinical suspicion of an IPMN (following the current 2012 guidelines), who also had a high-resolution imaging technique performed as a baseline examination was included in the registry. Once included, each patient was prospectively updated with the corresponding follow-up visits until August 2014. The IPMN registry consisted in one epidemiological form that was filled once per patient, and a second standardized form regarding symptoms, cyst features, imaging tests and surgery (if present) that was completed in each follow-up visit.

To define the risk factors for malignant progression in IPMNs, the patients from the registry were divided into two groups. The first group comprised patients with a surgical con-

firmation of malignancy (i.e. HGD or invasive carcinoma). The second group, which acted as the control group, included those patients who either underwent surgical resection and the final report was consistent with LGD, or those who had a clinical suspicion of a non-malignant lesion.

Overall, 1126 patients with a clinical suspicion of an IPMN from 1997 until 2013 were included in this analysis. Of these, 84 had a malignant diagnosis in the surgical specimen. Multivariate logistic analysis showed a statistically significant association between malignancy in IPMNs and a positive smoking history, body mass index and presence of symptoms (more specifically, jaundice and steatorrhea). Univariate analysis showed a strong association between cyst size, mural nodules and main duct involvement and the presence of malignancy.

In this study, a large, IPMN-focused cohort was analyzed. A prevalence of malignancy of 7.4% was noted. Previously reported values were slightly lower, however, we believe that this increased malignancy found in our study is probably due to the aim of focusing only on IPMN lesions. The majority of the studies reported to date analyzed PCNs in general, including the typically benign SCAs.

Accordingly to current guidelines that consider the cyst size as one of the main parameters to define the follow-up intervals, in our study malignancy was clearly correlated with larger cysts. Despite this, there is much controversy regarding the real role of the cyst size in the malignant potential of PCNs. Recently, some studies have postulated that, if present alone without other worrisome features (such as mural nodules or main duct dilation), cysts greater than 30 mm can be managed conservatively.

In contrast, in the malignant group there was a higher prevalence of main duct involvement, which was an expected result as the contribution of the MD dilation as a risk factor in the IPMN malignant progression is a common point of agreement in the current literature. Same situation occurs with mural nodules, with several studies corroborating their role as a risk factor for malignancy, including ours.

The presence of symptoms has already been contemplated as an important sign of malignant suspicion. However, in our study we hypothesized that not all symptoms harbor the same grade of malignancy. As expected, pancreas-related symptoms, such as jaundice and steatorrhea, were strongly related with underlying malignancy, whereas unspecific symptoms such as abdominal pain were not. This is a remarkable fact as this symptom is a common clinical complaint in daily practice and, if misinterpreted, it could lead to the performance of unnecessary tests or even surgery.

To determine the accuracy of cytology, CEA and amylase levels as preoperative tests for the differential diagnosis between IPMNs and non-IPMNs cysts, as well as distinguish malignancy among IPMNs, those patients from the registry who underwent surgical resection were identified, and only those who had an EUS-guided FNA of the pancreatic cyst performed prior to surgery were included in the analysis.

A total of 230 patients underwent pancreatic surgical resection from 1997 to 2014 due to a suspicion of malignancy. Of these, 180 patients met the inclusion criteria as they had a EUS-guided FNA performed before the surgical procedure. Cytological analysis for neoplastic cells in IPMNs showed high specificity (88%) but low sensitivity (39%). Cyst fluid CEA showed an area under the curve (AUC) of 0.87 when distinguishing IPMNs from non-mucinous cysts. The optimal cut-off value was 129 ng/ml, with a sensitivity of 77% and a specificity of 83%, (yielding a positive predictive value (PPV) of 96% and a negative pre-

dictive value (NPV) of 42%). In contrast, CEA in cyst fluid was a poor predictor of malignancy among IPMNs with an AUC of 0.55. Finally, cyst-fluid Amylase accuracy was insufficient for distinguishing MCAs from IPMNs (AUC 0.65) or mucinous from non-mucinous lesions (AUC 0.27).

This study provides insight to the limitations of clinical diagnostic and prognostic accuracy. Overall, in our study the clinical diagnosis of IPMNs had modest accuracy because only 83% of the patients were confirmed to have an IPMN by the final histology of the surgical specimen. Furthermore, assuming that a suspicion of underlying malignancy led to surgery, only 39% were found to have HGD or invasive carcinoma.

Cytology of cyst fluid showed very modest results. However, it should be mentioned that the cyst features of this study cohort vary somewhat from what is now considered a high-risk cyst. We believe that this may be a consequence of a study population that comprises a period beginning in 1997, when IPMNs were first described. As a consequence, it mostly included small cysts (< 30 mm), without mural nodules and a predominance of BD-IPMNs. It has been reported that the accuracy of cytology drops if small BD-IPMNs are sampled.

Accordingly to current literature, cyst-fluid CEA proved to be a valuable tool for differentiating mucinous from non-mucinous cysts (AUC 0.87). Despite this, there is no clear consensus regarding the optimal cut-off value, which in our study was 129 ng/ml.

The role of amylase in PCNs remains unclear. It has been reported that IPMNs should present higher values than MCAs due to their patent communications with the pancreatic ducts. However, in our study the results showed an insufficient accuracy suggesting that Amylase was unable to discriminate among these lesions. Considering that the amount of

the cystic fluid is usually quite scarce, the avoidance of this test may provide an opportunity for expanded biomarker discovery in cyst fluid biobanks.

Based on the results of these two studies, current clinical criteria and diagnostic test lack of sufficient accuracy and, therefore, improved diagnostic and prognostic biomarkers are required to discriminate which patients benefit from surgical resection.

5 CONCLUSIONS

1 There has been an increased trend of incidentally detected pancreatic cystic lesions from 2005 to 2014.

2 The changes in the magnetic resonance imaging capabilities are a contributing factor for the observed rise of pancreatic cystic lesions rates.

3 Risk factors for malignancy in intraductal papillary mucinous neoplasms of the pancreas include: a) demographic variables, such as body mass index and positive smoking history; b) morphological features, such as main duct involvement and presence of mural nodules; and c) specific pancreatic symptoms, such as steatorrhea or jaundice.

4 Cytology of cyst fluid has a limited diagnostic role for intraductal papillary mucinous neoplasms due to its lack of sensitivity.

5 Carcinoembriogenic antigen concentrations in cyst fluid have modest accuracy for differentiating between intraductal papillary mucinous neoplasms and non-mucinous lesions, and should not be solely considered to guide the management strategy of intraductal papillary mucinous neoplasms due to its lack of discrimination between malignant and benign lesions.

6 Cyst fluid amylase levels yield no diagnostic contribution to diagnosing intraductal papillary mucinous neoplasms or differentiating these lesions from mucinous cystadenomas.

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7 ANNEX

7.1 OTHER SCIENTIFIC ACTIVITIES CARRIED OUT DURING THE ELABORATION OF THIS DOCTORAL THESIS

7.1.1 Presentations at international scientific meetings

• Maria Moris, Michael Wallace, Massimo Raimondo, Timothy Woodward, Verna Skinner, Paolo G. Arcidiacono, Cinzia Boemo, M. Chiara Petrone, Claudio De Angelis, Pietro Fusaroli, Michele Lewis Su1492. Risk Factors for Malignant Progression of Intraductal Papillary Mucinous Neoplasms (IPMN): An International Registry Cohort. Gastroenterology , Volume 146 , Issue 5 , S-483

Poster with distinction. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2014. Chicago, Illinois. USA.

• Michael Wallace; Massimo Raimondo; Timothy Woodward; Maria Moris; Joy Hardee; Amrita Sethi; Mohammad Al-Haddad; Douglas Faigel. Mo1417 A Multicenter, Prospective, Randomized Study on Endosonographic Fine Needle Aspiration of Pancreatic Cystic Lesions Using Standard and Nitinol Needles: Phase I Results. Gastrointestinal Endoscopy, Volume 79, No. 5S : 2014.

Poster. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2014. Chicago, Illinois. USA.

• Saowanee Ngamruengphong, Kristina Seeger, Luke McCrone, Maria Moris Felgueroso, Stephen Garrison, Surakit Pungpapong, Andrew Keaveny, Massimo Raimondo. Prevalence and Outcomes of Cystic Neoplasm of the Pancreas in Immunosuppressed Patients With Solid Organ Transplantation.Am J Gastroenterol 2014; 109:S69.

Poster. American College of Gastroenterology Annual Meeting. October 2014. Philadelphia, Pennsylvania. USA.

• Maria Moris, Michael Wallace, Massimo Raimondo, Timothy Woodward, Verna Skinner, Paolo G. Arcidiacono, Cinzia Boemo, Maria C. Petrone, Claudio De Angelis, Selene Manfrè, Pietro Fusaroli, Michele Lewis. International multicenter IPMN registry: Role of EUS-FNA Cytology, CEA and Amylase in the diagnosis of Intraductal Papillary Mucinous Neoplasms.Am J Gastroenterol 2014; 109:S664.
Poster. American College of Gastroenterology Annual Meeting. October 2014. Philadelphia, Pennsylvania. USA.

• Maria Moris, Murli Krishna, Ariston Librero, Eugene Richie, Massimo Raimondo, Timothy Woodward, John Stauffer, Horacio Asbun, Michael Wallace. Pancreatic Cyst Ablation: An Experimental Study with a New EUS Needle Prototype. Am J Gastroenterol 2014; 109:S63-4.
Poster. American College of Gastroenterology Annual Meeting. October 2014. Philadelphia, Pennsylvania. USA.

• Maria Moris, Michael Wallace, Massimo Raimondo, Timothy Woodward, Verna Skinner, Paolo G. Arcidiacono, Cinzia Boemo, Maria C. Petrone, Claudio De Angelis, Selene Manfrè, Pietro Fusaroli, Michele Lewis.Risk Factors for Malignant Progression of Intraductal Papillary Mucinous Neoplasms (IPMN): An International Registry Cohort. Am J Gastroenterol 109: S664.
Oral communication. American College of Gastroenterology Annual Meeting. October 2014. Philadelphia, Pennsylvania. USA.

• Maria Moris, Liuyan Jiang, Qihui Zhai, Kenneth Takeuchi, Howard Crawford, Michael Wallace. Plectin-1 as a biomarker for malignant progression in intraductal papillary mucinous neoplasms (IPMNs) of the pancreas.Gastroenterology, Volume 148, Issue 4, Supplement 1, April 2015, Pages S-523-S-524.
Poster. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2015. Washington D.C., USA.

• Maria Moris, Melena Bridges, Massimo Raimondo, Timothy Woodward, John Stauffer, Horacio Asbun, Michael Wallace. Advances in high resolution cross section imaging and the rising prevalence of pancreatic cysts over the past decade. Gastroenterology, Volume 148, Issue 4, Supplement 1, April 2015, Page S-524.
Poster with distinction. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2015. Washington D.C., USA.

• Maria Moris, Massimo Raimondo, Timothy Woodward, Verna Skinner, Paolo Arcidiacono, Maria Petrone, Claudio De Angelis, Selene Manfrè, Pietro Fusaroli, Horacio Asbun, John Stauffer, Michael Wallace.International multicenter IPMN registry: Role of EUS-FNA Cytology, CEA and Amylase in the diagnosis of Intraductal Papillary Mucinous Neoplasms.Gastrointestinal Endoscopy, Volume 81, Issue 5, Supplement, May 2015, Page AB113.
Oral communication. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2015. Washington D.C., USA.

• Maria Moris, Melena Bridges, Massimo Raimondo, Timothy Woodward, John Stauffer, Horacio Asbun, Michael Wallace. Advances in high resolution cross section imaging and the rising prevalence of pancreatic cysts over the past decade.
Poster. United European Gastroenterology Week. October 2015. Barcelona, Spain.

• Maria Moris, Massimo Raimondo, Timothy Woodward, Verna Skinner, Paolo G. Arcidiacono, Maria C. Petrone, Claudio De Angelis, Selene Manfrè, Manol Jovani, Silvia Carrara, Pietro Fusaroli, Michael Wallace. Intraductal papillary mucinous neoplasms international registry: Long-term analysis.

Poster. United European Gastroenterology Week. October 2015. Barcelona, Spain.

• Maria Moris, Mustafa Atar, Abdurrahman Kadayfici, Murli Krishna, Ariston Librero, Eugene Richie, Michael Wallace, William Brugge. Ex-vivo cyst ablation with a new EUS-needle prototype device.

Oral communication. United European Gastroenterology Week. October 2015. Barcelona, Spain.

• Wei-Chung Chen, Michael J Bartel, Maria Moris, Michael B Wallace, Timothy A. Woodward, Massimo Raimondo. Mural Nodule on EUS Does Not Fully Correlate With High Grade Dysplasia or Cancer on Surgical Pathology of Pancreatic Cysts.

Poster. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2016. San Diego, California, USA.

• Maia Kayal, Lyndon Luk, Maria Moris, Michael B. Wallace, Amrita Sethi, John M. Poneros, Frank G. Gress, Elizabeth Hecht, Tamas A. Gonda. Long Term Surveillance and Risk of Progression of Low-Intermediate Risk Branch Duct Intraductal Papillary Mucinous Neoplasms.

Poster. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2016. San Diego, California, USA.

• Maria Moris, Maia Kayal, Elizabeth Hecht, Lyndon Luk, Amrita Sethi, John M. Poneros, Frank G. Gress, Beth Schrope, John A. Chabot, Marco J. Bruno, Djuna Cahen, Michael B. Wallace, Tamas A. Gonda. Multicenter Results of Long Term Surveillance of Intraductal Papillary Mucinous Neoplasms Without Worrisome Features.
Poster. Digestive Disease Week. AASLD/AGA/ASGE/SSAT. May 2016. San Diego, California, USA.

7.1.2 Scientific manuscripts

• Saowanee Ngamruengphong, Kristina M Seeger, Luke M McCrone, Maria Moris, Stephen J Garrison, Surakit Pungpapong, Andrew P Keaveny, Massimo Raimondo. Prevalence and Outcomes of Cystic neoplasm of the Pancreas in Immunosuppressed Patients with Solid Organ Transplantation. Dig Liver Dis.2015; 47(5):417-22.