Risk Factors for Progression in Low Risk Intraductal Papillary Mucinous Neoplasms

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ABSTRACT

The management of low-risk intraductal papillary mucinous neoplasms of the pancreas continues to represent an important clinical dilemma. Current guidelines lack of sufficient good-quality evidence, especially regarding the natural history of branch duct intraductal papillary mucinous neoplasms with no worrisome features. Herein, we aimed to summarize the current approach towards these lesions and the main controversial points regarding their management.

INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are part of the so-called "pancreatic cystic neoplasms" (PCN), a wide spectrum of cystic lesions with a potential for malignant transformation. They were firstly described in 1980 [1] and since 1996 are considered an independent entity [2].

IPMNs are localized within the pancreatic ductal system and are characterized by a mucin-producing epithelium that may present papillary projection into the pancreatic duct (PD) lumen [3]. They present along a spectrum of log-grade dysplasia (LGD) to high-grade dysplasia (HGD) to invasive pancreatic adenocarcinoma (PAC) [4, 5]. Currently, only invasive PAC is considered malignant [6]. Despite this, it has been recently postulated that HGD should also be included in the malignant classification given the reported cases of metastatic disease after HGD resection [7]. At present, the available guidelines recommend surgical resection if HGD is diagnosed, although it has not been clearly identified as malignant.

The only accepted curative treatment for IPMNs is surgical resection. Depending on the localization and extent of the lesion, the surgical procedure may carry significant risks, as well as posterior comorbidities [8, 9]. The pre-operative surgical candidate selection is, thereby, crucial, moreover considering that not all lesions harbor the same grade of malignancy and some of them may remain unchanged over the years.

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Abbreviations BD branch duct; CEA carcinoembryogenic antigen; CT computed tomography scan; ERCP endoscopic retrograde cholangiopancreatography; EUS endoscopic ultrasound; FNA fine needle aspiration; HGD high-grade dysplasia; IPMN intraductal papillary mucinous neoplasm; LGD low-grade dysplasia; MD main duct; MRI magnetic resonance imaging; PAC pancreatic adenocarcinoma; PCN pancreatic cystic neoplasm; PD pancreatic duct
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IPMN Subtypes

Based on the duct of origin, there are two main types of IPMNs: branch duct (BD) and main duct (MD). BD-IPMNs are defined as >5 mm in diameter cysts that connect with the MD, whereas MD-IPMNs are >5 mm segmental or diffuse MD dilations [10]. A third type of IPMN has been traditionally described, the mixed-type, which involves both the branch and the main ducts. However, it has been recently proposed that this last category should not be considered independently given its same clinical and biological behavior as the MD-type.

MD dilation is a well-established risk factor for malignancy [11, 12, 13, 14]. The 2012 consensus guidelines [10] considered a MD-dilation between 5-9 mm to be a "worrisome feature", whereas dilation ≥ 10 mm was defined as a "high-risk stigmata" and, if present, should lead the patient directly to surgery. Thus, the classification of IPMNs into one of these categories is of significant importance given the clinical and prognostic implications.

Little has changed over the years regarding the management of MD and mixed-type IPMNs with a ≥ 10 mm MD dilation. These lesions have a broadly documented potential for malignant transformation ranging between 38-90% [15, 16, 17]. Hence, if any of these cysts are identified under high-resolution imaging studies, such as magnetic resonance imaging (MRI) or computed tomography scans (CT), surgical resection is recommended with no further diagnostic tests required [10]. The presence of obstructive jaundice or enhancing solid component within the cyst is also considered "high-risk stigmata" and surgical resection is, again, indicated.

At present, the main concern regarding IPMN management involves the BD-IPMNs [18]. The reported rates of malignant transformation have decreased over the years as observational cohorts (instead of surgical ones) have been analyzed. In fact, recent studies have highlighted the indolent natural history of some of these lesions with reported rates of malignancy as low as 6 to 8% [19, 20]. Moreover, a recent meta-analysis that focused on 20 studies including 2177 BD-IPMN patients, showed a proportion of malignancy of 4% with a pooled estimated rate of 0.007/patient years [21]. Based on their results, BD-IPMNs have a low risk of malignancy-related mortality, especially if compared with the surgically related mortality rates. Consequently, a more conservative approach has been adopted in the last few years.

Worrisome Features

To address the concerns regarding the low-risk lesions management, the Fukuoka guidelines defined the already mentioned "worrisome features" (cyst size ≥ 3 cm, thickened/enhancing cyst walls, MD measuring 5-9 mm, non-enhancing mural nodules and abrupt PD caliber change associated with distal pancreatic atrophy). If any of these criteria is present, an endoscopic ultrasound (EUS) should be performed to further characterize these lesions.

The first problem that is encountered with these criteria is that they all rely on the imaging accuracy. Despite that these findings are described using high-resolution imaging techniques, the reported agreement between the preoperative diagnosis and the final surgical pathology is still insufficient (ranging between 68-78%) [22, 23]. A recent retrospective study evaluated 174 randomly selected patients with a PCN that underwent surgical resection and also had pre-operative imaging [24]. They concluded that there was a discrepancy between the pre and post-operative diagnosis in 31% of the lesions and, more specifically, in 27% of the presumed BD-IPMNs.

Even if any of the "worrisome features" are found, their clinical significance is still unclear. Since the publication of the 2012 guidelines, several studies have tried to clarify this matter with heterogeneous results. A meta-analysis that included 3304 surgically resected BD-IPMNs concluded that cyst size >3 cm was the stronger predictor of malignancy, followed by the presence of mural nodules [25]. On the other hand, a different meta-analysis that focused on 1373 patients with BD-IPMNs concluded that the presence of mural nodules was highly indicative of malignancy, whereas cysts size >3 cm or dilated MD 5 to 9 mm could be carefully managed conservately [26]. Interestingly, a recent retrospective study including 350 BD-IPMN patients reported that both mural nodules and MD dilation >5 mm were risk factors for malignant transformation, however, cyst size >3 cm was not even related with malignant progression [27]. In contrast, last year a multicentric study [28] that involved 574 BD-IPMNs reported that cyst size greater than 3 cm, mural nodules, pain symptoms, weight loss and jaundice, were significantly associated with high-risk disease (HGD or invasive carcinoma).

These data suggest that the presence of a cyst size >3 cm, if present alone, is the most debatable risk factor for malignant progression. Initially, the first consensus guidelines published in 2006, recommended resection of all BD-IPMNs measuring >3 cm in diameter (even if no other risk factors were present) [29]. The results evidenced a proportion of malignancy and invasive cancer in surgically resected cohorts of just 24% and 17%, respectively [10]. Hence, the reviewed 2012 guidelines included this risk factor in the "worrisome features" category, which avoids direct surgical resection and recommends further characterization of the lesion. In fact, a growing body of evidence suggests that cysts >3 cm without mural nodules or associated MD dilation can be managed conservatively [30].

EUS Characterization

As previously mentioned, EUS has become an essential diagnostic tool to discriminate and further characterize low-risk IPMNs [31, 32]. Its importance lies, not only on its imaging accuracy, but especially on the possibility of performing fine needle aspiration (FNA) to obtain tissue/cyst fluid [33].

Currently, EUS is the preferred endoscopic method to diagnose PCNs. It has been reported that the diagnostic accuracy may increase up to 54% when a high-resolution imaging technique is combined with EUS-FNA [34]. The main limitation, however, is the inter-observer variability [35] among the described structural findings. To overcome this limitation, new techniques have been implemented. Among these, the contrast-enhanced EUS seemed to facilitate the characterization of mural nodules, which can be challenging to distinguish from adherent mucin globules. Use of contrast enhanced Doppler EUS allows detection of blood flow within apparent mural nodules, thus excluding false positive mucin globules [36, 37]. Also, based on a recent study [38], the combination of both through-the-needle confocal laser-induced endomicroscopy and cystoscopy has an improved diagnostic accuracy of 93% when discriminating mucinous cysts.

Cytology

Sampling the targeted cyst and obtaining fluid or tissue is crucial to typify cystic lesions, especially the low-risk ones. Conventional FNA-obtained cytology has insufficient sensitivity primarily due to the lack of cellularity [39, 40]. A study that exclusively focused on IPMNs reported a sensitivity and a specificity to predict HGD or malignancy of 77% and 80%, respectively [41]. However, if only low-risk IPMNs (BD-IPMNs measuring <3 cm) were analyzed, the sensitivity went down to 67%.

As a result, new methods are being developed to increase the diagnostic accuracy of cytology. A recently published study that included BD-IPMNs used pancreatic juice for cytology instead of cystic fluid [42]. Moreover, cellblock-staining method (rather than conventional smear

method) and immunohistochemistry were carried out. The aim was to determine the sensitivity and specificity of cytology to detect malignancy. The results showed sensitivity and a specificity of 79% and 100%, respectively. The downside of this technique is the need to perform an endoscopic retrograde cholangiopancreatography (ERCP) to obtain pancreatic juice. Based on current literature, the post-ERCP adverse events (such as acute pancreatitis) have shown to outweigh the benefits when performed in low-risk BD-IPMNs [43]. Overall, immunohistochemistry of EUS-FNA cytology may enhance lesion classification and prognostication. Tomishima et al. in a preliminary report, suggested that mucin glyocoproteins (MUC 1, 2, 5) staining in FNA cytology is associated with progression of BD-IPMN [44]. With further refinement, this technology may allow less invasive and more widely available sampling.

Carcinoembryogenic Antigen

The utility of cyst fluid carcinoembryogenic antigen (CEA) in the diagnosis and staging of PCNs, and particularly IPMNs, has been broadly discussed. The literature findings concur that, although it seems to be a reliable biomarker to discriminate mucinous from non-mucinous cysts [45], its accuracy to detect malignant progression is clearly insufficient [46, 47]. Several studies have proposed different cut-off values with heterogeneous outcomes. Despite this, 192 ng/ml is the most agreed value with a corresponding sensitivity of 75% and a specificity of 84% when discriminating mucinous cysts. Recently, a study [48] has questioned the clinical significance of an isolated interval rise of cystic fluid CEA during PCLs follow-up, especially if present concomitantly with a stable EUS exploration (20% of the study cohort presented with a change in the 192 ng/ml cut-off value with no associated significant EUS changes). Based on their results, serial measurements of CEA are not a reliable biomarker for following-up these lesions.

Molecular DNA Analysis

Given the lack of accurate biomarkers, in the recent years several studies have focused on molecular DNA analysis of cystic fluid. KRAS and GNAS mutations are the most frequent DNA-based assays tested for IPMNs, given that one or both of these mutations are present in over 90% of these lesions [49]. KRAS mutations are the most commonly found and are specifically associated with BD-IPMNs. On the other hand, GNAS mutations are unique for IPMNs (present in up to 64% patients) and typically seen in the MD subtype [50].

There seems to be some discrepancy on the utility of these tests for the diagnosis, and especially the malignancy staging, of mucinous cysts. One study [51] showed that, if combined with cyst fluid cytology and CEA, molecular analysis may improve the diagnostic accuracy for discriminating mucinous cysts from 56%, if performed alone, to 73%. Moreover, a different study [52] reported that integrated molecular pathology determined the malignant potential of PCLs more accurately than the 2012 guidelines. On the other hand, the PANDA study [53] prospectively evaluated 113 patients and concluded that KRAS mutations were similarly present in premalignant and malignant cysts. However, in the follow-up results that included 63 patients and were reported by the same group [54], the results showed that KRAS mutations at codons 12 and 13 were independently associated with a malignant progression. Another study [55] reported that GNAS mutations did not improve the cytopathologic malignant diagnosis (alone or combined with KRAS), whereas KRAS mutations increased the accuracy to 80%. Lastly, a meta-analysis that focused on molecular DNA tests in IPMN patients concluded that KRAS and GNAS mutations were useful to diagnose IPMNs but were not significantly associated with malignant progression in these lesions [56].

Lastly, Rodriguez SA et al. carried out a prospective study including patients with solid pancreatic lesions [57]. They aimed to determine if EUS-FNA-obtained RNA could discriminate malignancy. Their outcomes showed that RNAseq distinguished ductal adenocarcinoma from benign pancreatic solid masses with a sensitivity of 87% and a specificity of 75%. Following these promising results, this technique could potentially be implemented in the near future for PCLs.

Current strategies

Based on the recent studies, a more conservative approach regarding low-risk IPMNs seems to be the right path to follow. Current guidelines [10] clearly state that patients with a BD-IPMN and no “worrisome features” or “high-risk stigmata” should undergo imaging surveillance. Also, those patients with “worrisome features” at imaging and a EUS-FNA that excluded underlying PAC/HGD can be managed conservatively. Despite these indications, the frequency and diagnostic method for follow-up is still unclear. Nevertheless, the available guidelines are considered consensus guidelines (i.e. based on expert opinion) and, therefore, lack of sufficient evidence.

As previously mentioned, the timing of follow-up continues to be a subject of debate. The Fukuoka guidelines defined the surveillance timelines based on the presence of any worrisome features (3-6 months) and if absent, based on cyst size (<1 cm: 2-3 years, 1-2 cm: yearly for the first 2 years, 2-3 cm: 3-6 months). Interestingly, the European guidelines [58] did not contemplate the cyst size as a limiting factor and defined the surveillance as follows: MRI/EUS every 6 months for the first year, yearly during the next 4 years, and every 6 months after the fifth year. This rationale is based on the hypothesis evidenced in some studies [59] that the risk of malignancy increases with time. Oppositely to this, the American guidelines [60] followed similar surveillance criteria as the European ones for the first 4 years. However, they recommended discontinuing surveillance after the fifth year if no significant changes were seen during the initial follow-up. A recent study comparing the potential outcomes of AGA

versus Fukuoka versus European guidelines suggested that the more conservative AGA guidelines would have avoided surgery in 28% of cases but at the cost of missing 12% of individuals with malignancy (HGD or PAC) [61].

CONCLUSION

The natural history of low-risk BD-IPMNs, especially regarding long-term follow-up, is still unclear. The available diagnostic tools lack of sufficient accuracy to be used independently. Thereby, a multidisciplinary approach is definitely required to evaluate and manage these low-risk lesions, always tailoring the strategy to each patient's personal circumstances.

Further, prospective, long-term (>5 years), observational studies are needed to elucidate the behavior of BD-IPMNs and enunciate accurate and evidence-based guidelines. Also, molecular markers seem to be the key to identify those patients at higher risk of malignant progression and, thereby, avoid performing unnecessary pancreatic surgical resections in benign lesions or missing malignant progression in surveillance patients.

Conflicts of Interest

Dr. Wallace received grant funding from Boston Scientific, Medtronic, Olympus. Dr. Moris has no conflict of interest.

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