Pancreatic cystic neoplasms in 2018: The final cut

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INTRODUCTION: PANCREATIC CYSTIC LESIONS: HIGH PREVALENCE AND LOW EVIDENCE

The incidental diagnosis of pancreatic cystic lesions (PCLs) is increasing, being a significant health-care problem and economic burden. Indeed, up to 10% of the adult population has PCLs occasionally detected when undergoing procedures such as computed tomography scan and magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography. Anyway, the prevalence of PCLs increases with age, approaching 50%[1] in the elderly. Notably, the majority of these lesions are intraductal papillary mucinous neoplasms (IPMNs) with a potential premalignant significance. In this context, there is the need to develop evidence-based and cost-effective guidelines based on the solid data to guide the clinical process. Unfortunately, while the number of published original research articles on the topic is increasing, the quality of the evidence is low. While the number of hits on PubMed for the search terms "IPMN or IPMT or Intraductal Papillary Mucinous Neoplasms" is equal to 2326 in April 2018, with original studies increasing from 103 in 2007 to 183 in 2017, only 4 of >2000 articles are randomized controlled trials (RCTs). In this scenario, there are probably no other health disorders so prevalent and potentially relevant for which evidence is so low. An attempt to summarize the best available evidence for the clinical management of PCLs has been made by experts in the field with the preparation of several guidelines.[2-9] The present paper will discuss critical issues and limitations of current guidelines in the management of PCLs and will highlight novel findings potentially leading to an improvement of the current scenario.

CORRECT DIAGNOSIS OF PANCREATIC CYSTIC LESIONS: MORE COMPLICATED THAN IT SEEMS

The main limitation of most available data on IPMNs is that they are obtained in surgical series, and applying their results to nonsurgical cohorts represents a typical spectrum bias, like when the performance of a diagnostic test obtained in a certain clinical settings is wrongly applied to another, while each setting has a different mix of patients. However, the cultural journey of IPMNs has recently switched from the

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analysis of surgical series to the follow-up of cystic lesions stratified according to noninvasive morphological imaging. In this view, the correct initial diagnosis and stratification of malignant potential are crucial issues. However, when preoperative assessment and postoperative histology of PCLs have been compared, a surprising high rate of misdiagnosis was observed.[10-16] Most patients with PCLs receive MRI as first-line investigation, with EUS with fine-needle aspiration, and evaluation of intracystic fluid being employed as second-line tests when diagnosis is uncertain or malignant behavior is suspected. As the accuracy of these tests remains suboptimal, novel EUS-based technologies are under evaluation.

Contrast harmonic EUS has preliminary shown to strongly increase specificity and positive predictive value for malignancy when used for evaluating mural nodules detected at basal EUS; quantitative evaluation of echo intensity changes through time-intensity curve analysis may further stratify between IPMN with low- or intermediate-grade dysplasia and those with high-grade dysplasia or invasive carcinoma.[17] Needle-based confocal laser endomicroscopy returns real-time cellular and architectural imaging and has demonstrated a high positive predictive value when detecting typical patterns of mucinous or nonmucinous cystic lesions; however, in the absence of such patterns, sensitivity remains suboptimal but may be increased through the contemporary use of cystoscopy through SpyGlass probe.[18] Anyway, the diagnostic gain is limited by the lack of standardization and by the reported rate of adverse events.

The need to overcome the low accuracy of traditional cystic aspiration sampling has led to the development of a through-the-needle biopsy forceps allowing histological evaluation of cystic walls, septa, or nodules. In one preliminary study, this histopathological evaluation has proved similar to traditional (but including routine molecular analysis) cystic fluid evaluation in differentiating between mucinous and nonmucinous cysts and in detecting high-risk cysts but superior in differentiating between IPMNs and MCNs.[19]

Molecular biomarkers obtained in either tissues, duodenal aspirates, cystic fluid, or serum have been evaluated for their potential ability to differentiate between different PCLs and between degrees of dysplasia. In particular, in a recent study, mutations of KRAS/GNAS in the cystic fluid were reported to have a sensitivity of 89% and specificity of 100% for the diagnosis of mucinous lesions, and the combinations of KRAS/GNAS mutations with those of TP53/PIK3CA/PTEN a 89% sensitivity and 100% specificity for the diagnosis of advanced neoplasia.[20] However, apart from KRAS and GNAS mutations, the use of such "molecular signatures" in predicting cyst behavior is still not recommended,[5] and an "ideal perfect potion" with a compromise between sensibility and specificity does not exist.

SURGICAL INDICATION: IS IT JUST A QUESTION OF MILLIMETERS?

When referring to the indication for surgery of asymptomatic PCLs, the main differences between existing guidelines are about the thresholds of pancreatic cyst and Wirsung duct diameters. When referring to branch-duct IPMNs (BD-IPMNs), the new European guidelines[5] do not consider the size of the peripheral cyst among factors representing an absolute indication for surgery, while a size of 40 mm represents a relative indication, to be considered with patients' features. Previous guidelines[2,4] consider a diameter >30 mm as a "worrisome feature" requiring further investigation or eventually a surgical indication in young individuals. The American Gastroenterological Association (AGA) guidelines[3] consider cyst size >30 mm an indication to perform EUS only in the presence of at least another high-risk feature (*i.e.*, dilated Wirsung duct or the presence of a solid component). In any case, the size of a BD-IPMN *per se* should not be considered as an absolute indication for surgery.

As far as regards the diameter of the Wirsung duct, the cutoff of 10 mm is an indication for surgery according with the European, Italian, and International Association of Pancreatology (IAP) guidelines,[2,4,5] while the AGA ones[3] generically mention "Wirsung duct dilation." The European guidelines also include a diameter above 5 mm among "relative indications" for surgery because there are studies reporting a high rate of malignancies with Wirsung duct >5 mm and calculating the best cutoff at 7 mm.[21,22]

Intuitively, the larger is the diameter of the Wirsung duct the higher is the risk of malignancy, but as the rate of IPMN patients with a dilation >10 mm is rather small, the fraction of patients carrying that risk is limited. This is why this risk factor turns out to be nonsignificant in some published series, with the category of 5–9 mm being more relevant.[23,24]

Furthermore, data supporting these different policies are obtained in retrospective surgical series with all inherent biases. Even more, it is unclear how this delicate "millimeters' cutoff" should be measured, given the reported low agreement between MRI and EUS in reporting the size of both BD-IPMNs and Wirsung duct.[25]

There are few publications comparing available guidelines for their accuracy in providing a correct indication for surgery. Interestingly, the rate of overtreatment, which is around 80% with the IAP and European guidelines, is only 56% when employing the AGA criteria, but the latter is also the only guidelines missing 11% of cases with high-grade dysplasia or cancer compared to 0% with IAP or European ones.[26] This stresses the importance of relying on factors other than the characteristics of the cyst. Among these, family history of pancreatic cancer does not seem to substantially increase the risk.[27] Research efforts should be focused in creating a combined set of variables including not only "cyst factors" (such as size) but also "patients' variables" (*e.g.*, smoking and family history) and possibly "molecular/genetic markers" to better predict cyst behavior.

IS IT POSSIBLE TO PERSONALIZE THE FOLLOW-UP OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS?

If one optimistically takes for granted that we are sufficiently accurate in stratifying the malignant potential of a PCL, the question becomes how long are we going to follow-up patients for whom we did not recommend resection? Several papers have demonstrated that malignant potential of low-risk BD-IPMNs is generally low but increases over time,[28] and a significant proportion of this progression appears beyond 5 years from diagnosis,[29] thus making it questionable to interrupt the follow-up at a defined interval. While waiting for further data on long-term follow-up of conservatively managed cohorts, fitness for surgery must be considered the only significant parameter limiting follow-up length.[5]

We are improving our ability in stratifying the malignant potential of one cyst, but we almost grope in the dark when we are required to define how to adapt that risk to different categories of patients. In this individualized balance, fitness for surgery and life expectancy of a patient and location of the cyst (determining the type and invasiveness of pancreatic resection) can become as important as cyst morphological appearance. It has been demonstrated that patients with advanced age or comorbidities are more likely to die from their fragility (or eventually from the pancreatic resection) rather than from the cancerization of their IPMN.[30] The shaping role of the Charlson comorbidity index in the decisional process has been explored by some authors,[31] confirming that factors beyond cyst features have a definite impact on the risk of death. However, to date, no validated nomogram integrates patient- and cyst-related factors in tailoring prognosis and management, and guidelines are fundamentally "cyst-centric." Future efforts in the area of PCL research should concentrate on realizing well-conducted RCTs comparing different strategies and on combining patients' environmental and genetic characteristics with morphological and molecular features of the cyst to establish the most appropriate management of these common lesions. Given the low annual risk of malignant transformation in most IPMNs,[32] these studies need both multicentric efforts and long follow-up intervals to record a sufficient number of significant events.

Conflict of interest

There are no conflicts of interest.

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