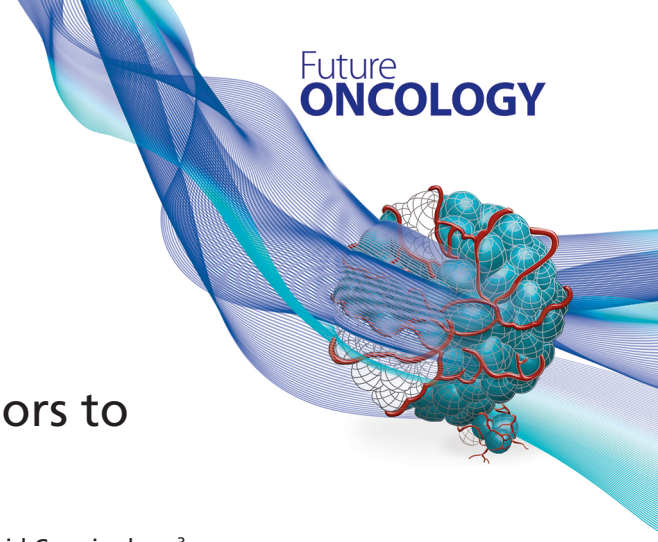
Special Report



Can we predict the progression of premalignant pancreatic cystic tumors to ductal adenocarcinoma?

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Pancreatic ductal adenocarcinoma (PDAC) is the most prevalent malignant pancreatic tumor. Few studies have shown how often PDACs arise from cystic precursor lesions. This special report aims to summarize the evidence on the progression of precancerous lesions to PDAC. A review of the literature found four studies that discussed pancreatic intraepithelial lesions (PanINs), three that discussed mucinous cystic neoplasms (MCN) and five that discussed intraductal papillary neoplasms (IPMNs). PanINs were the most common precursors lesion, with approximately 80% of PDACs originating from this lesion. The lack of evidence characterizing the features of PDAC precursor cystic lesions potentially leads to a subset of patients undergoing surgery unnecessarily. Advancements in molecular techniques could allow the study of cystic lesions at a genetic level, leading to more personalized management.

Plain language summary: Cancer arising from the ducts within the pancreas is the most common type of pancreatic cancer. Some cancers develop from precancerous changes, but these are not currently well described. Therefore, we have summarized the existing knowledge on the precancerous changes causing pancreatic cancer. We found three main precancerous changes: pancreatic intraepithelial lesions; mucinous cystic neoplasms; and intraductal papillary neoplasms. Pancreatic intraepithelial lesions were the most common pancreatic precancerous lesion, leading to 80% of cancers of the pancreatic ducts. A few studies indicate that patients would benefit from surgery to remove precancerous lesions. We believe that, due to advances in genetic studies, personalized strategies for treating pancreatic cancers will emerge in the future.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) represents approximately 90% of all pancreatic cancers and is the fourth leading cause of cancer-related mortality in western countries, with a mortality rate equivalent to its incidence and a low 5-year survival rate of 5–7% [1–3]. Previous studies on the tumorigenesis of PDAC have identified three precursor cystic lesions. Pancreatic cysts are sac-like pockets of fluid and are categorized as pancreatic intraepithelial lesions (PanINs), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) [2]. IPMN and MCN are often found radiologically, whereas PanIN is a histological feature. More recently, possible alternative PDAC precursors described as atypical flat lesions (AFLs) have been identified in patients with familial pancreatic cancer. The most recent publication from the European Study Group on Cystic Tumours of the Pancreas provides guidance on how these precursor lesions should be managed, including criteria for surgery [4]. However, given the late presentation of PDAC, these precursor lesions are often missed or identified only incidentally. The development of ways to detect these precancerous lesions will not only enable us to diagnose PDAC earlier but also allow us to understand its prognostication, progression and prognosis.

Table 1. Summary of prevalence of precursor pancreatic cyst lesions in pancreatic adenocarcinoma.

Study	Type of precursor lesion	Sample size	Age (years)	Sex, males (n)	Tumor size	Tumor location	CA19-9 level	Prevalence (%)	Ref.
Andea *et al.*	PanIN	82	66.7	33	–	–	–	82 (all grades) 59 (PanIN 2 &3)	[7]
Crippa *et al.*	MCNs	163	45	5	50 mm	Tail of pancreas (97%)	28 (>37 U/l)	17.5	[8]
Hwang *et al.*	PanIN	125	63	69	–	Head of pancreas (69.6%)		57% 18 (PanIN-1) 21 (PanIN-2) 32 (PanIN-3)	[9]
Matsuda *et al.*	IPMN	379	67	234	–	Head of pancreas (42.5%)	–	10.5	[10]
McGinnis *et al.*	PanIN IPMN	52 20	62.5 69.0	33 13	–	Head of pancreas (87%) Head of pancreas (70%)	26 (>37 U/l) 8 (>37 U/l)	72.2 27.8	[11]
Strobel *et al.*	IPMN	937		504	–	Head of pancreas (76%)	674 (>37 U/l)	10.6	[12]
Valsangkar *et al.*	IPMN (38%) MCN (23%)	851	60	32 (MCN) 153 (IPMN)	28.8 mm (MD-IPMN) 29.1 mm (BD-IPMN) 44.1 mm (MCN)	134 body/tail (MCN) 215 head/body/uncinate (IPMN)	–	23	[13]
Winter *et al.*	IPMN, MCN	1175	66	628	30	–	Median of 139 U/ml	6.0	[6]
Yu *et al.*	PanIN	95	64	58	32 mm	Head of the pancreas (58%)	38 (>37 U/l)	59.0 (all grades) 28.6 (PanIN 2) 64.3 (PanIN 3)	[14]

MCN: Mucinous cystic neoplasm; IPMN: Intrapapillary mucinous neoplasm; PanIN: Pancreatic intraepithelial neoplasia; PDAC: Pancreatic adenocarcinoma.

Epidemiology of the premalignant lesions

The most common cysts with neoplastic potential are intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystadenoma (SCA) and solid pseudopapillary neoplasm (SPN). Of these, IPMNs and MCNs are mucin-producing cysts that have a higher risk of malignant transformation to pancreatic adenocarcinoma and so require resection at the early stages of identification. However, not all mucinous cysts lead to PDAC (Table 1). For example, in the prospective SHIP-2 cohort of northern Germany, the prevalence and incidence of pancreatic cysts were estimated at 49.1 and 12.9%, respectively [5]. However, the mortality from these lesions over long-term follow-up was 0%. Only 6% of detected cysts, and 2.5% of the total cohort initially presented with cysts greater than 1 cm, which may have clinical relevance. In the largest single-center experience, Winter *et al.* analyzed 1175 patients who underwent pancreatic resection over a 35-year period and reported that just 6% had an IPMN origin [6]. Hence, although the incidence of cysts may be high, not all progress to a PDAC, and retrospectively evaluating which PDACs originated from an IPMN shows that this is actually a smaller percentage.

Intraductal papillary mucinous neoplasms

Others have sought to establish the relevance of cystic origin in the context of prognostication. For example, Strobel *et al.,* excluded IPMN carcinomas but included more advanced (>pT2) conventional PDAC arising in the context of IPMN [12]. This led to a slightly higher percentage (10.6%) of PDACs arising in the context of IPMNs, although not all may have arisen from an actual IPMN. Univariate analysis further revealed that resection of tumors arising in the IPMN context led to an observed increase in the 5-year survival of patients. However, this was not observed in the multivariate analysis, likely due to accounting for confounding variables such as lower tumor stages of IPMN-associated PDAC [12]. In another study, Matsuda *et al.,* reviewed the clinicopathological data of a consecutive series of 379 patients with PDAC treated by partial pancreatectomy between 1992 and 2015. In this cohort, 40 patients had a concomitant IPMN, in whom the likelihood of tumor recurrence in the remnant pancreas after resection was 4-times higher in PDACs with a IPMN context, making IPMN presence an independent prognostic factor [10]. Although there is much work characterizing the proportion of IPMNs that are malignant, there is little work retrospectively identifying the number of PDACs that originated from an IPMN.

Mucinous cystic neoplasms

MCNs of the pancreas are the most infrequent precursor lesions of PDAC, so it is difficult to determine their prevalence. MCNs occur more frequently in women and are usually located in pancreatic body and tail. Valsangkar *et al.,* reported a prevalence of 23% of MCNs in 851 patients with resected cystic tumors over a 33-year period [13]. Other large case series report a variation from 3 to 36% of invasive MCNs [15,16]. Resection for invasive MCN that is picked up early has a very favorable prognosis with 5-year survival rates reaching 60% [8]. Because of this, the mortality from PDAC with MCN origin is low. As a result, there are still no large-scale data reporting the contribution of MCNs to the incidence or mortality from PDAC.

Pancreatic intraepithelial lesions

PanINs are microscopic flat or papillary lesions arising in the small intralobular pancreatic ducts, and are part of the multistep tumor progression model in pancreatic cancer [17]. Unlike cystic lesions, they are usually asymptomatic. Yet they are the commonest precursor lesion in PDAC [18]. Unlike IPMNs and MCNs, there are several small case series retrospectively describing the development of PDAC from PanINs. For example, Schwartz *et al.,* reported that 82% of PDAC samples had originated from a PanIN, and a further 40% harbored a high-grade PanIN-3 [19]. In another analysis, Andea *et al.,* demonstrated a progressive increase in the number and grade of PanINs in PDAC compared with control pancreas tissues, and Makohon-Moore *et al.,* showed that PanINs were detected not just in PDAC but also in pancreatic tissue adjacent to the tumor site [7,20]. Others have demonstrated a role for PanIN in not just tumor progression but also recurrence and survival, especially compared with other cystic precursor lesions [11,14]. Unlike IPMNs and MCNs, PanINs also present an explanation for the interaction of other patient-related factors such as obesity, smoking, genetic conditions and inflammatory conditions of the pancreas [9]. In this way, compared with IPMNs and MCNs, there is a larger scope of evidence retrospectively linking PDACs to PanINs in their progression and prognosis.

Guidelines for management of cystic lesions

The earliest guidelines for management of pancreatic cysts were published in 2006. Tanaka *et al.,* recognized two types of noninflammatory pancreatic cysts – namely, IPMN and MCN [21]. On the basis of several case series and the phenomenon of 'clonal progression' of tumors toward malignancy, they advocated for resection of all main duct and mixed variant IPMNs as long as the patient is a good surgical candidate. In patients with branch IPMNs, a 'watch and wait' approach can be employed if patients are asymptomatic given the low progression to malignancy. However, surgery was advised in symptomatic cases, or if size exceeds 30 mm. Furthermore, surgery was recommended for all MCNs unless there are contraindications for operation. The revised guidelines in 2012 delved into greater detail in the classification of the various lesions; fine-tuned the incorporation of imaging and preoperative investigations; and proposed new criteria based on symptoms, size, presence of duct dilation and location of cyst, all of which generally correlated with the guidelines set out by the European Study Group on Cystic Tumours of the Pancreas in 2018 [22].

The typical patient pathway involves either symptomatic presentation or incidental finding of cystic lesions, followed by blood tests, endoscopic sampling and computed tomography imaging. At each step, the identification of specific features increases the predictive accuracy of the lesion becoming a PDAC, and this varies between the three types of lesions. Among these, MCNs have the least malignant potential. Features that suggest a higher risk of malignancy include symptoms, size >40 mm and the presence of mural nodule on imaging [23]. There is stronger evidence for features of IPMNs that truly suggest malignancy. These include the presence of an enhancing mural nodule ≥5 mm (sensitivity 73–85%; specificity 71–100%) or a solid component, positive cytology or a main pancreatic duct (MPD) measuring ≥10 mm. However, the accuracy of these features can be as low as 60% at times [24].Currently, there are no accurate biomarkers, including CEA, CA19-9, amylase, DNA, RNA or proteins, to differentiate between IPMNs and MCNs, or to predict progression to PDAC. This is largely due to their presence in nonmalignant conditions, owing to the high false-positive rate. Furthermore, while many patients undergo endoscopic ultrasound with cyst sampling, the diagnostic accuracy of cyst fluid analysis has a huge range that renders it to be of low diagnostic accuracy [25–29]. Overall, there is insufficient evidence to characterize true features of a cyst that will become a PDAC, and where available, the studies are not always the most rigorous in design and methodology.

The case for molecular basis in risk stratification of cystic lesions

An understanding of the main driver mutations is helpful in the molecular characterization of premalignant cysts. In IPMNs, the most frequent genetic alteration is an oncogenic *KRAS* mutation, which is seen in more than 80% of patients. Sixty-five percent of IPMNs also have somatic mutations in the oncogene *GNAS*. Mutations of *KRAS* and *GNAS* lead to constitutive activation of G-coupled receptor proteins that drives tumorigenesis in up to 90% of patients who eventually develop a PDAC. In addition, mutations of the tumor suppressor gene *RNF43*, which is involved in regulating the Wnt/β-catenin signaling pathway, occurs in 14–38% of IPMNs, with frequent loss of heterozygosity. Other potential genes mutated in IPMNs include *TP53, PIK3CA, PTEN, CDKN2A* and *SMAD4*. The genetic alterations found in MCNs are similar to those in IPMNs, with the prevalence proportional to the degree of dysplasia. However, GNAS mutations are distinctly not observed as frequently in MCNs. Although an abundance of data exists for mutations in PDAC, there are few data on the origin of premalignant lesions themselves, and this is an area for further work.

Genomic instability leads to genetic diversity by providing the raw material for the generation of tumor heterogeneity and has been reported in premalignant cystic lesion. Intratumoral heterogeneity can manifest as spatial or temporal heterogeneity. Spatial heterogeneity refers to uneven distribution of genetically different subpopulations across different disease sites or within a single tumor. Temporal heterogeneity is the variation in tumor cells over time. For example, Tan *et al.,* showed that the frequencies of *KRAS* and *GNAS* mutations varied significantly between different histologic subtypes of IPMN [30]. In another study, Fisher *et al.,* used whole genome sequencing to show that IPMNs contained multiple independent clones, each with distinct mutations, instead of a single clone [31]. There was also significant evidence of convergence in *RNF43* and *TP53* mutations in the late stages of tumorigenesis. Taken together, the evolution of tumors over time can be attributed to ongoing mutations. The tumor heterogeneity certainly makes the diagnosis, risk stratification and prognostication a challenging task.

Analysis of genetic mutations in patients may help to stratify which patients are at higher risk. For example, KRAS mutations can be seen in patients with both low and high grade PanINs. In contrast, *CKN2A, TP53* and *SMAD4* mutations are typically found in high-grade PanINs and, at times, in invasive PDACs [32–34]. Even in MCNs, which have a lower malignancy risk, Izeradjene *et al.,* characterized a reliable genetic mutational pathway where a loss of heterozygosity at the *DPC4* tumor suppressor gene increases the risk for progression to malignancy [35]. In the case of PanINs, more than 90% of PDACs that originate from PanINs have a KRAS mutation. Although the inactivation of *p16/CDKN2A* is detectable in the early PanIN stages, the inactivation of *TP53* and *SMAD4/DPC4* is more typical with later alterations in the tumor progression model. Similar alterations to *DPC4* were also seen in several studies for IPMN [36]. The presence of circulating tumor cells and ctDNA has been detected in patients with high-risk features and advanced disease, and this promises to be another noninvasive method to assess which patients will need resection [37].

Tumorigenesis involves both genetic and epigenetic changes. miRNAs are small noncoding RNAs (18–25 nucleotides) that regulate gene expression post-transcriptionally [38]. Work from our own group has shown that the malignant process had already started at a genetic level when PCTs were identified regardless of the type of PCTs [39]. Laboratory studies have shown that miRNAs are involved in the silencing of tumor suppressor genes and activation of oncogenes. The correct combination of pro- and anti-oncogenic miRNAs may play a role in driving tumor progression, and detecting these can help to risk-stratify patients as well [40].

Which lesions should undergo surgical intervention?

The majority of work on outcomes of surgery for cystic neoplasm PDAC resection have selected patients based on earlier guidelines (Figure 1) [41]. These guidelines stratify patients into either high-risk or low-risk categories for developing PDAC using predefined criteria [42,43]. Available studies reaffirm that patients with high-risk features benefit from the intervention in the short and long term if evaluated from the end point (i.e., PDAC). However, when evaluating cystic lesions that were resected, few turn out to be malignant, and several lesions could have been monitored instead. For example, in one study, of the 567 mucinous tumours resected, 29% were MCNs, and of these, 12% harbored invasive cancer, accounting for 3.48% of the total cohort [8]. Yet the surgical intervention led to a 24% pancreatic fistula rate and a 49% overall morbidity, with more than 10% of patients requiring either an interventional radiology procedure or reoperation. A similar picture exists for both IPMNs and PanINs, although there is also evidence to suggest that surgery for correctly identified precursor lesions vastly improves tumor prognosis [10,12]. Amid this, few studies, as outlined here, have looked back at how many PDACs truly originated from cystic lesions.

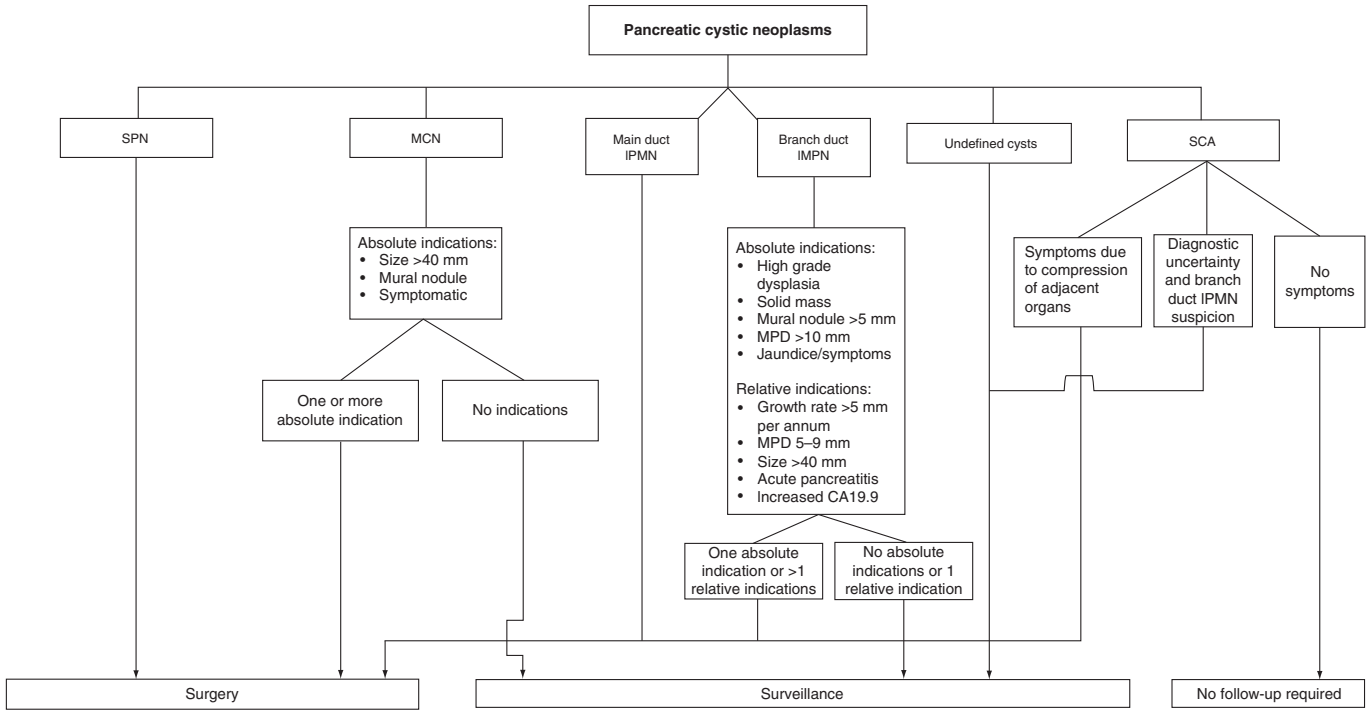

Figure 1. Summary of the main guidelines for management and surveillance of pancreatic cystic neoplasms. Based on European evidence-based guideline, International Guidelines of International Association of Pancreatology and American Gastroenterological Association guidelines.
IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; MPD: Main pancreatic duct; SCA: Serous cystadenoma; SPN: Solid pseudopapillary neoplasm.

The evidence for low-risk patients, who do not fall into the obvious categories with no absolute indications for surgery, is sparse because few studies have retrospectively correlated low-risk features with a cancer diagnosis. Currently, our assessment of cystic lesions relies on clinical presentation, biochemical abnormalities on blood tests and radiological features looking for features of malignancy. Thus, the risk of malignancy from an IPMN is high in a patient who presents with jaundice; has a CA 19-9 level exceeding 37 U/ml; and imaging shows a dilated main pancreatic duct more than 10 mm or a cyst diameter >40 mm. Such a patient will definitely need surgery. However, the risk is very low in an asymptomatic patient younger than 50 years, low level of comorbid disease, no family history of the cystic disease, an unequivocal CA 19-9 level and dilated MPD of 5 mm or less. This patient may not need surgery, but there is scarce evidence quantifying their long-term risk of cancer.

All of this generates several questions but, most pertinently, whether we are resecting the correct lesions; if we are operating on too few or too many cystic lesions; if so, how we can better identify which cystic lesions need intervention; and for patients not requiring surgery, what should be the follow-up plan? Currently, there is little high-grade evidence on large cohorts to answer these questions [44]. Further work should aim to characterize both the patients and cystic precursor lesions to stratify them on their risk of progressing to PDAC and what the long-term management plan should be for low-risk patients. The incorporation of better diagnostic methods, including more novel biochemical tests and genetic testing, will enable us to characterize the disease process at a molecular level and aid in devising a risk stratification system for pancreatic cystic lesions.

IPMNs and MCNs account for a smaller fraction of the PDACs than PanINs, which are the most frequent precursor lesions. There is no rigorous evidence accurately characterizing the features of precursor cystic lesions that progress to PDAC. As such, the preoperative investigations and workup have to lie on the cautious side, leading to a situation in which patients may unnecessarily undergo surgery. There is no reliable evidence that incorporates the patient and the pathology to guide managing patients without clear-cut features of malignancy. The latest technology is available to study cystic lesions and patients at a molecular level. Further work should be aimed at larger scale prospective clinical studies to characterize cystic lesions and to incorporate molecular technologies in the same regard.

Future perspective

In the future, advancements in understanding of true risk factors of malignant progression of pancreatic cysts will allow for more stratification of patients into low- and high-risk groups and more personalized surveillance and management strategies. This will potentially lead to a decreased number of resections for these cysts in low-risk individuals and increased numbers of patients under intense surveillance protocols. This, in turn, could result in better overall health-related quality-of-life across the cohort of patients with pancreatic cystic neoplasms, in light of the potential negative effects distal pancreatectomy or pancreaticoduodenectomy have on multiple aspects of life. These advancements will most likely be associated with more widely available molecular and genetic techniques, allowing for more accurate prognosis of malignant transformation based on mutation pattern and epigenetics, moving away from relying only on radiological and histopathological features, which are currently used for risk stratification.

Executive summary

Pancreatic cysts with neoplastic potential

- The commonest cysts with neoplastic potential are intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, serous cystadenoma, solid pseudopapillary neoplasm and pancreatic intraepithelial lesions.
- There is little evidence on which cysts progress to pancreatic ductal adenocarcinoma, resulting in potential overresection of cystic lesions.

True risk factors for malignant transformation

- Cyst size and location on radiological imaging can be used to predict malignant transformation; however, the accuracy of these parameters is low.
- Biochemical biomarkers such as CA 19-9 have low specificity and sensitivity in predicting malignant transformation of pancreatic cysts.

Future directions

- Analysis of genetic mutations can allow for more accurate risk stratification and personalized management and surveillances plan for patients with pancreatic cysts.
- More prospective surveillance studies are needed to elucidate the true incidence of ductal adenocarcinoma arising from each of the pancreatic cyst types.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Garrido-Laguna I, Hidalgo M. Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. *Nat. Rev. Clin. Oncol.* 12(6), 319–34 (2015).
2. Vincent A, Herman J, Schulick R *et al.* Pancreatic cancer. *Lancet* 378(9791), 607–620 (2011).
3. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. *Lancet* 388(10039), 73–85 (2016).
4. Del Chiaro M, Besselink MG, Scholten L *et al.* European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 67, 789–804 (2018).

•• **This article presents the most up-to-date guidelines for management of pancreatic cystic tumors by the European Study Group on Cystic Tumours of the Pancreas.**

5. Kromrey ML, Bülow R, Hübner J *et al.* Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut* 67(1), 138–145 (2018).

6. Winter JM, Cameron JL, Campbell KA *et al.* 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J. Gastrointest. Surg.* 10(9), 1199–210 (2006).
7. Andea A, Sarkar F, Adsay VN. Clinicopathological correlates of pancreatic intraepithelial neoplasia: a comparative analysis of 82 cases with and 152 cases without pancreatic ductal adenocarcinoma. *Mod. Pathol.* 16(10), 996–1006 (2003).
8. Crippa S, Salvia R, Warshaw AL *et al.* Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. *Ann. Surg.* 247(4), 571–9 (2008).
9. Hwang IK, Kim H, Lee YS *et al.* Presence of pancreatic intraepithelial neoplasia-3 in a background of chronic pancreatitis in pancreatic cancer patients. *Cancer Sci.* 106(10), 1408–13 (2015).
10. Matsuda R, Miyasaka Y, Ohishi Y *et al.* Concomitant intraductal papillary mucinous neoplasm in pancreatic ductal adenocarcinoma is an independent predictive factor for the occurrence of new cancer in the remnant pancreas. *Ann. Surg.* 271(5), 941–948 (2020).
11. McGinnis T, Bantis LE, Madan R *et al.* Survival outcomes of pancreatic intraepithelial neoplasm (PanIN) versus intraductal papillary mucinous neoplasm (IPMN) associated pancreatic adenocarcinoma. *J. Clin. Med.* 9, 3102 (2020).
12. Strobel O, Lorenz P, Hinz U *et al.* Actual five-year survival after upfront resection for pancreatic ductal adenocarcinoma. *Ann. Surg.* 275(5), 962–971 (2020).
13. Valsangkar NP, Morales-Oyarvide V, Thayer SP *et al.* 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. *Surg. (United States)* 152(3 Suppl. 1), S4–12 (2012).
14. Yu DY, Yu YD, Kim WB *et al.* Clinical significance of pancreatic intraepithelial neoplasia in resectable pancreatic cancer on survivals. *Ann. Surg. Treat. Res.* 94(5), 247–253 (2018).
15. Thompson LDR, Becker RC, Przygodzki RM *et al*. Mucinous cystic neoplasm (mucinous cystadenocarcinoma of low-grade malignant potential) of the pancreas: A clinicopathologic study of 130 cases. *Am. J. Surg. Pathol.* 23(1), 1–16 (1999).
16. Izumo A, Yamaguchi K, Eguchi T *et al.* Mucinous cystic tumor of the pancreas: immunohistochemical assessment of ovarian-type stroma. *Oncol. Rep.* 10(3), 515–25 (2003).
17. Hruban RH, Takaori K, Klimstra DS *et al.* An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am. J. Surg. Pathol.* 28(8), 977–87 (2004).
18. Hruban RH, Fukushima N. Pancreatic adenocarcinoma: update on the surgical pathology of carcinomas of ductal origin and panins. *Mod. Pathol.* 20, S61–S70 (2007).

- **This review articles summarizes the evidence on pancreatic intraepithelial lesions and their progression to pancreatic ductal adenocarcinomas (PDACs). It also discusses stratification of PDAC subtypes and the implications of such stratification.**

19. Schwartz AM, Henson DE. Familial and sporadic pancreatic carcinoma, epidemiologic concordance. *Am. J. Surg. Pathol.* 31(4), 645–6 (2007).
20. Makohon-Moore AP, Matsukuma K, Zhang M *et al.* Precancerous neoplastic cells can move through the pancreatic ductal system. *Nature* 561(7722), 201–205 (2018).
21. Tanaka M, Chari S, Adsay V *et al.* International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology* 6(1-2), 17–32 (2006).
22. Tanaka M, Fernández-Del Castillo C, Adsay V *et al.* International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 12(3), 183–97 (2012).
23. Nilsson LN, Keane MG, Shamali A *et al.* Nature and management of pancreatic mucinous cystic neoplasm (MCN): a systematic review of the literature. *Pancreatology* 16(6), 1028–1036 (2016).
24. Gaddam S, Ge PS, Keach JW *et al.* Suboptimal accuracy of carcinoembryonic antigen in differentiation of mucinous and nonmucinous pancreatic cysts: results of a large multicenter study. *Gastrointest. Endosc* 82(6), 1060–1069 (2015).

- **This multicenter study describes features that can be used for differentiation between mucinous and nonmucinous pancreatic cysts, including fine-needle aspiration fluid analysis.**

25. De Jong K, Van Hooft JE, Nio CY *et al.* Accuracy of preoperative workup in a prospective series of surgically resected cystic pancreatic lesions. *Scand. J. Gastroenterol.* 47(8-9), 1056–63 (2012).
26. Ardengh JC, Lopes CV, De Lima-Filho ER *et al*. Impact of endoscopic ultrasound-guided fine-needle aspiration on incidental pancreatic cysts. A prospective study. *Scand. J. Gastroenterol.* 49(1), 114–20 (2014).
27. Gillis A, Cipollone I, Cousins G, Conlon K. Does EUS-FNA molecular analysis carry additional value when compared to cytology in the diagnosis of pancreatic cystic neoplasm? A systematic review. *HPB* 17(5), 377–386 (2015).
28. Brugge WR, Lewandrowski K, Lee-Lewandrowski E *et al.* Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 126(5), 1330–6 (2004).
29. Khalid A, Zahid M, Finkelstein SD *et al.* Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest. Endosc.* 69(6), 1095–102 (2009).
30. Tan MC, Basturk O, Brannon AR *et al.* GNAS and KRAS mutations define separate progression pathways in intraductal papillary mucinous neoplasm-associated carcinoma. *J. Am. Coll. Surg.* 220(5), 845–854.e1 (2015).

31. Fischer CG, Beleva Guthrie V, Braxton AM *et al.* Intraductal papillary mucinous neoplasms arise from multiple independent clones, each with distinct mutations. *Gastroenterology* 157(4), 1123–1137.e22 (2019).
32. Feldmann G, Beaty R, Hruban RH, Maitra A. Molecular genetics of pancreatic intraepithelial neoplasia. *J. Hepatobiliary Pancreat. Surg.* 14(3), 224–32 (2007).
33. Hosoda W, Chianchiano P, Griffin JF *et al.* Genetic analyses of isolated high-grade pancreatic intraepithelial neoplasia (HG-PanIN) reveal paucity of alterations in TP53 and SMAD4. *J. Pathol.* 242(1), 16–23 (2017).
34. Miyazaki T, Ohishi Y, Miyasaka Y *et al.* Molecular characteristics of pancreatic ductal adenocarcinomas with high-grade pancreatic intraepithelial neoplasia (PanIN) are different from those without high-grade PanIN. *Pathobiology* 84(4), 192–201 (2017).
35. Izeradjene K, Combs C, Best M *et al.* KrasG12D and Smad4/Dpc4 haploinsufficiency cooperate to induce mucinous cystic neoplasms and invasive adenocarcinoma of the pancreas. *Cancer Cell* 11(3), 229–243 (2007).

•• **This study discusses genetic signatures of mucinous cystic neoplasms and PDACs, as well as describing mutational pathway that can be used to predict PDAC progression for precursor lesions.**

36. Poultsides GA, Reddy S, Cameron JL *et al.* Histopathologic basis for the favorable survival after resection of intraductal papillary mucinous neoplasm-associated invasive adenocarcinoma of the pancreas. *Ann. Surg.* 251(3), 470–6 (2010).
37. Hugenschmidt H, Labori KJ, Brunborg C *et al.* Circulating tumor cells are an independent predictor of shorter survival in patients undergoing resection for pancreatic and periampullary adenocarcinoma. *Ann. Surg.* 271(3), 549–558 (2020).
38. Ichikawa D, Komatsu S, Konishi H, Otsuji E. Circulating microRNA in digestive tract cancers. *Gastroenterology* 142(5), 1074–1078.e1 (2012).
39. Frampton AE, Castellano L, Colombo T *et al.* MicroRNAs cooperatively inhibit a network of tumor suppressor genes to promote pancreatic tumor growth and progression. *Gastroenterology* 146(1), 268–77.e18 (2014).
40. Lee LS, Szafranska-Schwarzbach AE, Wylie D *et al.* Investigating MicroRNA expression profiles in pancreatic cystic neoplasms. *Clin. Transl. Gastroenterol.* 5(1), e47 (2014).
41. Del Chiaro M, Verbeke C, Salvia R *et al.* European experts consensus statement on cystic tumours of the pancreas. *Dig. Liver Dis.* 45(9), 703–11 (2013).
42. Goh BKP, Thng CH, Tan DMY *et al.* Evaluation of the Sendai and 2012 International Consensus Guidelines based on cross-sectional imaging findings performed for the initial triage of mucinous cystic lesions of the pancreas: A single institution experience with 114 surgically treated patient. *Am. J. Surg.* 208(2), 202–9 (2014).
43. Goh BKP, Tan DMY, Thng CH *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.* 21(6), 1919–26 (2014).
44. Marchegiani G, Salvia R. Guidelines on pancreatic cystic neoplasms: major inconsistencies with available evidence and clinical practice. Results from an international survey. *Gastroenterology* 160(7), 2234–2238 (2021).