Updates in Surgery (2019) 71:209–216
https://doi.org/10.1007/s13304-019-00661-0

REVIEW ARTICLE

The diagnosis and management of intraductal papillary mucinous neoplasms of the pancreas: has progress been made?

Jenny Lim[1] · **Peter J. Allen**[1,2]

Received: 29 May 2019 / Accepted: 31 May 2019 / Published online: 7 June 2019

Abstract

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are premalignant mucin-producing epithelial tumors that arise from the pancreatic ductal system. These cystic tumors represent 15–30% of cystic lesions of the pancreas [Basturk et al. in Am J Surg Pathol 39(12):1730–1741, 1; Ferrone et al. in Arch Surg (Chicago, Ill: 1960) 144(5):448–454, 2, Kosmahl et al. in Virchows Arch Int J Pathol 445(2):168–178, 3; Spinelli et al. in Ann Surg. 239(5):651–657, 4]. It is believed that IPMN can progress from low-grade dysplasia to high-grade dysplasia to invasive cancer, and this pathway of progression accounts for 20–30% of pancreatic cancer [Adsay et al. in Am J Surg Pathol 28(7):839–848, 5; Tanaka et al. in J Gastroenterol 40(7):669–675, 6; Wu et al. in Sci Transl Med 3(92):92ra66, 7]. Furthermore, it is also widely believed that IPMN represent a field defect of the pancreas in which the entire ductal system is at risk of developing invasive carcinoma, not only in the area of radiographically detectable IPMN, and thus the remaining gland should undergo surveillance after partial pancreatectomy [Salvia et al. in Ann Surg 239(5):678–685, 8; Izawa et al. in Cancer 92(7):1807–1817, 9; Yamaguchi and Tanaka in Jpn J Clin Oncol 41(7):836–840, 10]. Increasingly, surgeons are faced with the dilemma between recommending highly complex resections—that have significant morbidity and mortality—in patients who may have low-risk IPMN (low-grade dysplasia), or alternatively, recommending observation for those who could possibly be harboring a radiographically occult malignancy. Given the complexity of the management decisions for patients with IPMN, the purpose of this paper is to review the current literature and to provide a summary of how accurate we are currently with the identification of high-grade dysplasia or progression to carcinoma in patients who present with IPMN.

Keywords Pancreatic intraductal papillary mucinous neoplasms · Guidelines · Nomograms · Radiomics · Biomarkers

Introduction

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are premalignant mucin-producing epithelial tumors arising from the pancreatic ducts. These cystic tumors represent 15–30% of cystic lesions of the pancreas [1–4]. It is believed that IPMN can progress from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) and eventually to invasive carcinoma [5, 6]. This pathway of progression is presumed to account for 20–30% of pancreatic cancer. IPMN represent an opportunity to identify a high-risk population who may benefit from a preventative resection [11]. However, the challenge still remains in describing its natural history, as it is unknown how long, how frequent, or in which site of the pancreas progression to cancer will occur.

Because of the increasing use of high-quality cross-sectional imaging, a greater number of patients are being identified with small, incidentally discovered pancreatic cysts. Depending on the age of the population, between 2 and 15% of patients will have a cystic tumor of the pancreas identified on cross-sectional imaging, and many of these lesions will represent IPMN [12–18]. Radiographically, IPMN can be identified as main duct (MD), branch duct (BD) or mixed type (MT) depending on the presence or absence of main pancreatic duct dilatation. Branch duct IPMN is a more common lesion than MD- or MT-IPMN [17]. The risk of these lesions varies depending on whether or not the MD is dilated and ranges between 20 and 60%, with the risk

✉ Jenny Lim
jenny.lim@duke.edu

[1] Department of Surgical Oncology, Duke University, Durham, NC 27710, USA

[2] Duke Cancer Institute, Duke Health System, Durham, NC 27710, USA

higher for lesions involving the main pancreatic duct [19]. Although routine resection is generally recommended for patients with MD-IPMN, this recommendation will result in approximately 40% of patients undergoing resection for LGD. Branch duct lesions have been reported to be even less likely to harbor HGD or invasive cancer, with only 20% of resected patients having these high-risk lesions. Therefore, 80% of patients resected for BD-IPMN undergo resection for low-risk disease. Furthermore, it is generally accepted that IPMN represent a field defect of the pancreas, where the entire ductal system is at risk for developing invasive carcinoma, not only in the radiographically identifiable area [8–10]. Therefore, it is unknown how much risk reduction occurs with partial pancreatectomy for a dominant branch duct lesion. The inability to predict with a high degree of certainty in the presence of high-risk disease makes clinical decision making difficult. Surgeons are faced with the dilemma between recommending highly complex resections—that have significant morbidity and mortality—in patients who may have low-risk disease, or alternatively, recommending observation for a patient that could be harboring a radiographically occult malignancy.

Clinical predictors for high-grade dysplasia or carcinoma in patients with IPMN

There are several consensus guidelines that have been published with recommendations for the management of patients with IPMN [19–23]. The fact that there are multiple conflicting guidelines reflects the current challenge in predicting high-risk disease (HGD or carcinoma) in patients with IPMN. A common feature in all the current guidelines is the use of clinical features such as a history of pancreatitis, abdominal pain, or jaundice; and radiographic features such as main pancreatic duct diameter, cyst diameter, and the presence of a mural nodule. These data can be obtained with patient history and radiographic studies as outlined in Table 1. The consensus statement that recommends resection for the broadest range of indications is the European Experts Consensus statement (EURO), which recommends resection for patients who are symptomatic, or have cysts that are ≥ 4 cm in diameter, have the presence of mural nodules, or have main duct dilation ≥ 6 mm [20]. The most conservative guidelines are from American Gastroenterological Association (AGA) which recommends EUS with FNA to be performed if the lesion has two of the following features: cyst size ≥ 3 cm, dilated main duct, or presence of mural nodule. The AGA guidelines recommend resection only for those with positive cytology on EUS fine needle aspiration [22]. A comparison of these guidelines was performed by Lekkerkerker, and as would be expected, overtreatment was more common in the EURO guidelines, with 43% of resected specimens having less than HGD or carcinoma [24]. If the AGA guidelines had been followed, 29% of patients would have had low-risk disease, but 13% of patients with malignancy would have been missed [24]. These findings highlight the dilemma noted above regarding treatment recommendations. Overtreatment has been one of the greatest concerns for patients with BD-IPMN, as the majority of resected patients have been reported to have low-risk disease. Given this recognition, the International Association of Pancreatology (IAP) revised their consensus guidelines in 2017, and recommended a more selective approach to resection for BD-IPMN [25]. Updated EURO guidelines in 2018 also reflected a more conservative approach by recommending relative indications for surgery for IPMN with main duct dilatation between 5 and 9.9 mm, cyst diameter ≥ 40 mm, or enhancing nodule > 5 mm in size [21].

The above noted consensus guidelines make recommendations based on general risk, however, individual risk based on specific clinical and radiographic findings

Table 1 Clinical parameters used to recommend resection of IPMN

	International Association of Pancreatology Guidelines, 2012 (revised 2017) [19, 25]	European Experts Consensus Statement, 2013 (revised, 2018) [20, 21]	American Gastroenterological Association Guidelines, 2015 [22]
Age	–	–	–
Obstructive jaundice	Presence	Presence	–
Abdominal pain/history of pancreatitis	Not definitive	Presence	–
Main duct size	> 10 mm	≥ 10 mm	Dilated[a]
Mural nodule	Enhancement	Enhancement, ≥ 5 mm	Presence[a]
Cyst size	Not definitive	Not definitive	≥ 3 cm[a]
Cytology	Suspicious or positive	Positive	Positive
Serum CA19-9	–	Not definitive	–

(–) Parameter not included in guidelines

[a]EUS-FNA recommended that if at least two high-risk features are identified, only the one with positive cytology is resection recommended

are not possible within the framework of these guidelines. Because of this limitation, several groups including our own have developed nomograms that calculate an individual's risk of having HGD or invasive carcinoma. Table 2 presents the nomograms presented by three separate groups [26–28]. Many of the same variables were evaluated, but the predictors used to create the nomogram differ greatly. Only cyst size and the presence of a mural nodule were significant predictors of high-risk disease in all three models. Symptoms, which are part of the IAP guidelines, were only evaluated in the study by the Pancreatic Surgery Consortium (PSC) which included patients from four institutions: Memorial Sloan Kettering, John Hopkins Hospital, Massachusetts General Hospital, and University of Verona [28, 29]. In the PSC nomogram, it is important to note that jaundice was not included, as every patient but one who presented with jaundice had invasive carcinoma and thus this symptom was separated as one that should prompt resection regardless of other predictors [28]. The PSC nomogram appeared to have the best accuracy with the concordance index (*c* index) of 0.81. Therefore at this time, this model should be considered more accurate than the nomograms by Jang (AUC 0.737) and Shimizu (AUC 0.72). Jang et al. had the largest study group ($N = 1914$; of which 652 patients were included in the model development and remaining patients in validation groups) and evaluated the risk of malignancy for BD-IPMN only. They included serum carbohydrate antigen (CA) 19-9 levels in their algorithm. Serum tumor markers such as CA 19-9 and carcinoembryonic antigen (CEA) are elevated in 85% and 60% of patients with pancreatic cancer, respectively, however, the presence of an elevated CA19-9 in the setting of HGD is less reliable [30–32].

The nomogram published by Pancreatic Surgery Consortium may also be more applicable to surgeons, as the predictors are easily identifiable and can be applied not only to calculate probability of invasive carcinoma, but it also included those with HGD [28]. Most clinicians believe that resection of IPMN with HGD is the optimal setting as an invasive—and likely incurable—pancreatic cancer has not yet developed. Within the dataset from which the PSC nomogram was developed, 71% had HGD in the MD/MT-IPMN group and 29% for BD-IPMN [28]. These patients represent our greatest opportunity for prevention, and the development of tools to better identify HGD before invasion occurs will allow us to more appropriately select patients for operative resection. Prospective studies are needed to further validate the accuracy of these nomograms in the clinical setting, however, a risk calculator offers a more personalized management option for surgeons and their patients and should be employed in clinical practice.

Radiographic predictors of high-risk IPMN

High-quality cross-sectional imaging and evaluation by an experienced radiologist and surgeon are vital to the diagnosis and assessment of patients with IPMN. Multi-detector computed tomography (MdCT) is the most common method for evaluating a pancreatic cyst. This technique allows thin section scanning of the pancreas to provide excellent visualization of septa, mural nodules, calcifications and the

Table 2 Summary of predictors in the nomograms calculating the risk of high-risk lesions in IPMN

	Shimizu [26]	Jang [27]	Pancreatic Surgery Consortium [28]	
	All types	BD	BD	MD and mixed
N (in model)	466	652	402	318
Predictors	Malignancy	Malignancy	HGD/malignancy	
Age	−	+	+	−
Gender	−	−	+	−
Symptoms	−	NE	+	+
Prior malignancy	NE	NE	−	−
Weight loss	NE	NE	−	+
Mural nodules	+	+	+	+
Size of main duct	+	+	+	−
Cyst size	+	+	+	+
Serum CEA	−	+	−	−
Serum CA19-9	−	+	+*	+*
Validation	External	External	External	
AUC/*c* index[a]	0.72	0.737	0.81	

+ significant, − non-significant, *NE* not evaluated

*Found to be a significant predictor but not included in Nomogram due to significant missing data

[a]Reported from validation dataset

surrounding pancreatic parenchyma. The current guidelines noted above rely on radiographic features identified by this imaging such as main duct diameter, presence of a mural nodule and/or cyst diameter to assess risk for malignancy. The White Paper released by American College of Radiology in 2017 recommends the use of MdCT for evaluating pancreatic cysts using contrast-enhanced sequences or what is commonly known as a "pancreas protocol" [33]. This paper also recommended that specific nomenclature should be employed to describe the imaging with use of the terms "worrisome features" or "high-risk stigmata" as per the IAP guidelines [19, 33]. Worrisome features include the following findings: cysts ≥ 3 cm, thickened/enhancing cyst wall, nonenhancing mural nodule and main pancreatic duct dilatation between 5 and 9 mm. High-risk stigmata include: obstructive jaundice in patients with cystic lesions in the head of the pancreas, enhancing mural nodule ≥ to 5 mm, and main pancreatic duct diameter ≥ 10 mm [19]. Single-institution studies suggest MdCT and/or MRI can discriminate between mucinous or non-mucinous cysts with an accuracy of 82–85% and MdCT can correctly predict the malignant behavior of pancreatic cystic lesions in 56–82% of cases [16, 34–36].

Contrast-enhanced MRI has not been shown to be clearly superior to pancreas protocol MdCT for detecting worrisome features, high-risk stigmata, or malignancy [37–40]. When comparisons have been made between the imaging modalities with respect to the identification of important risk features, the results have been similar. In a study by Kang, the AUC was 0.82 for both modalities with good inter-modality agreement $K = 0.75$ [41]. However, MRI had higher sensitivity than MdCT in showing ductal communication of small cystic pancreatic lesions (100% vs 85.7%) [40]. In addition, MRI may have the ability to accurately assess the communication between the cyst and MPD and be comparable to endoscopic ultrasound with respect to this finding (EUS) [42]. Several advantages of MRI do exist. First, MRI does not utilize radiation, and thus in patients requiring long-term surveillance, one might consider MRI a safer approach. Second, MRI imaging for pancreatic cysts does not require contrast, as non-contrast MRI has been shown to be comparable in detecting dysplastic changes [43, 44]. Therefore, surveillance with non-contrast MRI is reasonable, especially for patients with renal dysfunction.

Endoscopic ultrasound (EUS) is generally recommended to assist in the initial evaluation after cross-sectional imaging has been performed, particularly when a worrisome feature is noted and/or the cyst is ≥ 2 cm [19]. EUS is an excellent imaging technique and has been reported to be comparable to enhanced MRI and enhanced MdCT [45]. Choi et al. compared all three modalities in diagnostic performance in predicting HGD or invasive carcinoma in IPMN based on IAP guidelines [45]. In this study, a total of 76 patients underwent testing with all three modalities and then underwent subsequent resection for IPMN. No significant differences were found between the three modalities in accurately identifying HGD and invasive IPMN using contrast-enhanced CT (AUC 0.792, 0.830), contrast-enhanced MRI (AUC 0.742, 0.776) and EUS (AUC 0.733) [45].

An advantage of EUS may be in the assessment of mural nodules in patients with BD-IPMN. Several studies have shown that mural nodules are missed in up to 28% of CT and MRI tests when compared to EUS in patients presenting with BD-IPMN [46]. EUS not only provides detailed images of the cyst wall, internal cyst architecture, and can identify mural nodules, but this approach also provides the ability to sample cyst fluid, and biopsy the nodule and the cyst wall. Analysis of cyst fluid can aid in diagnosis and potentially provide prognostic information. These potential benefits, however, must be balanced by the fact that it is an invasive procedure that is highly operator dependent. Only a fair agreement ($K = 0.24$) has been reported between experienced endosonographers in evaluating malignancy in cystic lesions [47].

Quantitative imaging to predict malignancy

Given the widespread use of high-quality MdCT, recent studies have evaluated advanced computer-based quantitative image analysis to extract additional information to identify features which may be predictive of high-risk IPMN. The field of radiomics, as it is called, has been used for the diagnosis of prostate cancer, breast carcinoma, non-small cell lung cancer and even pancreas cancer [48–51]. Tumor signal intensity, shape characterization, texture heterogeneity patterns, and the relationship of the tumor with surrounding tissues are some of the image-based features that have been evaluated as a means to predict tumor biology [52]. Preliminary studies have evaluated its use in predicting HGD in IPMN [51–54]. Hanania et al. evaluated 53 cases of IPMN and identified 14 imaging features (biomarkers) to differentiate between low-grade and high-grade dysplasia in IPMN. Using the top 10 of the 14 biomarkers, an AUC of 0.96 was achieved with sensitivity of 97% and specificity of 88% [53]. Permuth et al. also used radiomics with 14 radiologic biomarkers in 38 cases to differentiate malignant from benign IPMN, however, integrated 5-miRNA data and achieved AUC of 0.92 with sensitivity of 83% and specificity of 89% [52]. The largest study published so far was published by our group, and evaluated 103 cases with BD-IPMN and achieved AUC of 0.77 [51]. However, when clinical factors such as age, cyst size, reported presence of mural nodule, symptoms and gender were included, the accuracy improved to AUC of 0.79 with positive predictive value of 95% and negative predictive value of 79% [54]. Although in its infancy, integration of radiomics and clinical information

may be able to provide a distinctly improved preoperative model to discriminate between low-risk and high-risk IPMN.

Use of histologic and cyst fluid biomarkers as predictors for high-risk IPMN

To predict the natural course of IPMN, we need to have an understanding of the disease biology and pathogenesis. Histopathologically, IPMN can be classified as gastric, intestinal, pancreatobiliary, and oncocytic sub-types as outlined in Table 3 [55–57]. The two most common histologic sub-types are gastric and intestinal types. Gastric sub-types are seen in 60–70% of IPMN, of which most are BD-IPMN (> 95%) [58]. These lesions are typically low grade and are presumed to have a low rate of progression. However, approximately 5% of these lesions can be immediately associated with invasive tubular carcinoma which is histologically indistinguishable from conventional PDAC, and thus have poor prognosis [55]. Intestinal sub-type IPMN are seen in 30–40% of patients, most are MD-IPMNs and typically show HGD. Histologic progression of intestinal sub-type IPMN is phenotypically presumed to be to invasive colloid carcinoma, and both intestinal sub-type IPMN and colloid carcinoma have been found to be associated with mutations in GNAS [59]. Reports on the survival outcome for patients with invasive colloid IPMN demonstrate a significantly improved survival when compared to those with invasive tubular IPMN [60]. Pancreatobiliary sub-type IPMN is not as common, and may be identified in either BD-IPMN or MD-IPMN. These lesions are typically associated with HGD, and progress to tubular-type adenocarcinoma. Invasive tubular IPMN behaves similarly to conventional PDAC and confer a poor prognosis [61]. Oncocytic sub-type is the least common, typically has HGD and is generally presumed to have a better prognosis than other IPMN sub-types of similar grade [55]. Recent studies have not found KRAS or GNAS mutations in oncocytic sub-type lesions and thus some consider these as a distinct pathologic entity separate from IPMN [62].

Multiple investigators have looked at the cyst fluid as a potential source of markers for HGD or invasive cancer. Given the complexity and differences in mucin expression, some have assessed mucin expression as a means to identify high-risk disease. Overexpression of MUC1 has been associated with invasive carcinoma, and is expressed in pancreatobiliary and oncocytic sub-types [55, 56]. MUC4 expression has also been reported as associated with degree of dysplasia [63]. MUC2 expression is typically the opposite of MUC1, and is generally not seen in invasive carcinoma. MUC2 and MUC5A are often expressed in intestinal and gastric subtype IPMN, which generally are found to have LGD.

Other approaches to stratify patient risk through pancreatic cyst fluid analysis have included the multicenter Pancreatic Cyst DNA analysis (PANDA) study that evaluated cyst fluid from 113 patients and concluded that mutations in KRAS were able to identify mucinous cysts, however, they were not different between low-risk and high-risk lesions [64]. GNAS mutations were also found to be associated with IPMN, and helpful in its identification, but again unable to differentiate the degree of dysplasia [7, 59, 65]. The monoclonal antibody Das-1, which reacts to normal intestinal epithelium, has also been evaluated by performing ELISA on cystic fluid from 38 patients with IPMN. This study found that Das-1 differentiated high-risk lesions from LGD with sensitivity of 85% and specificity of 95% [66]. These initial encouraging results are currently being evaluated in larger prospective studies. The International IPMN Cyst Fluid Collaborative evaluated different proteins, cytokines, mucins, DNA and miRNA targets using a single-platform PCR based assay and published a model that can discriminate

Table 3 Summary of histopathological sub-type characteristics of IPMN

	Histologic sub-type			
	Gastric	Intestinal	Pancreatobiliary	Oncocytic
Frequency (%)	60–70	30–40	< 10	< 5
Morphologic sub-type	BD > MD	MD > BD	MD or BD	MD or BD
Atypia	Low grade	High grade	High grade	High grade
Progression	Indolent	Indolent	Rapid	Rapid
Type of carcinoma	Tubular	Colloid	Tubular	Oncocytic
5, 10 years survival rate	0.937, 0.937	0.886, 0.685	0.520	0.839, 0.734
KRAS (%)	53-87	40-46	45-60	±
GNAS (%)	39-65	48-83	30	±
MUC1	−	−	+	±
MUC2	−	+	−	±
MUC5AC	+	+	+	+
MUC6	+	−	+	+

References: [55–57, 59]

high- from low-risk lesions up to an AUC of 0.86 [67]. Our group has focused on the relationship between inflammation and IPMN progression, and has sought to define a panel of inflammatory markers that can be measured in the cyst fluid and are predictive of high-risk lesions [68]. Incorporation of these inflammatory cyst markers into our previously published nomogram resulted in a model up to an AUC of 0.84 [68]. Currently, a prospective trial is being conducted to further validate these markers.

As EUS-FNA is highly operator dependent, the reliability of cystic fluid and tissue may be variable. However, Bournet et al. found that DNA extraction can be performed successfully with minimal amount using a micro-kit [69]. Even so, EUS is an invasive procedure and serial sampling may not feasible and would be costly. New technologies are currently being evaluated that will use serum samples to quantify circulating cell-free DNA and biomarkers such as KRAS and GNAS. Changes in these serum levels may provide additional ability to detect progression prior to the development of an invasive lesion [68, 70].

Conclusion

Management recommendations for patients with IPMN have changed tremendously over the last 2 decades, as our understanding of the natural history of this disease has improved. This evolution has occurred because many studies have identified possible clinical, radiographic and biologic predictors that may accurately identify IPMN with high-grade dysplasia and invasive carcinoma. With emerging technology, our ability to individualize treatment is improving, as we are better able to combine clinical factors with quantitative image analysis and molecular markers from the cyst fluid and even serum. Through the combination of clinical and imaging features with promising cyst fluid markers, models are being developed with significant accuracy. Improving our ability to identify those at highest risk for developing cancer will allow for more appropriate selection of patients for operation. Because of the relative rarity of this disease, the international community will need to continue to collaborate to successfully form a prevention strategy to reduce incidence of pancreatic cancer arising from IPMN.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals The research did not involve human participant or animals.

Informed consent Not applicable for this type of study.

References

1. Basturk O, Hong SM, Wood LD et al (2015) A revised classification system and recommendations from the baltimore consensus meeting for neoplastic precursor lesions in the pancreas. Am J Surg Pathol 39(12):1730–1741
2. Ferrone CR, Correa-Gallego C, Warshaw AL et al (2009) Current trends in pancreatic cystic neoplasms. Arch Surg (Chicago, Ill: 1960) 144(5):448–454
3. Kosmahl M, Pauser U, Peters K et al (2004) Cystic neoplasms of the pancreas and tumor-like lesions with cystic features: a review of 418 cases and a classification proposal. Virchows Arch Int J Pathol 445(2):168–178
4. Spinelli KS, Fromwiller TE, Daniel RA et al (2004) Cystic pancreatic neoplasms: observe or operate. Ann Surg. 239(5):651–657 **(discussion 657–659)**
5. Adsay NV, Merati K, Basturk O et al (2004) Pathologically and biologically distinct types of epithelium in intraductal papillary mucinous neoplasms: delineation of an "intestinal" pathway of carcinogenesis in the pancreas. Am J Surg Pathol 28(7):839–848
6. Tanaka M, Kobayashi K, Mizumoto K, Yamaguchi K (2005) Clinical aspects of intraductal papillary mucinous neoplasm of the pancreas. J Gastroenterol 40(7):669–675
7. Wu J, Matthaei H, Maitra A et al (2011) Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med 3(92):92ra66
8. Salvia R, Fernandez-del Castillo C, Bassi C et al (2004) Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg 239(5):678–685 **(discussion 685–677)**
9. Izawa T, Obara T, Tanno S, Mizukami Y, Yanagawa N, Kohgo Y (2001) Clonality and field cancerization in intraductal papillary-mucinous tumors of the pancreas. Cancer 92(7):1807–1817
10. Yamaguchi K, Tanaka M (2011) EBM-based clinical guidelines for pancreatic cancer 2009 from the Japan Pancreas Society: a synopsis. Jpn J Clin Oncol 41(7):836–840
11. Wu J, Jiao Y, Dal Molin M et al (2011) Whole-exome sequencing of neoplastic cysts of the pancreas reveals recurrent mutations in components of ubiquitin-dependent pathways. Proc Natl Acad Sci USA 108(52):21188–21193
12. de Jong K, Nio CY, Mearadji B et al (2012) Disappointing interobserver agreement among radiologists for a classifying diagnosis of pancreatic cysts using magnetic resonance imaging. Pancreas 41(2):278–282
13. Laffan TA, Horton KM, Klein AP et al (2008) Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol 191(3):802–807
14. Gorin AD, Sackier JM (1997) Incidental detection of cystic neoplasms of the pancreas. Md Med J (Baltimore, Md: 1985) 46(2):79–82
15. Fernandez-del Castillo C, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL (2003) Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. Arch Surg (Chicago, Ill: 1960) 138(4):427–434 **(discussion 433–424)**
16. Lee JH, Lee KT, Park J et al (2010) Predictive factors associated with malignancy of intraductal papillary mucinous pancreatic neoplasms. World J Gastroenterol 16(42):5353–5358
17. Gaujoux S, Brennan MF, Gonen M et al (2011) Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. J Am Coll Surg 212(4):590–600 **(discussion 600–593)**
18. Valsangkar NP, Morales-Oyarvide V, Thayer SP et al (2012) 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. Surgery 152(3 Suppl 1):S4–12

19. Tanaka M, Fernandez-del Castillo C, Adsay V et al (2012) International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 12(3):183–197
20. Del Chiaro M, Verbeke C, Salvia R et al (2013) European experts consensus statement on cystic tumours of the pancreas. Dig Liver Dis 45(9):703–711
21. European Study Group on Cystic Tumours of the P (2018) European evidence-based guidelines on pancreatic cystic neoplasms. Gut 67(5):789–804
22. Vege SS, Ziring B, Jain R, Moayyedi P (2015) American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 148(4):819–822 **(quize 812–813)**
23. Nakamura M, Miyasaka Y, Sadakari Y, Date K, Ohtsuka T (2017) Comparison of guidelines for intraductal papillary mucinous neoplasm: what is the next step beyond the current guidelines? Ann Gastroenterol Surg 1(2):90–98
24. Lekkerkerker SJ, Besselink MG, Busch OR et al (2017) Comparing 3 guidelines on the management of surgically removed pancreatic cysts with regard to pathological outcome. Gastrointest Endosc 85(5):1025–1031
25. Tanaka M, Fernandez-Del Castillo C, Kamisawa T et al (2017) Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology 17(5):738–753
26. Shimizu Y, Yamaue H, Maguchi H et al (2015) Validation of a nomogram for predicting the probability of carcinoma in patients with intraductal papillary mucinous neoplasm in 180 pancreatic resection patients at 3 high-volume centers. Pancreas 44(3):459–464
27. Jang JY, Park T, Lee S et al (2017) Proposed nomogram predicting the individual risk of malignancy in the patients with branch duct type intraductal papillary mucinous neoplasms of the pancreas. Ann Surg 266(6):1062–1068
28. Attiyeh MA, Fernandez-Del Castillo C, Al Efishat M et al (2018) Development and validation of a multi-institutional preoperative nomogram for predicting grade of dysplasia in intraductal papillary mucinous neoplasms (IPMNs) of the pancreas: a report from the pancreatic surgery consortium. Ann Surg 267(1):157–163
29. Correa-Gallego C, Do R, Lafemina J et al (2013) Predicting dysplasia and invasive carcinoma in intraductal papillary mucinous neoplasms of the pancreas: development of a preoperative nomogram. Ann Surg Oncol 20(13):4348–4355
30. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-delCastillo C, Warshaw AL (2006) Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol 24(18):2897–2902
31. Sandblom G, Granroth S, Rasmussen IC (2008) TPS, CA 19-9, VEGF-A, and CEA as diagnostic and prognostic factors in patients with mass lesions in the pancreatic head. Ups J Med Sci 113(1):57–64
32. Sultana A, Jackson R, Tim G et al (2015) What is the best way to identify malignant transformation within pancreatic IPMN: a systematic review and meta-analyses. Clin Transl Gastroenterol 6:e130
33. Megibow AJ, Baker ME, Morgan DE et al (2017) Management of incidental pancreatic cysts: a white paper of the ACR incidental findings committee. J Am Coll Radiol JACR 14(7):911–923
34. Sahani DV, Kambadakone A, Macari M, Takahashi N, Chari S, Fernandez-del Castillo C (2013) Diagnosis and management of cystic pancreatic lesions. AJR Am J Roentgenol 200(2):343–354
35. Visser BC, Yeh BM, Qayyum A, Way LW, McCulloch CE, Coakley FV (2007) Characterization of cystic pancreatic masses: relative accuracy of CT and MRI. AJR Am J Roentgenol 189(3):648–656
36. Chaudhari VV, Raman SS, Vuong NL et al (2008) Pancreatic cystic lesions: discrimination accuracy based on clinical data and high-resolution computed tomographic features. J Comput Assist Tomogr 32(5):757–763
37. Nougaret S, Reinhold C, Chong J et al (2014) Incidental pancreatic cysts: natural history and diagnostic accuracy of a limited serial pancreatic cyst MRI protocol. Eur Radiol 24(5):1020–1029
38. Chen FM, Ni JM, Zhang ZY, Zhang L, Li B, Jiang CJ (2016) Presurgical evaluation of pancreatic cancer: a comprehensive imaging comparison of CT versus MRI. AJR Am J Roentgenol 206(3):526–535
39. Hwang DW, Jang JY, Lim CS et al (2011) Determination of malignant and invasive predictors in branch duct type intraductal papillary mucinous neoplasms of the pancreas: a suggested scoring formula. J Korean Med Sci 26(6):740–746
40. Sainani NI, Saokar A, Deshpande V, Fernandez-del Castillo C, Hahn P, Sahani DV (2009) Comparative performance of MDCT and MRI with MR cholangiopancreatography in characterizing small pancreatic cysts. AJR Am J Roentgenol 193(3):722–731
41. Kang KM, Lee JM, Shin CI et al (2013) Added value of diffusion-weighted imaging to MR cholangiopancreatography with unenhanced mr imaging for predicting malignancy or invasiveness of intraductal papillary mucinous neoplasm of the pancreas. J Magn Reson Imaging JMRI. 38(3):555–563
42. Kim JH, Eun HW, Park HJ, Hong SS, Kim YJ (2012) Diagnostic performance of MRI and EUS in the differentiation of benign from malignant pancreatic cyst and cyst communication with the main duct. Eur J Radiol 81(11):2927–2935
43. Macari M, Finn ME, Bennett GL et al (2009) Differentiating pancreatic cystic neoplasms from pancreatic pseudocysts at MR imaging: value of perceived internal debris. Radiology 251(1):77–84
44. Pozzi-Mucelli RM, Rinta-Kiikka I, Wunsche K et al (2017) Pancreatic MRI for the surveillance of cystic neoplasms: comparison of a short with a comprehensive imaging protocol. Eur Radiol 27(1):41–50
45. Choi SY, Kim JH, Yu MH, Eun HW, Lee HK, Han JK (2017) Diagnostic performance and imaging features for predicting the malignant potential of intraductal papillary mucinous neoplasm of the pancreas: a comparison of EUS, contrast-enhanced CT and MRI. Abdom Radiol (N Y) 42(5):1449–1458
46. Ridtitid W, DeWitt JM, Schmidt CM et al (2016) Management of branch-duct intraductal papillary mucinous neoplasms: a large single-center study to assess predictors of malignancy and long-term outcomes. Gastrointest Endosc 84(3):436–445
47. Ahmad NA, Kochman ML, Lewis JD, Ginsberg GG (2001) Can EUS alone differentiate between malignant and benign cystic lesions of the pancreas? Am J Gastroenterol 96(12):3295–3300
48. Emaminejad N, Qian W, Guan Y et al (2016) Fusion of quantitative image and genomic biomarkers to improve prognosis assessment of early stage lung cancer patients. IEEE Trans Biomed Eng 63(5):1034–1043
49. Lloyd MC, Allam-Nandyala P, Purohit CN, Burke N, Coppola D, Bui MM (2010) Using image analysis as a tool for assessment of prognostic and predictive biomarkers for breast cancer: how reliable is it? J Pathol Inform 1:29
50. Cameron A, Khalvati F, Haider MA, Wong A (2016) MAPS: a quantitative radiomics approach for prostate cancer detection. IEEE Trans Biomed Eng 63(6):1145–1156
51. Chakraborty J, Midya A, Gazit L et al (2018) CT radiomics to predict high-risk intraductal papillary mucinous neoplasms of the pancreas. Med Phys 45(11):5019–5029
52. Permuth JB, Choi J, Balarunathan Y et al (2016) Combining radiomic features with a miRNA classifier may improve prediction of malignant pathology for pancreatic intraductal papillary mucinous neoplasms. Oncotarget 7(52):85785–85797

53. Hanania AN, Bantis LE, Feng Z et al (2016) Quantitative imaging to evaluate malignant potential of IPMNs. Oncotarget 7(52):85776–85784
54. Attiyeh MA, Chakraborty J, Gazit L et al (2019) Preoperative risk prediction for intraductal papillary mucinous neoplasms by quantitative CT image analysis. HPB 21(2):212–218
55. Furukawa T, Kloppel G, Volkan Adsay N et al (2005) Classification of types of intraductal papillary-mucinous neoplasm of the pancreas: a consensus study. Virchows Archi Int J Pathol 447(5):794–799
56. Furukawa T, Hatori T, Fujita I et al (2011) Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. Gut 60(4):509–516
57. Patra KC, Bardeesy N, Mizukami Y (2017) Diversity of precursor lesions for pancreatic cancer: the genetics and biology of intraductal papillary mucinous neoplasm. Clin Transl Gastroenterol 8(4):e86
58. Al-Refaie WB, Choi EA, Tseng JF et al (2006) Intraductal papillary mucinous neoplasms of the pancreas. Med Princ Pract Int J Kuwait Univ Health Sci Cent 15(4):245–252
59. Tan MC, Basturk O, Brannon AR et al (2015) GNAS and KRAS mutations define separate progression pathways in intraductal papillary mucinous neoplasm-associated carcinoma. J Am Coll Surg 220(5):845–854.e841
60. Yopp AC, Katabi N, Janakos M et al (2011) Invasive carcinoma arising in intraductal papillary mucinous neoplasms of the pancreas: a matched control study with conventional pancreatic ductal adenocarcinoma. Ann Surg 253(5):968–974
61. Winter JM, Jiang W, Basturk O et al (2016) Recurrence and survival after resection of small intraductal papillary mucinous neoplasm-associated carcinomas ($\leq$20-mm invasive component): a multi-institutional analysis. Ann Surg 263(4):793–801
62. Basturk O, Tan M, Bhanot U et al (2016) The oncocytic subtype is genetically distinct from other pancreatic intraductal papillary mucinous neoplasm subtypes. Mod Pathol 29(9):1058–1069
63. Maker AV, Katabi N, Gonen M et al (2011) Pancreatic cyst fluid and serum mucin levels predict dysplasia in intraductal papillary mucinous neoplasms of the pancreas. Ann Surg Oncol 18(1):199–206
64. Khalid A, Zahid M, Finkelstein SD et al (2009) Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc 69(6):1095–1102
65. Singhi AD, Nikiforova MN, McGrath K (2017) DNA testing of pancreatic cyst fluid: is it ready for prime time? Lancet Gastroenterol Hepatol 2(1):63–72
66. Das KK, Xiao H, Geng X et al (2014) mAb Das-1 is specific for high-risk and malignant intraductal papillary mucinous neoplasm (IPMN). Gut 63(10):1626–1634
67. Maker AV, Hu V, Kadkol SS et al (2019) Cyst fluid biosignature to predict intraductal papillary mucinous neoplasms of the pancreas with high malignant potential. J Am Coll Surg 228(5):721–729
68. Al Efishat MA, Attiyeh MA, Eaton AA et al (2018) Multi-institutional validation study of pancreatic cyst fluid protein analysis for prediction of high-risk intraductal papillary mucinous neoplasms of the pancreas. Ann Surg 268(2):340–347
69. Bournet B, Vignolle-Vidoni A, Grand D et al (2016) Endoscopic ultrasound-guided fine-needle aspiration plus KRAS and GNAS mutation in malignant intraductal papillary mucinous neoplasm of the pancreas. Endosc Int Open 4(12):E1228–e1235
70. Sausen M, Phallen J, Adleff V et al (2015) Clinical implications of genomic alterations in the tumour and circulation of pancreatic cancer patients. Nat Commun 6:7686