Clinical Management of Pancreatic Premalignant Lesions

Pancreatic cancer is on the rise, with a particularly high incidence rate in North America and Europe.[1] Two features of the disease make the prognosis overall poor—first, pancreatic cancer is notoriously difficult to treat, and second, most patients are diagnosed at a very advanced disease stage. Consequently, earlier detection at a premalignant, noninvasive stage is urgently needed.

Although pancreatic cancer is understood to develop through precursor lesions that are defined by several morphologic, molecular, cross-sectional imaging features,[2] the predictive value for the early detection of premalignant lesions is low. Screening in the general population is not recommended because of the overall low prevalence of pancreatic cancer and the low diagnostic yield of currently available tools.[3] However, the widespread use of computed tomography (CT) and magnetic resonance imaging (MRI) scans have produced an increasing number of incidentally discovered lesions in the pancreas, some of which may be premalignant conditions to pancreatic cancer. Considerable controversy regarding the management of such lesions has emerged as a result.

Premalignant Conditions of the Pancreas

The most common precursor lesion is the pancreatic intraepithelial neoplasia (PanIN). However, because this is only a microscopy-based finding on histopathology, it is invisible on current conventional imaging studies. Most other relevant premalignant lesions come in the form of mucinous lesions (Figure 1*A*) that present as 1 or more visible cysts. Notably, cysts can also represent benign or nonneoplastic entities, such as a retention cyst or pseudocyst. Cystic degeneration of a pancreatic ductal adenocarcinoma (PDAC) and cystic neuroendocrine tumors of the pancreas are described, too. Furthermore, nonmucinous lesions with malignant potential, such as a solid pseudopapillary neoplasia, may present with cystic components. From a practical point of view, the premalignant lesions frequently come in the form of an incidental pancreatic cyst detected on cross-sectional imaging usually done for another medical indication in otherwise asymptomatic persons.[4] The prevalence of an incidentally detected cyst varies with geographic region (3 times higher in the United States compared to Asian countries), with the population studied (higher in the elderly population), and with the imaging modality used (higher with use of MRI compared to CT).[5] Incidental pancreatic cysts are estimated to occur on 3%–20% of all abdominal imaging scans.[6]

Unfortunately, the pancreas is not a readily accessible organ for repeat direct investigations for premalignant conditions compared to other sites in the gastrointestinal tract. Precursors in the colon or the esophagus (colonic polyps and adenomas, Barrett's esophagus) may be subjected to repeat (invasive) investigations, with repeat biopsies and even liberal localized, minimally invasive removal of the precursor lesions (eg, colonic polypectomy, endoscopic mucosal resection) with low risk for severe complications. The more difficult access to the pancreas and risk for pancreatitis make close-up investigation and even tissue biopsy of any lesion more difficult, although novel endoscopic techniques (eg, pancreatoscopy) and endoscopic ultrasonography (EUS) have allowed for better in-depth investigations. Nevertheless, a definitive biopsy may sometimes be possible only through surgical resection, acknowledging the relevant rates of complications still associated with it. Hence, decision making and management are at risk for both over- and undertreatment for premalignant and cystic lesions of the pancreas. The detection of premalignant lesions represents an opportunity for prevention and early intervention for invasive cancer. Preferably, intervention should occur at a time when only high-grade dysplasia is present because this would lead to an actual chance of true cure from pancreatic cancer.

Malignancy Risk in Pancreatic Cysts

Although most of the cysts will never transform into malignant lesions, there are few robust data to inform exactly which lesions are innocent and which ones have a clearly malignant potential. Thus, the burden of cystic lesions that need formal evaluation in "pancreatic cyst clinics" or in multidisciplinary sessions is increasing. Consequently, the number of patients undergoing surveillance is accumulating, together with the clinical workload and use of health care resources. Adding to the complexity and confusion are the variable recommendations issued by several international societies and guidelines.[7] The overall aim of management would be to offer active surveillance to patients at risk and an operation to patients with cysts demonstrating signs of premalignant or high-risk features and to potentially discharge patients who are not surgical candidates or who have a low likelihood for developing a cancer (eg, similar to that of the age-matched general population).

Malignancy is rare (0.1%) in serous cystadenomas[8] and variable in a branch duct intraductal papillary mucinous neoplasm (IPMN) (ranging from 15% to 25% in many surgical series with an inherited bias toward resected cases), and mucinous cystic neoplasia may have a risk of 10%–36%.[9,10] The highest rates (35%–75%) are reported in main-duct or mixed-type IPMNs.[11,12] Several coexisting attributes may yield a higher or lower risk in an individual patient with a particular cyst, considering that is not possible to clearly label all newly diagnosed cyst with a diagnosis or predict the natural course of events. Still, the natural history of many cysts is not well known and, hence,

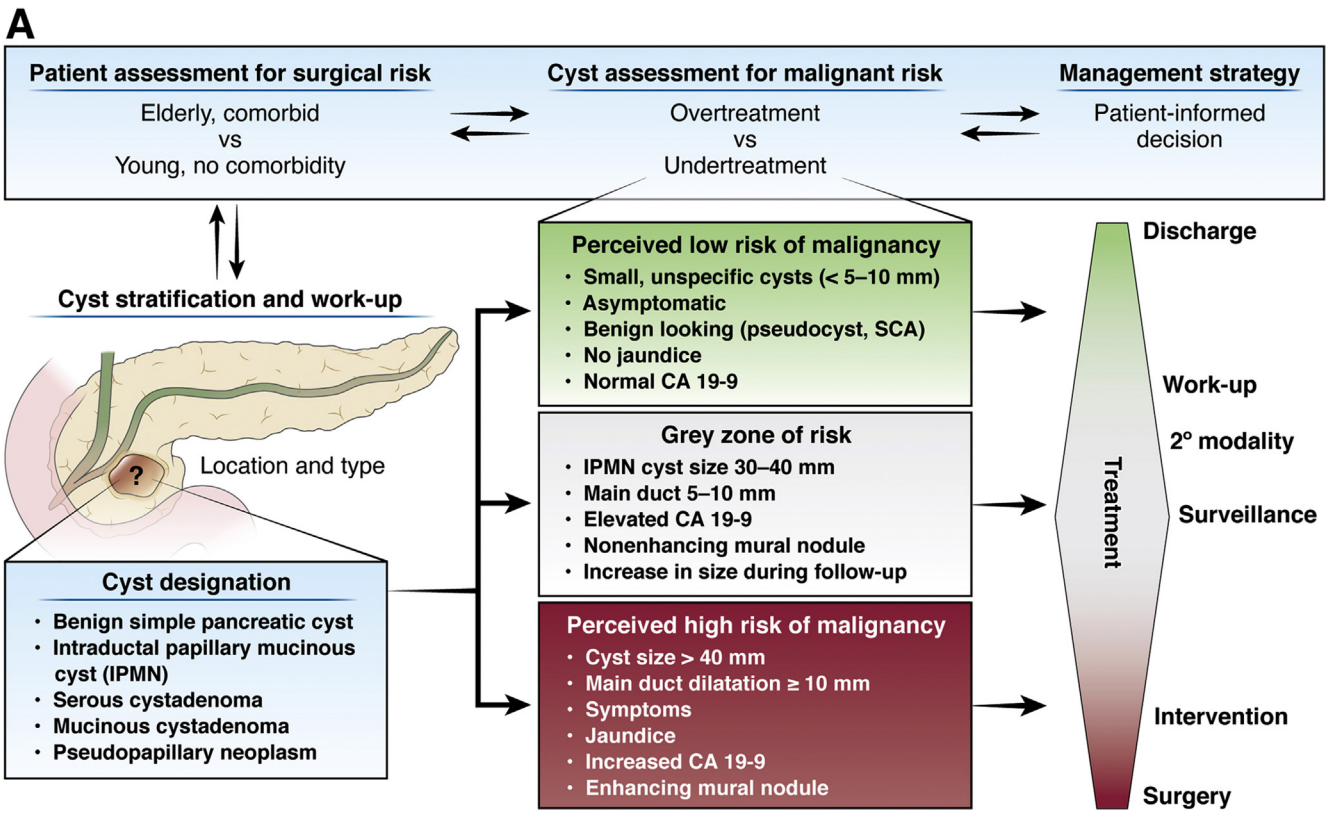

Figure 1. Components of managing premalignant lesions of the pancreas. (*A*) The pancreatic lesion, usually presenting as an undesignated cyst, requires further designation for both etiology and perceived risk. The clinical factors must be weighted in along with the patient's expressed wish before a decision plan can be made according to the lesion and risk at hand. The cyst risk factors vary slightly among current guidelines, with risk for over- and undertreatment, yet the majority will be considered in a gray area for which further surveillance is recommended. (*B*) Several risk factors need a combined and multidisciplinary approach. Clinical factors are considered in relation to diagnostic findings and further need for endoscopy with evaluation of cystic fluid content. Designation into cyst category may be difficult in smaller lesions. Presence of cyst risk stigmata (variably defined across guidelines) should be considered at presentation and during surveillance to add the likely unchanged or developing natural history to the clinical information. Very rarely, cysts may disappear. BD, branch duct; BMI, body mass index; CA19.9, carbohydrate antigen 19.9; FU, follow up; MCN, mucinous cystic neoplasia; MD, main duct; NET, neuroendocrine tumor; SCA, serous cystic adenoma; SCN, serous cystic neoplasia; SPN, solid pseudopapillary neoplasia.

predicting which cysts will become clinically relevant or have a true malignant potential is not clear. Notably, it may not always be possible to make a clear-cut distinction between one type of lesion and another, particularly because incidental lesions have increasingly become detected at smaller sizes over the years, and typical imaging features may be less prominent at smaller sizes. Intriguingly, a subcentimeter cystic lesion (<10 mm) may be either a large PanIN (presumably rare) or, more likely, an incipient small IPMN.[13] Although both lesions are precursors to the development of PDAC, current limitations in imaging technology prevent the diagnosis and, hence, the ability to follow up most low-grade PanINs. Except for a few clinical exceptions (eg, hereditary kindreds under intense surveillance), most low-grade PanINs are detected only in resected pancreatic specimens. In contrast, most presumed IPMNs are large enough to be detected as a cystic lesion on cross-sectional imaging studies. As a defined premalignant condition, a surveillance strategy is warranted for IPMNs. Indeed, the vast majority of cystic lesions (90%) are called IPMNs,[4] and of these, approximately 70% are branch duct IPMNs, with the remainder being either mixed-type or main-duct IPMNs. However, because of their relatively small size at diagnosis, a significant proportion of cysts may either be undesignated or even miscalled (eg, as branch duct IPMNs) based on unclear or insufficient imaging features.

Clinical Management of an Incidental Pancreatic Cyst

The estimated risk of cancer in a cyst is dependent on the cyst type and its natural history. Unfortunately, the true natural history of pancreatic cysts is not yet well understood. One should consider that most of the malignancy estimates stem from resected series at tertiary centers with some lag time in reporting (and based on institutional practice at the time of resection) and, hence, have a selection bias incurred.[14] Thus, there is a risk for both over- and undertreatment with any management strategy, which needs to be considered by the clinician as well as the patient.

From a practical point of view, an index event (Figure 2) suggestive of a

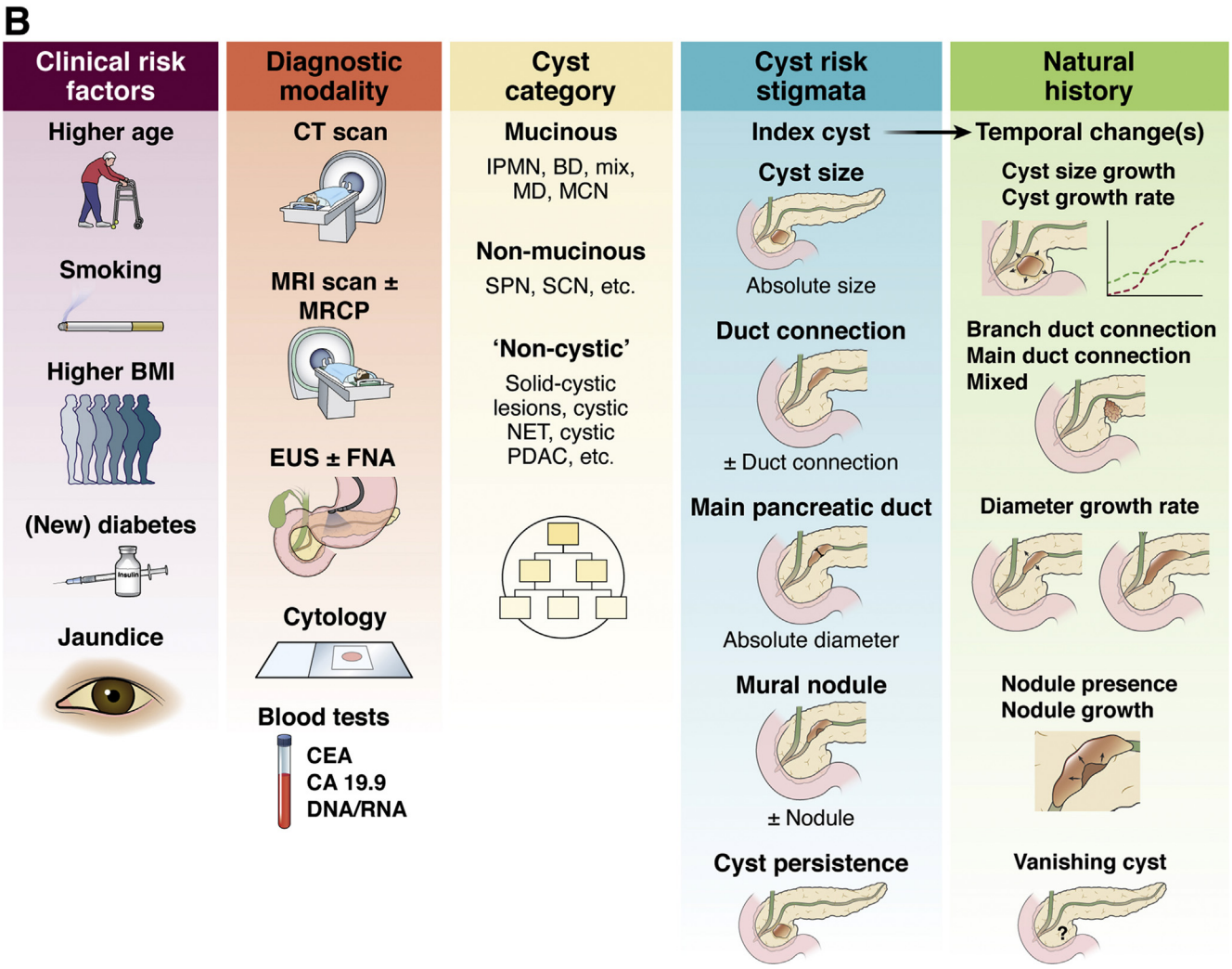

Figure 1.(*continued*).

pancreatic cystic lesion should initiate further diagnostic work-up specific to the pancreas, preferably with high-quality MRI and magnetic resonance cholangiopancreatography, which best allows the clarification of any connection to the pancreatic main or branch ducts and designation of the cyst features. As an alternative to MRI, a high-quality pancreatic CT protocol may be considered. An MRI is the preferred approach because it will be able to better define any contrast-enhancing nodules that would be suggestive of malignancy and indicate need for surgery or at least further workup (eg, EUS with cyst fluid evaluation and tumor biomarkers carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA 19-9]). Although cyst fluid biomarkers may help distinguish the type of cyst entity based on extreme values (eg, likely mucinous for very high CEA content or nonmucinous for very low or normal CEA), the overall accuracy is not optimal. Use of molecular analyses (such as *KRAS* and *GNAS* mutations) in cyst fluid may have a higher accuracy than CEA measurements,[15] but it is not in widespread clinical use yet.

EUS with fine needle aspiration (FNA) may be considered as a subsequent diagnostic procedure to differentiate between mucinous and nonmucinous lesions. Also, it allows one to further judge cyst fluid biomarkers and cytology in patients with cysts that carry worrisome features. Although the predictive value for several of the markers involved may prove highly variable (eg, strip test of fluid viscosity; fluid levels of glucose or amylase, CEA or CA 19-9, or mucin markers), the presence of malignant cells on cytopathology is a clear indication for surgery.

A balanced consideration of patient characteristics, use of cross-sectional imaging with CT and MRI, judicious use of EUS with or without FNA of the cyst fluid, and/or tissue biopsies with serum-based workup (eg, tumor marker CA 19-9) are essential for decision making, together with the patient's expressed wishes (Figure 1*B*). The health care payer systems may influence the decision as to which and how frequent various tests may be used based on cost coverage and availability to patients. When informing patients, it is important to recognize the rather weak data used to create the current recommendations and guidelines. Also, recommendations are aimed at various professions

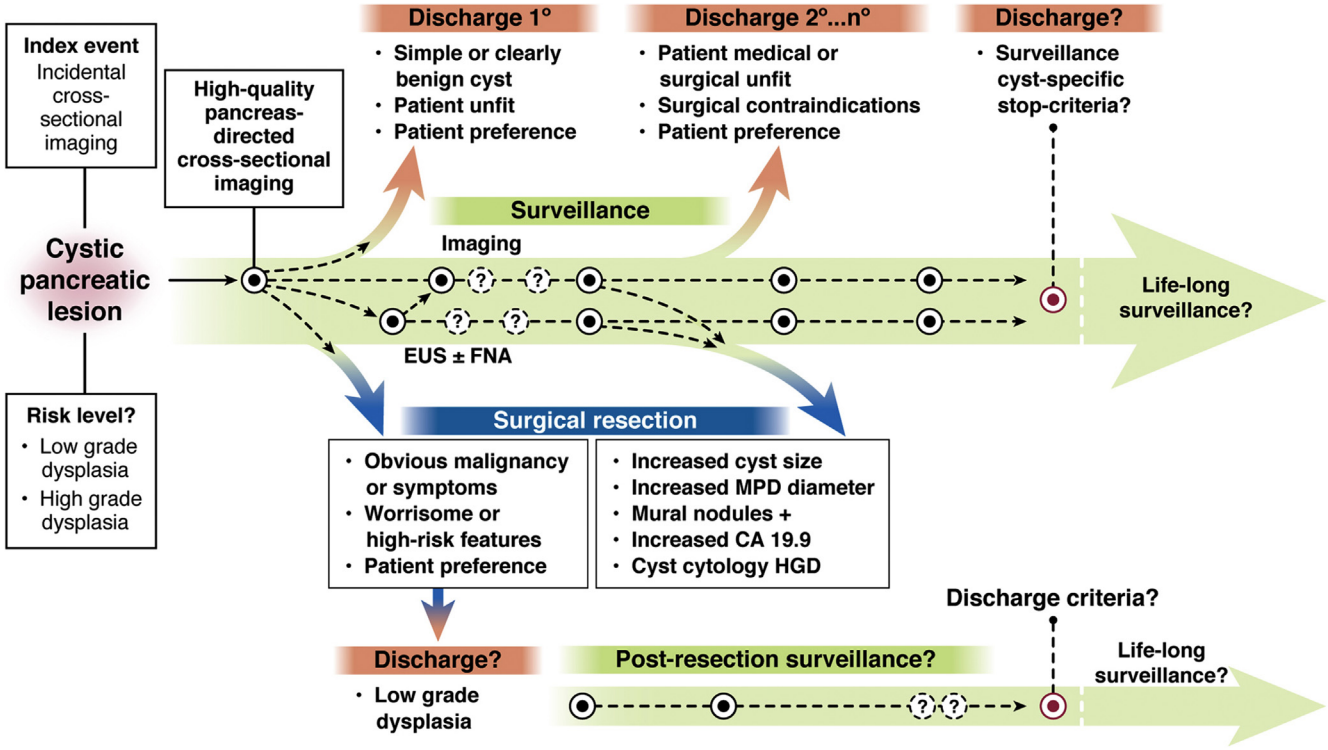

Figure 2. Clinical pathways to manage pancreatic premalignant lesions. An index event of a cystic pancreatic lesion necessitates further workup with high-quality pancreatic imaging to assess likely risk. Current criteria to discharge from further surveillance are vague or nonexistent, which introduces a high risk for overtreatment and use of health care resources. Furthermore, there are currently no clear stop criteria during surveillance except for poor candidates for surgery, judged by either very high age or the presence (or development) of severe comorbidity. Lifelong surveillance is currently proposed but based on scarce data. Surveillance strategies are based on use of cross-sectional imaging and variable use of EUS with FNA in select cases. Surgical resection is based on proposed guideline criteria, with considerable variation in practice. Postsurgery surveillance is recommended, but actual risk, surveillance intervals, and discharge criteria are poorly investigated. Areas of uncertainty and low data are marked with dotted lines. HGD, high grade dysplasia.

(either for gastroenterologists, radiologists, or multidisciplinary)[16] rather than patients per se. An obvious tradeoff of between events, costs, and resources is present in either intense or more lax surveillance strategies.[17] Also, the lexicon of "worrisome features" and "high-risk stigmata" as risk factors is, in part, inconsistently defined (eg, for cyst size cutoffs) and used between guidelines and continues to be debated.[18]

Although using different lexicons with only partial overlap in definitions,[18] all guidelines identify some risk factors for malignancy that require immediate surgery, including jaundice, enhancing mural nodule of >5 mm, a solid mass in the pancreas, or an MPD diameter of 10 mm and greater. In surgically fit patients, the presence of 1 or several of these features should prompt surgery to remove what is a highly likely incipient/already malignant lesion.

Secondary risk factors or worrisome features include cyst size (eg, >40 mm), although with disagreement among guidelines; elevated CA 19-9; a main pancreatic duct of 5–9.9 mm; smaller mural nodules (<5 mm); and the growth rate of cysts (various size increases per year across guidelines, when reported). Such features would usually indicate the need for EUS and FNA, either at the index workup or when developed during surveillance. Surgery may be discussed in otherwise fit patients who have 1 or several worrisome features and a long life expectancy.

Notably, each single risk factor is not equal in weight for the risk of invasive cancer. Cyst size alone has been deemed to be an inefficient marker of risk, and the size of the main pancreatic duct dilatation is also debated for its role. The presence of enhancing mural nodules of >5 mm and jaundice warrant upfront resection because underlying malignancy is of the highest concern.[19]

Choosing a Strategy for Management With the Individual Patient

Clinical management can follow through several pathways of either discharge, surveillance, or surgery as a definitive treatment. The prospective PANCY (PANcreatic CYsts) study found that <6% of patients had surgery in the short term[4]; hence, the vast majority will be subject to some form of surveillance (Figure 2). The overall goal of decision making is to avoid both over- and undertreatment. The aim is to detect the lesions at highest risk and perform surgery at a time for when, preferably, only high-grade dysplasia is present because resection for invasive cancer has an inferior prognosis and, in some cases, would

essentially follow the prognosis of PDAC. Indication for resection should be considered at the balance of performing surgery for strictly benign lesions, because perioperative mortality for major pancreatic surgery is consistently reported at 2%–4%, even in high-volume centers.

Striking the right balance is difficult, exemplified by major inconsistencies reported in guidelines and clinical practice.[7] Also, developing PDAC during surveillance, either as a result from not reacting on specific findings or developing an interval cancer despite regular surveillance, would decrease the efficacy of any given surveillance program or strategy. Hence, the modality used and the intensity at which surveillance is done (Figure 2) is currently subject to a considerable gray zone, with few robust data to inform optimal practice. Suggested guidelines for risk assessment have considerable inconsistency among the suggestions, the accumulated data, and how to best interpret these, reflected in a wide variation in current practice patterns.[7] Also, there seems to have been a pendulum swing from liberal use of resections in the past to a more observational approach.[20,21] Still, resection rates vary considerably among institutions and regions,[14] and the diagnostic accuracy in resected specimens compared to that suggested on the imaging is suboptimal.[22]

For the elderly or frail patient who is not a surgical candidate with an incidental finding, no further follow-up or surveillance may be warranted in low-risk lesions.[23] Operability and fitness to tolerate surgery would be a prerequisite for further surveillance because the lesion detected may not become clinically relevant in the patient's expected lifetime. Emerging data show that comorbidity drives the overall mortality in frail patients diagnosed with pancreatic cystic lesions.[24] Appropriate information and counseling are, thus, mandatory to avoid overtreatment and excessive use of health care resources.

However, for younger and surgically fit patients, a long-term surveillance beyond 5 years of follow-up seems warranted,[25] although long-term risk is not well understood.[26] A meta-analysis reported an accumulating 8% risk of cancer in low-risk IPMNs and 25% in high-risk IPMNs with surveillance up to 10 years.[27] For smaller cysts (<15 mm) without worrisome features, risk seems to diminish after approximately 3 years of surveillance.[28] Among branch duct IPMNs, approximately 1 in 5 will develop signs of progression; approximately 12% will proceed to surgery; and of those resected, a third will have malignancy in the specimen.[29] Further characterization of risk and attributes that allow for discontinuation of surveillance and discharge from follow-up is urgently needed (Figure 2). Indeed, an accumulating number of patients are currently undergoing surveillance, with a high workload and increased resources used for imaging studies, endoscopy, and patients' concern where no or very little risk actually exists. The challenge lies in finding the appropriate and robust risk features that allow those at highest risk for cancer to be addressed, while allowing discontinuation of follow-up for those at very low risk of cancer. Keeping in mind that a zero-risk option does not exist, the yield should be set at identifying those individuals who are not at a higher risk than the age-matched general population. The use of molecular markers and novel sample techniques may allow for a more tailored strategy.

A further controversial topic is the need for further surveillance of the pancreatic remnant in those who have undergone resection. Some suggest that when the target lesion shows absence of high-grade dysplasia on final pathology and no further visible IPMNs are seen, surveillance may not be warranted. Others suggest long-term surveillance based on risk,[30] proposing a field effect in the pancreatic gland to be present in those who have had an IPMN.

The management of pancreatic premalignant conditions warrants a multidisciplinary approach among gastroenterologists, radiologists, endoscopists, and surgeons. The current challenge is the tradeoff between early, timely surgery and the risk of harm to patients subjected to surgical risk that exceeds the oncologic benefits. Also, a challenge exists in continuous surveillance for a given lesion that exceeds the clinical benefit to the patient. For now, the most efficient, accurate, and cost-effective clinical management has yet to be defined.

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References

1. GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2019;4:934–947.
2. Fischer CG, Wood LD. From somatic mutation to early detection: insights from molecular characterization of pancreatic cancer precursor lesions. J Pathol 2018; 246:395–404.
3. Singhi AD, Koay EJ, Chari ST, et al. Early detection of pancreatic cancer: opportunities and challenges. Gastroenterology 2019;156:2024–2040.
4. Pezzilli R, Buscarini E, Pollini T, et al. Epidemiology, clinical features and diagnostic work-up of cystic neoplasms of the pancreas: interim analysis of the prospective PANCY survey. Dig Liver Dis 2020; 52:547–554.
5. Zerboni G, Signoretti M, Crippa S, et al. Systematic review and meta-analysis: prevalence of incidentally detected pancreatic cystic lesions in asymptomatic individuals. Pancreatology 2019;19:2–9.
6. Boos J, Brook A, Chingkoe CM, et al. MDCT vs. MRI for incidental

pancreatic cysts: measurement variability and impact on clinical management. Abdom Radiol (NY) 2017;42:521–530.
7. Marchegiani G, Salvia R. Guidelines on pancreatic cystic neoplasms: major inconsistencies with available evidence and clinical practice—results from an international survey. Gastroenterology 2021;160:2234–2238.
8. Jais B, Rebours V, Malleo G, 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 2016; 65:305–312.
9. Keane MG, Shamali A, Nilsson LN, et al. Risk of malignancy in resected pancreatic mucinous cystic neoplasms. Br J Surg 2018; 105:439–446.
10. Marchegiani G, Andrianello S, Crippa S, et al. Actual malignancy risk of either operated or non-operated presumed mucinous cystic neoplasms of the pancreas under surveillance. Br J Surg 2021; 108:1097–1104.
11. Lennon AM, Canto MI. Pancreatic cysts—part 2: should we be less cyst centric? Pancreas 2017; 46:745–750.
12. Marchegiani G, Mino-Kenudson M, Sahora K, et al. IPMN involving the main pancreatic duct: biology, epidemiology, and long-term outcomes following resection. Ann Surg 2015;261:976–983.
13. Basturk O, Hong SM, Wood LD, et al. A revised classification system and recommendations from the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. Am J Surg Pathol 2015;39:1730–1741.
14. Pulvirenti A, Margonis GA, Morales-Oyarvide V, et al. Intraductal papillary mucinous neoplasms: have IAP consensus guidelines changed our approach? Results from a multi-institutional study. Ann Surg 2021; 274:e980–e987.
15. McCarty TR, Paleti S, Rustagi T. Molecular analysis of EUS-acquired pancreatic cyst fluid for *KRAS* and *GNAS* mutations for diagnosis of intraductal papillary mucinous neoplasia and mucinous cystic lesions: a systematic review and meta-analysis. Gastrointest Endosc 2021;93:1019–1033.
16. Ayoub F, Davis AM, Chapman CG. Pancreatic cysts—an overview and summary of Society guidelines, 2021. JAMA 2021;325:391–392.
17. Lobo JM, Scheiman JM, Zaydfudim VM, et al. Clinical and economic outcomes of patients undergoing guideline-directed management of pancreatic cysts. Am J Gastroenterol 2020;115:1689–1697.
18. Crippa S, Arcidiacono PG, De Cobelli F, et al. Review of the diagnosis and management of intraductal papillary mucinous neoplasms. United European Gastroenterol J 2020;8:249–255.
19. D'Onofrio M, Tedesco G, Cardobi N, et al. Magnetic resonance (MR) for mural nodule detection studying intraductal papillary mucinous neoplasms (IPMN) of pancreas: imaging-pathologic correlation. Pancreatology 2021;21:180–187.
20. Aunan JR, Jamieson NB, Søreide K. Observation or resection of pancreatic intraductal papillary mucinous neoplasm: an ongoing tug of war. World J Gastrointest Oncol 2019; 11:1092–1100.
21. Salvia R, Marchegiani G. Evolving management of pancreatic cystic neoplasms. Br J Surg 2020; 107:1393–1395.
22. de Pretis N, Mukewar S, Aryal-Khanal A, et al. Pancreatic cysts: diagnostic accuracy and risk of inappropriate resections. Pancreatology 2017;17:267–272.
23. Marchegiani G, Andrianello S, Pollini T, et al. "Trivial" cysts redefine the risk of cancer in presumed branch-duct intraductal papillary mucinous neoplasms of the pancreas: a potential target for follow-up discontinuation? Am J Gastroenterol 2019; 114:1678–1684.
24. Chhoda A, Yousaf MN, Madhani K, et al. Comorbidities drive the majority of overall mortality in low-risk mucinous pancreatic cysts under surveillance [published online ahead of print December 10, 2020]. Clin Gastroenterol Hepatol https://doi.org/10.1016/j.cgh.2020.12.008.
25. Lawrence SA, Attiyeh MA, Seier K, et al. Should patients with cystic lesions of the pancreas undergo long-term radiographic surveillance? Results of 3024 patients evaluated at a single institution. Ann Surg 2017; 266:536–544.
26. Marchegiani G, Pollini T, Andrianello S, et al. Progression vs cyst stability of branch-duct intraductal papillary mucinous neoplasms after observation and surgery. JAMA Surg 2021; 156:654–661.
27. Choi SH, Park SH, Kim KW, et al. Progression of unresected intraductal papillary mucinous neoplasms of the pancreas to cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2017;15:1509–1520.
28. Ciprani D, Weniger M, Qadan M, et al. Risk of malignancy in small pancreatic cysts decreases over time. Pancreatology 2020; 20:1213–1217.
29. Balduzzi A, Marchegiani G, Pollini T, et al. Systematic review and meta-analysis of observational studies on BD-IPMNS progression to malignancy. Pancreatology 2021;21:1135–1145.
30. Pflüger MJ, Griffin JF, Hackeng WM, et al. The impact of clinical and pathological features on intraductal papillary mucinous neoplasm recurrence after surgical resection [published online ahead of print November 17, 2020]. Ann Surg https://doi.org/10.1097/SLA.0000000000004427.

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