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Intraductal Papillary Mucinous Neoplasms of the Pancreas: Current Understanding and Future Directions for Stratification of Malignancy Risk

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Abstract

The incidence of intraductal papillary mucinous neoplasms (IPMNs) has been increasing over the past decade, mainly due to increased awareness and the increased use of cross-sectional imaging. The Sendai and Fukuoka consensus guidelines provide us with clinical management guidelines and algorithms, however the clinical management of IPMNs continues to be challenging. Our incomplete understanding of the natural history of the disease, and the events and pathways that permit progression to adenocarcinoma, result in difficulties predicting which tumors are high risk and will progress to invasive disease. In this review, we summarize the current management guidelines, and describe ongoing efforts to more clearly stratify IPMNs by risk of malignancy and identify IPMNs with malignant potential or ongoing malignant transformation.

Keywords

IPMN; risk of malignancy; pancreatic mucinous neoplasms; management of IPMNs

INTRODUCTION

Intraductal papillary mucinous neoplasms (IPMNs) were first described in 1982 by Ohhashi et al, who described four patients with successfully resected main duct IPMN (MD-IPMN).[1] These tumors have been referred to by several names over the past few decades, including mucinous duct ectasia, cystic adenocarcinoma, intraductal cystadenocarcinoma and mucin/

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mucous hypersecreting tumor, among others. The 1996 World Health Organization (WHO) classification designated these tumors as intraductal papillary mucinous tumors,[2] and this was revised to intraductal papillary mucinous neoplasm in the 2010 publication.[3] IPMNs result from the intraductal proliferation of mucin producing neoplastic epithelium, leading to hypercellular outgrowths that secrete frank, mucinous fluid.

The incidence of IPMNs has been increasing, in large part due to increased awareness and the increased use and quality of cross-sectional imaging[4], however the clinical management of IPMNs continues to present challenges. In the past, a more aggressive approach to surgical resection was recommended, mainly due to fears surrounding the presence of occult malignancies and the potential for malignant transformation. Currently, a more conservative approach is favored based largely on limited, retrospective clinical data that may still result in the overtreatment of a large number of patients with these pancreatic neoplasms. The challenge lies in predicting which tumors are high risk and will progress to invasive disease. This review summarizes the pathologic classification of lesions and current management guidelines, and it describes ongoing efforts to more clearly identify IPMNs with malignant potential and ongoing malignant transformation.

PATHOLOGIC CHARACTERIZATION

IPMNs are classified as main duct (MD-IPMN), branch duct (BD-IPMN) or mixed type according to the anatomic involvement of the pancreatic ductal system. MD-IPMN have a higher risk of malignant transformation; the risk of malignancy has been found to range from 19% to 30% in BD-IPMNs and as high as 40% to 60% in MD-IPMN.[5–8]

Pancreatic epithelial cells display varying degrees of dysplasia: low-grade dysplasia (previously termed adenoma), moderate dysplasia (previously termed borderline tumor), high-grade dysplasia (previously termed carcinoma in situ), and invasive carcinoma (Fig. 1). While this is thought to follow the adenoma-carcinoma sequence, it is likely that some IPMNs with low-grade dysplasia will not progress to high-grade dysplasia or invasive carcinoma. At the recent Baltimore Consensus Meeting for pancreatic neoplastic precursor lesions, the classification system was changed from a 3-tier to a 2-tier system, with the IPMNs formerly classified as low-grade as well as intermediate-grade, now being classified as low-grade IPMN.[9]

Histologically, IPMNs can be classified into four subtypes based on morphological and immunohistochemical characteristics: gastric, intestinal, pancreatobiliary and oncocytic (Table 1).[10] While not always the case, gastric type IPMNs typically displays low-grade dysplasia, intestinal type often displays moderate to high-grade dysplasia, while the less common pancreatobiliary type and oncocytic type often display high-grade dysplasia. The two main histopathological types of invasive IPMN are colloid carcinoma, which typically arises from intestinal type IPMN, and tubular carcinoma, which arises from pancreatobiliary type IPMN. Histologic subtypes are typically only determined following surgical resection and currently may not be used to dictate clinical management.

CONSENSUS GUIDELINES & RECOMMENDATIONS

The management of IPMNs is predicated on the accurate assessment of the risk of malignant transformation. Because definitive diagnosis of malignant transformation is difficult pre-operatively, this has been estimated by evaluating the presenting signs and symptoms, in concert with imaging features.

The “Sendai” international consensus guidelines, published in 2006, recommended resection for all MD-IPMNs and mixed type IPMNs if patients are good surgical candidates. Resection was also recommended for symptomatic patients with BD-IPMNs, or BD-IPMNs with main duct dilatation > 6mm or the presence of mural nodules. It was also recommended that lesions > 3 cm be resected, with the caveat that more data was required to determine whether all BD-IPMNs > 3 cm should be resected immediately. Follow up with CT/MRI was recommended for asymptomatic cystic lesions without main duct dilatation > 6 mm, without mural nodules and those < 3 cm in size, since they have a low risk of progressing to invasive cancer in short term (12–36 month) follow up. Yearly follow up was recommended for lesions < 1 cm in size, 6–12 monthly follow up for lesions 1–2 cm, and 3–6 monthly follow up for lesions > 2 cm.[11]

These guidelines were revised in 2012, during the Fukuoka consensus meeting (Fig 2).[12,13] Major changes included a decreased threshold of main duct dilatation for characterization of MD-IPMN to > 5 mm without other causes of obstruction. Resection was recommended for all surgically fit patients with MD-IPMN. Both “high risk stigmata” and “worrisome features” were defined, with surgical resection recommended for high-risk stigmata, namely obstructive jaundice in a patient with a cystic lesion in the head of the pancreas, enhancing mural nodules and main pancreatic duct diameter ≥ 10 mm.

Worrisome features included cyst size ≥ 3 cm, thickened or enhancing cyst walls, main duct size 5–9 mm, non-enhancing mural nodules, an abrupt change in pancreatic duct caliber with distal pancreatic atrophy, pancreatitis, and lymphadenopathy. The presence of any of these is an indication for endoscopic ultrasound (EUS). Definite mural nodules or main duct involvement (thickened walls, intraductal mucin or mural nodules) on EUS, or cytology that is suspicious or positive for malignancy remains an indication for surgical resection.

In the absence of worrisome features or high-risk stigmata, follow up with CT/MRI is recommended every 2–3 years for lesion size < 1 cm and yearly for 2 years with lengthening of interval evaluation if no change in size for lesion size 1–2 cm. Recommendations include consideration for surgical resection in young, healthy patients with lesions 2–3 cm, and strong consideration of the same for lesions > 3 cm. Additionally, for lesions 2–3 cm, an EUS is recommended in 3–6 months, with alternating MRI and EUS at lengthened intervals thereafter, and alternating MRI and EUS for surveillance every 3–6 months for lesions > 3 cm if surgical resection is not performed.

Despite the improvements in the management of IPMNs since the above guidelines, “over-treatment” remains a major problem for a large number of these patients. The decision to observe versus proceed with surgical resection is a complex one, and requires maintaining a balance between the risk of potential malignancy and the risk of pancreatic resection. Most

available data has been derived from retrospective studies with a substantial selection bias. Pancreatic resection for worrisome imaging features often demonstrates pathology consistent with low-grade dysplasia. A recently published multi-institutional study by Wilson et al, of 324 patients found that 44% of specimens resected according to current guidelines had only low-grade dysplasia.[14] Other studies have demonstrated similar percentages of low grade dysplasia in resected specimens.[15]

Many studies have evaluated the performance of the Sendai and Fukuoka guidelines.

Single Institution Studies

Han et al evaluated the utility of the Sendai and Fukuoka consensus guidelines in a retrospective review of 230 patients.[16] They reported a sensitivity and specificity of 90% and 34% with the Sendai guidelines, and 55% and 78% with the Fukuoka guidelines. Likewise, their reported positive predictive values (PPV) and negative predictive values (NPV) were 41% and 87% with the Sendai guidelines, and 55% and 78% with the Fukuoka guidelines. Jaundice, a main pancreatic duct diameter > 10 mm and abdominal pain were the only independent predictors of malignancy in this study. Mural nodules were not predictive for development of malignancy in this study.

Mural nodules, while included in the Sendai and Fukuoka guidelines, and often reported to be predictive of malignancy, are often not addressed on CT imaging reports. A study by Ridtitid et al report that 28% of mural nodules detected by EUS were missed by CT and MRI imaging.[17] Additionally their study found that the mean size of mural nodules on EUS were associated with malignancy; and in contradistinction to other studies that demonstrate nodule size > 7 to 10 mm being strongly associated with malignancy[18–20], their study detected significantly smaller mural nodules in malignant BD-IPMNs, with mean mural nodule size 3.7mm in malignant BD-IPMNs.[17]

Studies have also examined other radiologic features that are predictive of malignancy in IPMNs. In their recent study, Strauss et al reported common bile duct dilatation and parenchymal atrophy to be the best independent predictors of malignancy in BD-IPMNs.[21]

Shimizu et al. developed a nomogram to attempt to predict the probability of the presence of carcinoma in patients with IPMNs. Gender, type of lesion (MD-IPMN vs. BD-IPMN), size of mural nodules and pancreatic fluid cytology were all assigned points, and the value of the total points was assigned a predicted cancer probability. The sensitivity and specificity of this model were reported to be 97.1% and 68.1% respectively, when a predictive probability of > 10% was used to indicate the presence of carcinoma.[22]

Multi Institutional Studies

Kim et al, in a nationwide multicenter study in Korea, reported that cyst size > 3cm, enhancing mural nodules on CT imaging and mural nodules > 5mm on EUS were independent risk factors for the presence of malignancy in BD-IPMNs.[23] Cyst size > 3 cm had a sensitivity of 88% but a relatively low specificity of 52.9%. Sensitivity and specificity were 48.7% and 94.9% for enhancing mural nodules on CT and 84% and 77.7% for mural nodules > 5 mm on EUS.

Attiyeh et al developed a nomogram to preoperatively predict IPMN grade of dysplasia in MD-IPMNs and BD-IPMNs: weight loss, presence of symptoms, cyst size, mural nodule with solid component and main duct diameter > 1 cm were the variables included in the MD-IPMN nomogram, while age, gender, presence of symptoms, cyst size and mural nodule with solid component were included in the BD-IPMN nomogram used to predict high risk disease. This was studied in both training and validation cohorts with C-indices of 0.82 and 0.81 respectively.[24]

Systematic Reviews & Meta-analyses

Goh et al reviewed the literature for studies evaluating the utility of the Sendai consensus guidelines. They evaluated 12 studies with a pooled sample size of 690 resected BD-IPMNs and found that, while the NPV of the applied guidelines ranged from 90–100%, the PPV ranged from 11 to 52%.[25]

Anand et al performed a meta-analysis that examined 41 studies and reported that cyst size > 3 cm, presence of a mural nodule, dilation of main pancreatic duct and MD-IPMN were predictive of malignancy, with cyst size > 3 cm being the most strongly associated with malignancy.[26]

Sultana et al examined 37 studies and reported pooled sensitivities and specificities of risk factors predictive of malignancy of 80% and 76% for CT/MRI, but 96% and 91% for PET imaging. The presence of a mural nodule on imaging was the most sensitive variable in this study.[27]

Other Studies

The neutrophil to lymphocyte ration (NLR) is an inflammatory marker that has been correlated with poor survival in patients with pancreatic cancer and other solid tumors.[28]

Gemenetzis et al demonstrated that an elevated NLR > 4 was significantly associated with IPMN associated invasive carcinoma ($P < 0.001$). Additional significant variables were cyst size > 3 cm ($P < 0.001$), main pancreatic duct dilatation > 5mm ($P < 0.001$) and jaundice ($P < 0.001$). While the developed predictive model using these variables had a C-index of 0.895, this study only evaluated IPMN associated invasive carcinoma versus non-invasive carcinoma, and the latter group did contain IPMNs with high-grade dysplasia.[29]

FUTURE DIRECTIONS

Molecular Investigations

In addition to the clinical and radiological studies, attention has also turned to the search for molecular markers in order to help us better understand the progression from IPMNs with low-grade dysplasia to invasive carcinoma (Table 2). An early study by Nishihara et al in 1993 performed DNA flow cytometry on IPMNs and demonstrated that IPMNs with intermediate-grade dysplasia were diploid, whereas those with high-grade dysplasia were aneuploid.[30]

Shimura et al evaluated the MIB-1 labeling index as an indicator of the invasiveness of IPMNs. Immunohistochemical analysis demonstrated that the MIB-1 labelling index was significantly higher in patients with invasive IPMNs versus non-invasive IPMNs (13.4 [standard deviation, 15.8] versus 42.4 [standard deviation, 30.3]; $P < 0.001$), however this study included IPMNs with high-grade dysplasia in the non-invasive IPMN group.[31]

DNA Based Biomarkers—Fukuda et al demonstrated that Brg1 null IPMN-pancreatic ductal adenocarcinoma (PDAC) was less lethal than pancreatic intraepithelial neoplasia (Pan-IN) derived PDAC that is driven by mutant Kras and hemizygous p53 deletion. Transgenic mice with Brg1 deletion developed spontaneous cystic pancreatic neoplasms that closely resembled pancreatobiliary type IPMNs that then progressed to IPMN derived PDAC. Additionally, other genes such as Mmp7, Gabrp, Hmga2, Clic3 and Adams1 previously shown to be involved in Pan-IN derived PDAC were down regulated in IPMN-PDACs.[32]

Hong et al in a 2011 publication, reviewed studies that characterized the molecular signatures of pancreatic cancer, and demonstrated that activating point mutations of KRAS are present in approximately 50% of IPMNs with low-grade dysplasia, but the prevalence of KRAS mutations did increase with the degree of dysplasia. Additionally, inactivating CDKN2A and p53 mutations were found in IPMNs with high-grade dysplasia, as were aberrant methylation patterns.[33] KRAS mutations were also found to be more prevalent in invasive IPMNs than in premalignant IPMNs in some other studies,[34] but there are other studies in which this was not found to be the case.[35,36]

In a 2015 study evaluating mutations in pancreatic cancer and associated precursor lesions, Hosoda et al found frequent GNAS mutations in IPMNs as well as other pancreatic mucinous tumors, both with and without associated adenocarcinomas. Additionally, while mucinous IPMN associated adenocarcinomas were associated with a high prevalence of GNAS mutations, tubular type adenocarcinomas were more heterogeneous. This study did not find a difference in GNAS mutation patterns between IPMNs with and without associated adenocarcinoma.[37] Whole exome sequencing also revealed frequent GNAS mutations in IPMNs, but not in PDACs.[38]

Kuboki et al evaluated molecular biomarkers to assess their association with the progression of dysplasia in IPMNs. Their study demonstrated that both GNAS and KRAS mutations were present in approximately half of IPMNs. GNAS mutations were associated with intestinal type IPMNs, whereas KRAS mutations were associated with gastric and pancreatobiliary type IPMNs. Increased EGFR expression was associated with higher histological grade, as were increased expressions of AKT and p53 and loss of SMAD4. MAPK expression was more commonly observed in low-grade dysplasia. No EGFR mutation, loss of SMAD4 or p53 overexpression was seen in any IPMNs with low-grade dysplasia.[39] Abnormal P53 protein accumulation was also found to be more frequent in high-grade dysplasia and carcinoma compared to adenomas in the study by Mohri et al, however the reduction of SMAD4 expression did not correlate.[36]

Lee et al performed a meta-analysis to evaluate the incidence of KRAS, GNAS and RNF43 mutations in IPMNs. Although their pooled analysis did demonstrate a different mutational profile that was significantly related to the histologic subtype, they did not demonstrate any such association with the presence of adenocarcinoma in IPMNs.[40] Nissim et al performed a meta-analysis of 39 studies to determine the relationship between various genetic alterations and malignant transformation in IPMNs, and determined that expression of hTERT (the human telomerase reverse transcriptase gene that encodes the catalytic component of telomerase required to overcome telomere shortening and cellular senescence) and Shh (the secreted factor sonic hedgehog which plays an important role in regulating normal pancreas development) were strongly associated with malignant transformation with odds ratios of 11.4 (95% CI, 3.5–36.7) and 6.9 (95% CI, 2.4–20.2) respectively.[41]

In the study by Durante et al,[42] high resolution cytogenetic analysis was performed using formalin-fixed paraffin-embedded samples. IPMNs with low-intermediate grade dysplasia were found to have a nearly normal karyotype with either no copy number alterations or only 1 focal gain, whereas IPMNs with high-grade dysplasia had a complex karyotype with > 4 macroscopic copy number gains/losses and 10 copy number alterations each on average. Additionally a specific gain of chromosome arm 3q encompassing the PIK3CA, GATA2 and TERC oncogenes was detected in 92% of IPMNs with a complex karyotype. miRNA expression revealed a corresponding upregulation of PIK3CA (4-fold) and TERC (2-fold) in these IPMNs, while GATA2 was not upregulated.

Wu et al, in a whole exome sequencing of pancreatic cystic neoplasms, demonstrated that the most commonly mutated gene in IPMNs was RNF43, located on chromosome 17q, with this mutation found in 6 out of 8 IPMNs. This gene was also noted to be deleted in mucinous cystic neoplasms (MCNs).[43]

Cyst Fluid Analysis—Cyst fluid analysis is being studied so as to evaluate potential candidate biomarkers that may be used to pre-operatively, in a complementary fashion with clinical and radiological features, to differentiate between high grade and low grade IPMNs. Wu et al also evaluated pancreatic cyst fluid, and noted KRAS or GNAS mutations in 96% of 19 samples (KRAS mutation in 14 and GNAS mutations in 6 IPMNs respectively, with both mutations seen in more than half). The same mutations were noted in the cyst wall as well as the cyst fluid, thus confirming that cyst fluid mutations provide an accurate representation of neoplastic cells in the IPMN. However, neither of these mutations were able to distinguish high grade from low grade lesions.[44]

Nikiforova et al tested pancreatic cystic fluid obtained at the time of EUS for KRAS mutations, and noted that KRAS mutations had a specificity of 100% but a sensitivity of 54% for mucinous differentiation (67% for IPMNs and 14% for mucinous cystic neoplasms). However, their study noted that 53% of specimens were suboptimal or unsatisfactory for analysis.[45]

Singhi et al describe GNAS and KRAS testing on pancreatic cyst fluid obtained from EUS as part of routine clinical evaluation. GNAS mutations were detected in 30% of IPMNs and 22% of IPMNs with adenocarcinoma, KRAS mutations were detected in 68% of IPMNs and

78% of IPMNs with adenocarcinoma, and mutations in either gene were detected in 83% of IPMNs and 89% of IPMNs with adenocarcinoma. GNAS and KRAS mutations had 100% specificity and 65% sensitivity for mucinous differentiation.[46]

miRNA Based Biomarkers—Distinct miRNA profiles are also found to be associated with the malignant transformation of pancreatic cystic neoplasms (Table 3). miRNAs are excellent candidate biomarkers due to their tissue specific expression, stability in biofluids and involvement in several biological pathways.[47] In a study by Frampton et al, upregulation of miR-21, miR-155, and miR-708 was demonstrated to be associated with the malignant transformation of IPMNs.[48]

In a multicenter study, Caponi et al evaluated 3 specific candidate miRNAs that were selected based on prior studies: miR-21, miR-155 and miR-101 as potential biomarkers in IPMNs and demonstrated that miR-21 and miR-155 were upregulated in invasive IPMNs compared with noninvasive IPMNs, and in noninvasive IPMNs compared with normal tissue. miR-101 levels were upregulated in noninvasive IPMNs and normal tissues compared with invasive IPMNs. miR-21 was found to be an independent prognostic factor for mortality and disease progression.[49]

Matthaei et al identified 18 candidate miRNAs that separated high grade IPMNs from low grade IPMNs using cyst fluid analysis, and developed a logistic regression model using 9 miRNAs to separate high grade from low grade IPMNs with 89% sensitivity and 100% specificity. The most important miRNAs in the regression model included miR-24, miR-30a-3p, miR-18a, miR-92a, and miR-342-3p. Other miRNAs in the model included miR-99b, miR-106b, miR-142-3a and miR-532-3p.[50] Wang et al also performed exploratory next-generation sequencing based profiling of miRNAs in cyst fluid and determined that thirteen miRNAs were enriched (miR-138, miR-195, miR-204, miR-216a, miR-217, miR-218, miR-802, miR-155, miR- 214, miR-26a, miR- 30b, miR-31, miR-125) and two miRNAs were depleted (miR-451a, miR-4284) were depleted in cyst fluid from high grade and invasive IPMNs compared to low grade IPMNs.[51] Of note, 5 of these miRNAs were also reported in the prior miRNA profiling study by Matthaei et al, though they were not included in the published regression model.

Quantitative Imaging

Diffusion weighted imaging- a technique of magnetic resonance imaging that is based upon measuring the random Brownian motion of water molecules within a voxel of tissue- has been used for the detection and characterization of a number of types of tumors. Kim et al, in a retrospective study of 132 patients, evaluated diffusion restriction as well as the imaging parameters of high-risk stigmata and worrisome features based on the Fukuoka consensus guidelines. They reported that the presence of diffusion restriction in IPMNs was the only independent imaging parameter for prediction of malignancy and invasiveness, with a diagnostic accuracy that was significantly improved compared with utilizing only the high-risk stigmata.[52]

Radiomics is the high throughput extraction and analysis of large amounts of quantitative image features from radiographic studies in order to attempt to capture additional

information from these images. It is a rapidly expanding field and has been used for the detection of prostate cancer, renal cell carcinoma, non small cell lung cancer and other cancers. Radiomics is based on the hypothesis that genomic and proteomic patterns may be expressed as macroscopic image-based features. It involves analyzing high quality, standardized imaging, defining the tumor either by an experienced reviewer or, more recently, by the use of automated segmentation methods, and then extracting quantitative imaging features from the tumor and surrounding tissues of interest. Features analyzed include tumor signal intensity, shape characterization, texture heterogeneity patterns and the relationship of the tumor with surrounding tissues.

Hanania et al[53] evaluated 53 cases of IPMN (34 high grade and 19 low grade) and quantitatively analyzed the cysts and pancreatic parenchyma to differentiate high grade from low grade lesions using 14 imaging biomarkers (all within the Gray Level Co-Occurrence Matrix). A cross validated panel created using 10 of these markers yielded an AUC of 0.96 (95% CI, 0.92–0.99), at a sensitivity of 97% and specificity of 88%.

Permuth et al[54] combined both radiomic features and a miRNA genomic classifier data in order to differentiate malignant from benign IPMNs with a sensitivity of 83% and specificity of 89% (AUC = 0.92). These authors had previously performed a genome wide miRNA analysis and had demonstrated a 5 miRNA genomic classifier (miR-200a-3p, miR-1185-5p, miR-33a-5p, miR-574-4p, and miR-664b) that could discriminate between malignant (high grade dysplasia or invasive) and benign IPMNs with an AUC = 0.73. These miRNAs are thought to have a tumor suppressor role, since expression was noted to be 2- to 3- fold lower in malignant IPMNs compared with benign IPMNs.[55,56] Their current study revealed 14 radiomic features; 11 textural and 3 non-textural features (size and shape) that were used in combination with the miRNA genomic classifier to more accurately differentiate malignant from benign IPMNs.[54]

A major hurdle for this approach will be to address the heterogeneous nature of radiomic data, largely due to the non-standardization of imaging protocols and imaging machines across multiple institutions. This is thought to be the reason that studies performed at a single institution are difficult to reproduce elsewhere. This challenge is being actively studied in order to develop standardized protocols by various teams including our own, as part of the Molecular and Cellular Characterization Laboratory Consortium for Overdiagnosis, supported by the National Institute of Health (NIH).

CONCLUSIONS

While we have gained much our understanding of the molecular drivers and clinical behavior of IPMNs over the past decade, the management of IPMNs is still particularly challenging. The natural history of the disease and the events that permit progression to adenocarcinoma are still not entirely understood, highlighting the urgent need for a genetically engineered animal model of the disease. It is clear that IPMNs with high-grade dysplasia are high-risk lesions that will likely transform into invasive carcinoma, and should be treated with surgical resection in appropriate patients. While large cyst size, enhancing mural nodules and clinical symptoms such as jaundice are worrisome findings and should

result in surgical resection, smaller tumors are also noted to have high-grade dysplasia or invasive carcinoma when resected. The Sendai and Fukuoka guidelines help establish a working model for treatment. However, given the existing guidelines, there is evidence that physicians are still overtreating a large number of patients.

Genetic characterization of the disease has helped guide development of molecular panels of genes associated with disease progression. This approach is limited due to the use of surgically resected tissues, which is not helpful in differentiating between high grade and low grade IPMNs preoperatively. Pancreatic cyst fluid analysis is a developing field of study with tremendous clinical potential, and the identification of biomarkers that may be differentially expressed in low versus high grade IPMNs will help to identify patients who will most benefit from surgery. Studies in the field of radiomics and imaging characteristics of pancreatic tumors, while still in the very early stages, have shown promise.

Clinical decision-making in the treatment of IPMNs needs to be individualized for each patient, given their age, tumor appearance on radiologic imaging and endoscopic ultrasound and other risk factors, especially given the morbiditiy and mortality associated with the surgical procedures often required. Emerging technologies that provide us with additional ways to help differentiate low from high grade IPMNs preoperatively should be evaluated in multi-institutional studies to enable us to more accurately risk stratify patients who will benefit from surgical resection. Additionally, large multi-institutional studies are also necessary to help us continue to understand the progression of this disease, the burden of overtreatment and its involved costs and possible complications.

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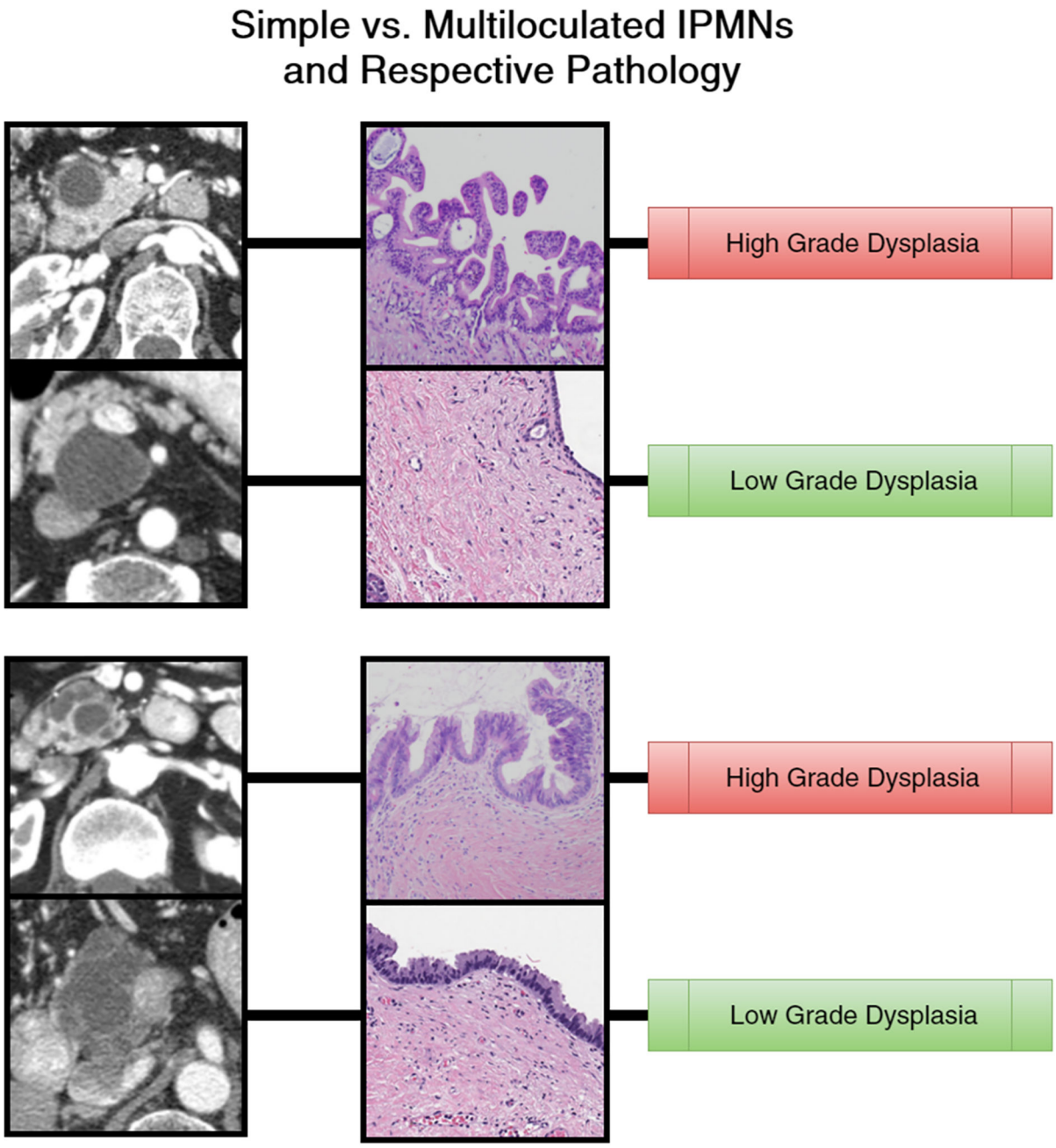

FIGURE 1.

Dysplastic changes seen in uniloculated and multiloculated IPMNs. Note the varying degrees of dysplasia in cysts that appear similar on imaging. Reproduced with permission from Hanania et al.[53]

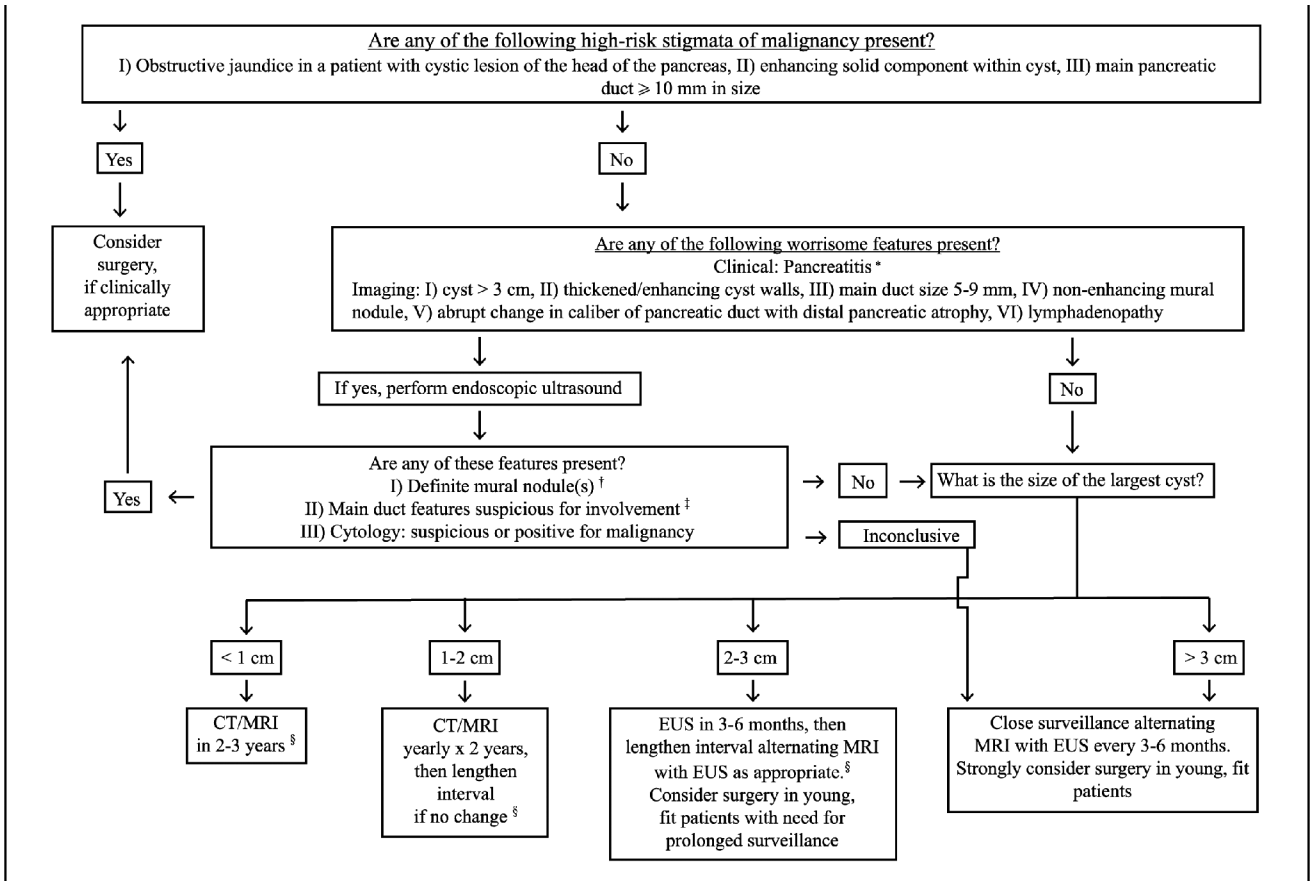

FIGURE 2.

Algorithm for the management of suspected BD-IPMNs based on the 2012 Fukuoka Guidelines. Reproduced with permission from Tanaka et al.[13]

*Pancreatitis may be an indicationi for surgery for relief of symptoms.

†Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage, and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow, and FNA of nodule showing tumor tissue.

‡Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement in inconclusive.

§Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.

TABLE 1

Four Histological Subtypes of IPMNs

Type	Histology	Atypia	MUC1	MUC2	MUC5AC	MUC6
Gastric	Columnar cells with basal nuclei and abundant apical cytoplasmic mucin; flat lesions or with low papillary pattern, consisting of thick finger-like papillae	Low grade	−	−	+	+
Intestinal	Columnar cells with enlarged cigar-like nuclei forming elongated papillae; histomorphology similar to villous adenomas of the colon	Intermediate or high grade	−	+	+	±
Pancreatobiliary	Cuboidal cells with rounded nuclei and prominent nucleoli, organized into thin complex and branching papillae with bridging and cribiform patterns	High grade	+	−	+	±
Oncocytic	Neoplastic cells with abundant granular eosinophilic cytoplasm (due to numerous mitochondria), with large round nuclei, prominent nucleoli and intracellular mucin, that form thick branching papillae	High grade	+	−	+	+

TABLE 2

DNA Based Studies

Author	Study Design	Study Results
Shimura et al[31]	Single-institute retrospective review of 53 tumors	MIB-1 labelling index significantly higher in patients with invasive IPMNs versus non-invasive IPMNs
Fukuda et al[32]	Mnou Mouse model	Brg1 null IPMN-PDA less lethal than Pan-IN derived PDA (mutant Kras and p53)
Hosoda et al[37]	Single institution review of 290 surgically resected pancreatic tumors	Frequent GNAS mutations in IPMNs (with or without associated adenocarcinoma)
Kuboki et al[39]	Single institution review of 172 surgically resected IPMNs	GNAS and KRAS mutations found in 50% of IPMNs
		Increased EGFR, AKT and P53 expression and loss of SMAD4 associated with higher histological grade
Lee et al[40]	Meta-analysis of 33 KRAS, 11 GNAS, and 4 RNF43 published studies including 1253, 835, and 143 cases	Incidence of KRAS, GNAS and RNF43 mutations not associated with IPMN associated adenocarcinoma
Nissim et al[41]	Meta-analysis of 39 studies including 1235 IPMN samples	hTERT and Shh expression associated with malignant transformation of IPMNs
Durante et al[42]	High resolution cytogenetic analysis of 20 FFPE IPMN samples; results validated by qPCR and FISH analysis	High grade IPMNs have complex karyotype; 3q gain detected in 92%
Wu et al[43]	Whole exome sequencing of 32 cysts and pancreatic cyst fluid analysis	RNF43 is most frequently mutated gene in IPMNs
		KRAS and GNAS mutations in 96% of IPMNs on cyst fluid analysis
Nikiforova et al[45]	Single institution study: pancreatic cyst fluid analysis from 618 pancreatic cysts; surgical resections of 142 pancreatic tumors	KRAS mutations have 100% specificity and 54% sensitivity for mucinous tumors
Singhi et al[46]	Single institution study: pancreatic cyst fluid analysis from 91 pancreatic cysts, followed by surgical resection	GNAS and KRAS mutations have a 100% specificity and 65% sensitivity for mucinous tumors

FFPE indicates formalin fixed paraffin embedded

TABLE 3

miRNA Based Studies

Author	Study Design; Biospecimen	Study Result
Frampton et al[48]	Multi-institutional study FFPE tissue from 55 samples including 5 PDAC and 10 normal tissue	Upregulation of miR-21, miR-155 and miR-708 associated with malignant transformation of IPMNs
Caponi et al[49]	Multi-institutional study	miR-21 and miR-155 upregulated in
	FFPE tissue from 81 samples (65 invasive and 16 non-invasive IPMNs)	invasive IPMNs miR-21 is independent prognostic factor for mortality and disease progression
Matthaei et al[50]	Single institution study	9 miRNA model (including miR-24,
	FFPE tissue from 55 IPMN samples; 65 cyst fluid specimens aspirated following surgical resection	miR-30a-3p, miR-18a, miR-92a, and miR-342-3p) to differentiate high grade from low grade IPMNs with 89% sensitivity and 100% specificity
Wang et al[51]	Single institution study	13 enriched miRNAs (miR-138, miR-
	Cyst fluid aspirated during EUS from 17 patients	195, miR-204, miR-216a, miR-217, miR-218, miR-802, miR-155, miR- 214, miR-26a, miR- 30b, miR-31, miR-125) and 2 depleted miRNAs (miR-451a, miR-4284) in high grade/ invasive IPMNs

FFPE indicates formalin fixed paraffin embedded