CYSTIC PANCREATIC LESIONS BEYOND THE GUIDELINES: CAN WE MAKE AN EVIDENCE-BASED DECISION WHETHER TO RESECT OR TO OBSERVE?

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ABSTRACT

Pancreatic cystic neoplasms (PCNs) are no longer considered as rare entities because their prevalence in the general population ranges from 3–20%. They are usually asymptomatic, incidentally discovered, and diagnosed in the seventh decade of life. The main clinical concern with regard to PCNs is related to their risk of malignant progression, which is relevant for those PCNs that produce mucin. Since 2006, several sets of international guidelines have proposed algorithms for the management of PCNs, and these have been subsequently validated by several studies. Retrospective review of the literature shows that current treatment of PCNs remains unsatisfactory because the guidelines are based on a low level of evidence. However, the guidelines are able to correctly identify lesions that can be safely followed and, as occurs in vaccination campaigns, they are able to exercise a preventive effect in the general population.

Keywords: Pancreatic cyst, cystic neoplasm of the pancreas, intraductal papillary mucinous neoplasms, mucinous, serous, Sendai, Fukuoka, guidelines, pancreatic cancer.

INTRODUCTION: FROM THE ORIGINS TO THE GUIDELINES ERA

The increasing prevalence of pancreatic cystic neoplasms (PCNs) during previous decades has led to the use of the term 'technopathies' to describe this heterogeneous group of tumours. In fact, the increasing use of high-quality, cross-sectional imaging in clinical practice has played the major role in the discovery and subsequent characterisation of these entities. It has been estimated that 3–14% of the general population has at least one PCN.[1-4] After the first report describing a PCN was published in the early 1980s,[5] an increasing number of case reports and clinical studies focussing on pancreatic cysts have been published. In daily clinical practice, clinicians face a high and increasing number of PCNs and must deal with the risk of either over or undertreatment of patients due to our currently incomplete knowledge of their biological behaviour. In the present article we summarise the most prominent publications defining the clinical and radiological aspects of PCNs, which were obtained following a comprehensive review of the literature; these publications range from articles describing original research to consensus guidelines based on various, generally low levels of evidence.

Intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and serous cystic neoplasms (SCNs) represent the most frequently observed entities in the family of PCNs. There are several other rare types of PCN with a very low prevalence,[6] but a full description of these is beyond the aims of the present review and therefore not included. Whenever a patient with suspected PCN is referred to a specialist, the typical clinical picture is that of an asymptomatic and nonspecific lesion in the pancreatic parenchyma. Identification of the lesion's cystic nature is often easily achieved via the initial diagnostic workup. However, the definition of the specific subtype of PCN (IPMN, MCN, or SCN) and the consequent risk of malignancy represents a

challenging diagnostic dilemma. For example, the connection between the cyst and the pancreatic ductal system, which differentiates the diagnosis of an IPMN from that of an MCN, can be difficult to assess even with high-quality, cross-sectional imaging. Moreover, the presence of a multicystic pattern is more frequently associated with SCNs (Figure 1), but a small oligocystic mass in the body/tail of the pancreas offers a difficult differential diagnosis between an SCN and an MCN. In many cases, only surgical resection provides a definitive diagnosis, and the rate of error can be as high as 30% at high-volume centres.[7]

The first landmark in the development of a policy for the diagnosis and treatment of PCNs was the publication of the international consensus guidelines in 2006.[8] These 'Sendai guidelines' greatly contributed to increasing awareness regarding PCNs and facilitated further studies (Table 1).[8-11]

INTERNATIONAL SENDAI CONSENSUS GUIDELINES (2006)

Since reducing the risk of a misdiagnosis represents a critical issue for pancreatic specialists, the Sendai guidelines contain practical indications that are useful for the prediction of malignancy in a pancreatic cyst. Historically, IPMNs involving the main duct (MD-IPMNs; Figure 2) have been considered as a major indication for resection because they have a high likelihood of harbouring malignancy.[12] During imaging, this type of PCN frequently appears as a dilatation of the main pancreatic duct (MPD) rather than an obvious cystic lesion, with a diameter between 5 and 9 mm considered as presumptive for the diagnosis. Mixed-type IPMNs (MT-IPMNs) have been categorised together with MD-IPMNs because the involvement of the MPD is the principal determinant of the tumour's biology. In contrast, indications as to whether to resect or not are less evident when a cystic neoplasm develops at a site distal from the MPD. The Sendai guidelines specify the dimensions of the cyst as being the main parameter, with an empirical 3 cm threshold. Even if no other 'worrisome features' are present, recommendation to schedule the patient for resection is given by this parameter alone. Other indications to resect a cystic neoplasm are the presence of mural nodules, symptoms such as jaundice or pancreatitis, MPD dilatation >6 mm, and positive cytology. The 2006 Sendai guidelines have been validated by a number of case series,[13-18] with diagnostic sensitivity shown to be extremely high, but approximately 75% of the resections were performed on tumours found to be benign/borderline. The morbidity and mortality rates associated with pancreatic resections, which are as high as 40% and 3% respectively,[19] demand a superior means of predicting malignancy so that unnecessary procedures can be avoided.

INTERNATIONAL FUKUOKA CONSENSUS GUIDELINES (2012)

The volume of literature and new evidence that became available following the publication of the Sendai guidelines advocated for an update. The new 'Fukuoka guidelines' stratified pancreatic cysts into different categories depending on their characteristics and related clinical symptoms.[9] Jaundice, enhancing solid component in the cyst, and an MPD size >10 mm have been defined as 'high-risk stigmata', and their presence indicates resection because of a relevant association with an invasive tumour in 6–27% of cases.[14] A cyst size >3 cm, thick or enhancing cyst walls, non-enhancing nodules, MPD size between 5 and 9 mm, abrupt change in MPD calibre with concomitant atrophy, and suspect lymphadenopathy or pancreatitis are worrisome features, and should undergo a second-level follow-up with endoscopic ultrasonography (EUS). At this point, if any mural nodules, involvement of MPD, or suspicious/positive cytology are detected, then resection is warranted. In the absence of both high-risk stigmata and worrisome features, the dimension of the cyst represents the crucial parameter to establish the correct timing of the follow-up.

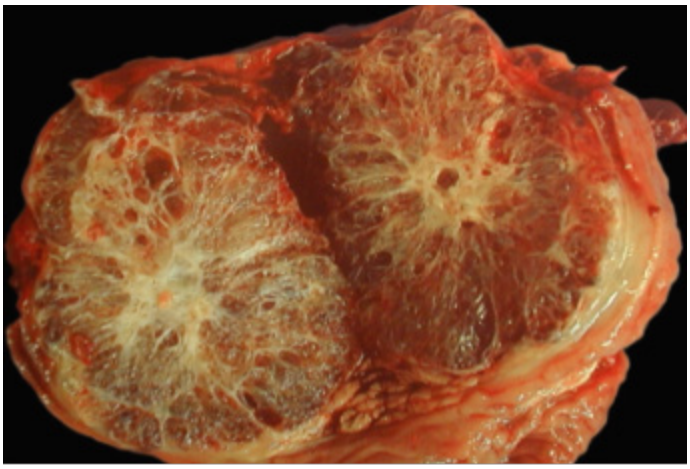

Figure 1: Gross pathology of a serous cystic neoplasm.

Table 1: Current clinical guidelines on the management of pancreatic cystic neoplasms.

Sendai consensus guidelines[8] (applied to all mucin-producing pancreatic cystic neoplasms)	
MD-IPMN	MPD >10 mm
Sendai-positive BD-IPMN	Size >3 cm Size <3 cm with symptoms, mural nodules, MPD dilatation >6 mm, and/or positive cytology
Fukuoka consensus guidelines[9] (applied to all mucin-producing pancreatic cystic neoplasms)	
High-risk stigmata	Proximal lesion with obstructive jaundice Enhancing nodules Dilated MPD >10 mm
Worrisome features	Size >3 cm Pancreatitis Non-enhancing mural nodules Thickened, enhancing walls Dilated MPD (5–10 mm) Change in MPD calibre with distal atrophy Lymphadenopathy
European consensus guidelines[10] (applied to all mucin-producing pancreatic cystic neoplasms)	
Risk factors	Symptoms Size >4 cm Mural nodules Dilated MPD >6 mm Elevated CA 19-9 (relative risk)
American Gastroenterological Association guidelines[11] (applied to asymptomatic mucinous cysts)	
Low risk	Size <3 cm No solid component
High risk	Size >3 cm Dilated MPD Solid component Concerning feature on EUS

BD-IPMN: branch-duct intraductal papillary mucinous neoplasm; CA 19-9: carbohydrate antigen 19-9; EUS: endoscopic ultrasonography; MD-IPMN: main-duct intraductal papillary mucinous neoplasm; MPD: main pancreatic duct.

The most relevant novelty of these guidelines is a more conservative approach towards mucinous-producing cystic tumours, which aimed to reduce the false-positive rate for malignancy compared with the previous version.

EUROPEAN EXPERTS CONSENSUS STATEMENT ON PCNS (2013)

Another 'experts' consensus meeting' was held in 2013, this time in Europe, and brand new guidelines for the management of cystic neoplasms of the pancreas were generated.[10] The trend towards a more conservative approach dependent on the size of the cyst was confirmed, with a cut-off size of 4 cm used for deciding whether to resect a tumour or not. There needs to be a note of caution with this cut-off value, however, because malignancy can be found in smaller lesions too, with a frequency of up to 25% in lesions <4 cm.[9] However, this risk needs to be considered alongside the risk of mortality associated with a major pancreatic resection. Other indications to resect a PCN are the related symptoms, mural nodules, MPD ≥6 mm, elevated serum carbohydrate antigen 19-9, and an increase in cyst size >2 mm/year. With regards to diagnostic methodology, both computed tomography (CT) and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) are considered the gold standard, whilst EUS with fine-needle aspiration (FNA) should be reserved for selected cases because of its low accuracy and inter-observer variability.[20-22]

Several sets of national guidelines have been published since 2013, such as the Italian guidelines in 2014, but the level of evidence remains low and unable to provide substantially different indications to support decision-making.[23]

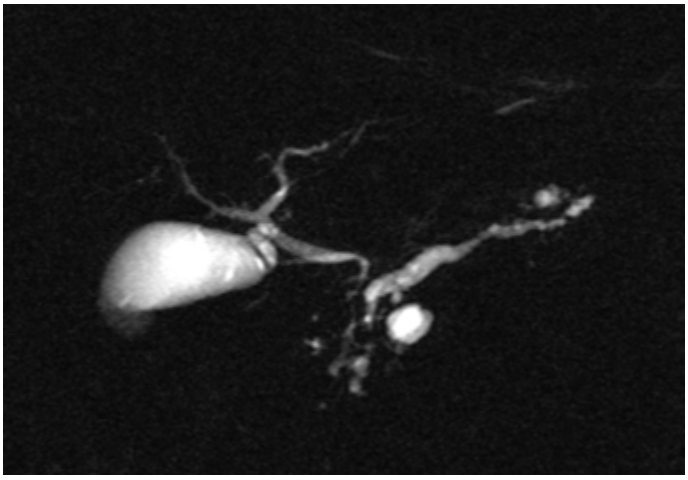

Figure 2: Magnetic resonance cholangiopancreatography of a mixed-type intraductal papillary mucinous neoplasm.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION INSTITUTE GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF ASYMPTOMATIC PCNS (2015)

The most recent policy in the field is represented by the American Gastroenterological Association (AGA) guidelines published in 2015.[11] The AGA guidelines refer only to asymptomatic cysts of the pancreas with side-branch involvement; MD-IPMN, symptomatic cysts, and cystic differentiation of other malignant tumours are therefore excluded. According to the AGA guidelines, cysts <3 cm and without solid components or dilated MPD can be followed up through MRI. Cysts with ≥2 high-risk features, such as size >3 cm, dilated MPD, or presence of solid components should undergo EUS-FNA to better assess the risk of malignancy. Patients without concerning results from EUS-FNA could be followed up with MRI, although the negative predictive value of FNA is low. Significant changes during the surveillance programme represent an indication for subsequent EUS risk assessment. After 5 years of follow-up, or whenever a patient is no longer a surgical candidate, radiological surveillance may be discontinued. Finally, surgical resection is advocated when either a solid component and MPD dilatation is found, or when there are concerning results from EUS or positive cytology.

THE MANAGEMENT OF PANCREATIC CYSTS BEYOND THE GUIDELINES

The first and foremost result of the publication of international guidelines by world-renowned experts has been to increase awareness that PCNs are entities that are not as uncommon as previously thought. At the same time, internal policies on the management of PCNs at different centres with expertise in the field have been rearranged and modified according to the guidelines. As a result, a bulk of literature with a focus of validating the guidelines has been published, with the 2-fold aim of assessing their accuracy and possibly improving them.

The first data that can be extracted from the post-guidelines literature are the standardisation of diagnosis and research of PCNs. Clinicians and gastrointestinal specialists all over the world have acknowledged that tomographic imaging through CT and MRI with MRCP represents the first fundamental step in correctly assessing a cystic lesion in the pancreas.[8] In this regard, EUS-FNA is now considered a second-level examination and is not systematically indicated as a first approach to guide the management strategy.[9] In experienced hands, EUS can be a valid diagnostic tool for detecting solid components in PCNs, the relationship with the ductal system, septa, and cystic fluid features.[24] However, it remains an operator-sensitive technique and the addition of cytological examination can even reduce its sensitivity because there is low inter-observer agreement in defining cytology grading for PCNs.[21] Other diagnostic tools, such as positron emission tomography, have not reached a sufficient level of accuracy for defining the features of PCNs and predicting their biological behaviour, and therefore do not have a role in either the initial work-up or the follow-up. However, the main concept when assessing the true nature of a PCN is that diagnostic accuracy is low, even in the setting of a correct algorithm used at high-volume centres.[7] As the possibility to correctly define a PCN is, by definition, only possible at pathological examination, most of the studies validating the guidelines are retrospective surgical series.

In contrast to what can be extrapolated from the policies of the guidelines, debate on the correct management of SCNs still exists. We are now aware that the growth rate can be predicted by the morphological features and follows a bimodal curve.[25] These factors should be taken into account

in decision making and integrate the guideline concept that serous cystic adenomas (SCAs) should not be resected. The fact that malignant SCAs are practically non-existent has been reinforced by a recent large multi-institutional series of 1,363 resected cases, in which only three were invasive (0.2%).[26] With regard to MCNs, surgical series validating the guideline policy to always resect this premalignant neoplasm have shown low rates of either high-grade dysplasia or invasive cancers ranging from 5.5–13.4% and 3.9–12%, respectively.[8,27,28] Moreover, combining the results of six major studies that met International Academy of Pathology criteria for diagnosis of MCNs showed that only 0.26% of MCNs <3 cm in diameter were malignant.[28-33] Indeed, the authors of these recent studies suggest following up MCNs of small dimensions and in the absence of solid components.[34-36] Among all PCNs, IPMNs represent by far the most debated entity in terms of assessing the reliability of the guidelines. Further large series have shown that the Sendai guidelines lack specificity, so that the more recent Fukuoka guidelines have a more conservative approach in order to prevent unnecessary pancreatic surgeries, as high-risk stigmata, jaundice, and enhancing nodules have had their predictive value for malignancy confirmed.[13,15,16] The correct cut-off for MPD size has been debated more, because reducing the cut-off value to 5 mm seems to improve its accuracy as a predictor of malignancy.[15,16] However, the most controversial parameter of those taken into account as predictors of malignancy in IPMNs is the diameter of the cyst. Several studies have tested the 3 cm cut-off in order to assess the risk of malignancy, and most of them have concluded that it seems reasonable to continue observing a small PCN in the absence of other triggers for surgery.[13,15-18] Other studies have claimed the opposite, however, and have reported relevant rates of malignancy, even in small branch-duct IPMN (BD-IPMN) <3 cm.[37-40] All of the other worrisome features, such as thick or enhancing cyst walls, non-enhancing nodules, abrupt change in MPD with distal atrophy, pancreatitis, and the presence of lymphadenopathy, have been variably associated with malignancy. However, whenever a statistically significant correlation has been identified, the diagnostic value was fairly poor, with low specificity and sensitivity.[13-16,18] The application of both the Sendai and Fukuoka guidelines has been very recently evaluated in 1,382 resected patients by Goh and colleagues.[14] The revised guidelines have a low positive predictive value ranging from 27–62% and with an overall value of 36%. The stratification of cases into two subgroups at different risk results in an improved positive predictive value of 66% in the group of patients displaying high-risk stigmata. Moreover, the negative predictive value ranges from 82–100%. In their conclusions, the authors point out that a relevant cohort of IPMNs classified as 'low risk of malignancy' showed either high-grade dysplasia or invasive carcinoma.[14] With regard to the surveillance of BD-IPMN, it seems reasonable to follow up lesions not presenting with high-risk stigmata. Large observational studies have shown that a minority of the patients will undergo surgery for cysts that increase in size or due to the development of symptoms (around 20%), and practically none of these will be found with unresectable cancer.[17]

DISCUSSION

In multiple fields of surgical oncology, clinical guidelines are needed in order to guide clinicians when taking crucial decisions in the management of patients. In this regard, PCNs do not represent an exception, especially because of their recent discovery and presumed relatively low prevalence in the general population. Now we are aware that PCNs are not rare entities thanks to the widespread use of tomographic imaging. Moreover, increasing evidence has been published during the last decades and expert opinions are being tested by the data coming from surgical series. Unfortunately, because of the peculiar biology of the disease, randomised controlled trials capable of achieving the appropriate level of evidence are far from being established. At the same time, we are aware that the use of experts' opinions as guidelines represents the bottom of the 'evidence pyramid', and that they should represent the starting point of a scientific process instead of a fixed policy.

Analysis of literature published after the different international guidelines and aiming to validate their accuracy has raised several important issues. SCNs do not represent an indication for surgery and undergo resection mainly due to a diagnostic error or because they cause mass-related symptoms.[25] Mucin-producing cystic neoplasms still represent a potential indication for surgery because the literature has failed to exclude their potential to progress to invasive carcinoma. However, the guidelines and subsequent literature reveal the need for parameters able to determine whether

the risk of harbouring invasive carcinoma exceeds that arising from a difficult surgical procedure. Surgeons are aware that pancreatic resections carry with them a relevant risk of both morbidity and mortality, even nowadays and at high-volume centres.[41] In this setting, surgeons are aware that they are not operating on a cyst, but on an individual who has a 3% likelihood of dying because of the procedure and a risk of serious complications that exceeds 30%. There are no truly 'minimally invasive' procedures to remove pancreatic neoplasms, which is in contrast to other types of premalignant lesions that can be safely excised whilst at a premalignant stage, such as colon polyps. Enucleations and laparoscopic techniques are also burdened with relevant rates of morbidity,[42,43] and clinicians should always keep this in mind during decision-making. At the same time, accurate analysis of the guidelines and subsequent literature has revealed that leaving a potentially fatal tumour technically amenable to resection in the pancreas should be considered as a fatal mistake. In fact, guidelines more prone to a significant rate of false-positive cysts seem more acceptable than those leading to the opposite type of diagnostic error. In this setting, the policies of the Fukuoka guidelines with respect of IPMNs have been shown to be fairly safe. Debate still remains because recent publications on small 'negative-for-resection-criteria' IPMNs have reported high rates of malignancy.[37,44] These data appear difficult to read, and one may speculate that the different ways in which different pathologists classify the same grade of dysplasia may be having an effect in this setting. The need for a 'common language' in the pathological assessment of PCNs was recently highlighted at a multidisciplinary expert meeting held in Verona. The aim of the meeting was not to generate new guidelines, but to find a way to increase the level of evidence in the field. Indeed, the first study promoted by those in attendance has led to a standardisation of the definitions used by pathologists with regard to PCNs.[45]

The new AGA guidelines were published almost immediately after the scientific community appeared to be moving towards a common method of promoting more multicentric prospective studies aimed at improving the level of evidence in the post-guidelines era. Far from being evaluated in validation studies, the AGA guidelines importantly disclose that they are based on low-quality evidence. It therefore looks unlikely that they could fill the gaps between international policies and local clinical practice. In fact, the trend towards a more conservative approach, even for mucinous PCNs, in past years demands answers from large cohort studies with long-term follow-up. Moreover, expectations are growing regarding the use of molecular analyses of cystic fluid and other next-generation biomarkers to improve our ability to predict the risk of progression to malignancy in a specific lesion.[22]

CONCLUSIONS

The question of whether to resect or to observe PCNs is still far from being answered in an evidence-based setting. Critical analysis of the available guidelines indicates that their application in clinical practice seems to resemble the effect of vaccinations; they are able to 'protect' the vast majority of the population affected by a PCN. Mistakes cannot be totally avoided, however, because we cannot guarantee each patient that our policies are 100% safe with regard to not missing a malignant tumour or resecting a benign one. Only large prospective studies will help us to increase our knowledge and drive clinical practice forward by allowing us to tailor treatment to individual patients.

REFERENCES

1. Zhang X-M et al. Pancreatic cysts: depiction on single-shot fast spin-echo MR images. Radiology. 2002;223(2): 547-53.

2. Laffan TA et al. Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol. 2008;191(3):802-7.

3. Chernyak V et al. Incidental pancreatic cystic lesions: is there a relationship with the development of pancreatic adenocarcinoma and all-cause mortality? Radiology. 2015;274(1):161-9.

4. de Jong K et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol. 2010;8(9):806-11.

5. Itai Y et al. "Ductectatic" mucinous cystadenoma and cystadenocarcinoma of the pancreas. Radiology. 1986;161(3): 697-700.

6. Farrell JJ, Fernández-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. Gastroenterology. 2013;144(6):1303-15.

7. Salvia R et al. Pancreatic resections for cystic neoplasms: from the surgeon's presumption to the pathologist's reality. Surgery. 2012;152(3 Suppl 1):S135-42.

8. Tanaka M et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6(1-2): 17-32.

9. Tanaka M et al; International Association

of Pancreatology International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183-97.

10. Del Chiaro M et al. European experts consensus statement on cystic tumours of the pancreas. 2013;45(9):703-11.

11. Vege SS et al; Clinical Guidelines Committee; American Gastroenterology Association. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148(4): 819-22.

12. Malleo G et al. Observational study of the incidence of pancreatic and extrapancreatic malignancies during surveillance of patients with branch-duct intraductal papillary mucinous neoplasm. Ann Surg. 2015;261(5):984-90.

13. Goh BK et al. Are the Sendai and Fukuoka consensus guidelines for cystic mucinous neoplasms of the pancreas useful in the initial triage of all suspected pancreatic cystic neoplasms? A single-institution experience with 317 surgically-treated patients. Ann Surg Oncol. 2014;21(6):1919-26.

14. Goh BK et al. Evaluation of the Fukuoka Consensus Guidelines for intraductal papillary mucinous neoplasms of the pancreas: Results from a systematic review of 1,382 surgically resected patients. Surgery. 2015;doi:10.1016/j.surg.2015.03.021. [Epub ahead of print].

15. Seo N et al. Validation of the 2012 International Consensus Guidelines Using Computed Tomography and Magnetic Resonance Imaging: Branch Duct and Main Duct Intraductal Papillary Mucinous Neoplasms of the Pancreas. Ann Surg. 2015. [Epub ahead of print].

16. Jang JY et al. Validation of international consensus guidelines for the resection of branch duct-type intraductal papillary mucinous neoplasms. Br J Surg. 2014;101(6):686-92.

17. Sahora K et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. Ann Surg. 2013;258(3):466-75.

18. Aso T et al. "High-risk stigmata" of the 2012 international consensus guidelines correlate with the malignant grade of branch duct intraductal papillary mucinous neoplasms of the pancreas. Pancreas. 2014;43(8):1239-43.

19. Vollmer CM Jr et al; Pancreatic Surgery Mortality Study Group. A root-cause analysis of mortality following major pancreatectomy. J Gastrointest Surg. 2012;16(1):89-102.

20. Woolf KM et al. False-negative rate of endoscopic ultrasound-guided fine-needle aspiration for pancreatic solid and cystic lesions with matched surgical resections as the gold standard: one institution's experience. Cancer Cytopathol. 2013;121(8):449-58.

21. Sigel CS et al. Low interobserver agreement in cytology grading of mucinous pancreatic neoplasms. Cancer Cytopathol. 2014;123(1):40-50.

22. Maker AV et al. Cyst fluid biomarkers for intraductal papillary mucinous neoplasms of the pancreas: a critical review from the international expert meeting on pancreatic branch-duct-intraductal papillary mucinous neoplasms. 2015;220(2):243-53.

23. Buscarini E et al; Italian Association of Hospital Gastroenterologists and Endoscopists; Italian Association for the Study of the Pancreas; Cystic Pancreatic Neoplasm Study Group. Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms. Dig Liver Dis. 2014;46(6):479-93.

24. Ahmad NA et al. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. Gastrointest Endosc. 2003;58(1):59-64.

25. Malleo G et al. Growth pattern of serous cystic neoplasms of the pancreas: observational study with long-term magnetic resonance surveillance and recommendations for treatment. Gut. 2012;61:746-51.

26. Jais B et al. Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas). Gut. 2015;doi:10.1136/gutjnl-2015-309638. [Epub ahead of print].

27. Yamao K et al. Clinicopathological features and prognosis of mucinous cystic neoplasm with ovarian-type stroma: a multi-institutional study of the Japan pancreas society. Pancreas. 2011;40(1): 67-71.

28. Crippa S et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 2008;247(4):571-9.

29. Nguyen D et al. Mucinous cystic neoplasms of the pancreas: are we overestimating malignant potential? Am Surg. 2014;80(10):915-9.

30. Zamboni G et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. Am J Surg Pathol. 1999;23(4):410-22.

31. Reddy RP et al. Pancreatic mucinous cystic neoplasm defined by ovarian stroma: demographics, clinical features, and prevalence of cancer. Clin Gastroenterol Hepatol. 2004;2(11): 1026-31.

32. Izumo A et al. Mucinous cystic tumor of the pancreas: immunohistochemical assessment of "ovarian-type stroma". Oncol Rep. 2003;10(3):515-25.

33. Gil E et al. Mucinous cystic neoplasms of the pancreas with ovarian stroma. ANZ J Surg. 2013;83(12):985-90.

34. Allen PJ et al. A selective approach to the resection of cystic lesions of the pancreas: results from 539 consecutive patients. Ann Surg. 2006;244(4):572-82.

35. Lahav M et al. Nonsurgical management of asymptomatic incidental pancreatic cysts. Clin Gastroenterol Hepatol. 2007;5(7):813-7.

36. Park JW et al. Mucinous cystic neoplasm of the pancreas: Is surgical resection recommended for all surgically fit patients? Pancreatology. 2014;14(2): 131-6.

37. Fritz S et al. Branch duct intraductal papillary mucinous neoplasms of the pancreas: watch and wait is not harmless. Pancreas. 2013;42(2):358.

38. Fritz S et al. Pancreatic intraductal papillary mucinous neoplasm--where is the challenge? Dig Dis. 2015;33(1):99-105.

39. Fritz S et al. Pancreatic main-duct involvement in branch-duct IPMNs: an underestimated risk. Ann Surg. 2014; 260(5):848-56.

40. Wong J et al. High-grade dysplasia and adenocarcinoma are frequent in side-branch intraductal papillary mucinous neoplasm measuring less than 3 cm on endoscopic ultrasound. J Gastrointest Surg. 2013;17(1):78-85.

41. Balzano G et al. Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. Br J Surg. 2008;95(3):357-62.

42. Zhang T et al. Enucleation of pancreatic lesions: indications, outcomes, and risk factors for clinical pancreatic fistula. J Gastrointest Surg. 2013;17(12):2099-104.

43. Stauffer JA, Asbun HJ. Minimally invasive pancreatic surgery. Semin Oncol. 2015;42(1):123-33.

44. Fritz S et al. Small (Sendai negative) branch-duct IPMNs: not harmless. Ann Surg. 2012;256(2):313-20.

45. Adsay V et al; Members of the Verona Consensus Meeting, 2013. Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract: Recommendations of Verona Consensus Meeting. Ann Surg. 2015. [Epub ahead of print].