ORIGINAL ARTICLE

Incidental Mucinous Neoplasms of the Pancreas: Performance of the AGA, European, and IAP Guidelines in Advising Further Management After Endoscopic Ultrasound-Guided Fine-Needle Aspiration Biopsy

Débora Pacheco, PhD,[1,2] Otávio Micelli-Neto MD,[2,3] Eloy Taglieri PhD,[2,3] Fernando Issamu Tabushi PhD,[1] Osvaldo Malafaia PhD,[1] Rodrigo Cañada Trofo Surjan PhD,[4] Marcel Autran Machado PhD,[4] Filadélfio Euclides Venco MD,[5]Rafael Kemp PhD,[6]José Sebastião dos Santos PhD,[6] José Celso Ardengh PhD.[2,6,7]

Objectives: We compared the performance of AGA-2015, ESG-2018, and IAP-2024 guidelines in referring patients for surgery versus surveillance when applied to incidental after diagnosis by EUS-FNA.
Methods: Single-center, retrospective study with prospective data collection. PLs identified incidentally on CT or MRI/MRCP performed for other diseases with inconclusive imaging results were eligible for analysis. After EUS-FNA and microhistological diagnosis, each of the guidelines was applied; sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were compared.
Results: 140 asymptomatic patients (mean age 64.7 years, 61% female) had a confirmed diagnosis of MN. Of these, 42 (30%) had "*high rik stigmata*" and 16 (11.4%) were malignant. AGA-2015, ESG-2018, and IAP-2024, criteria would have advised surgery unnecessarily in 66%, 15%, and 46%, respectively ($p<0.001$). AGA-2015, ESG-2018, and IAP-2024, and criteria failed to identify 59%, 46.1%, and 33.3% of HGD/IC, respectively ($p=1.00$).
Conclusion: The AGA-2015 criteria were highly specific, while IAP-2024 had superior sensitivity. All had moderate sensitivity to indicate surgery, and all missed similar numbers of malignant lesions. Performing EUS-FNA before application of guidelines seems appropriate to guide further management of asymptomatic PLs, preventing unnecessary surgery and referring patients appropriately for surveillance. The ESG-2018 guideline proved most accurate for this purpose.
Keywords: Pancreatic neoplasms, Pancreatic cysts; Pancreatic Intraductal Neoplasms; Endoscopic ultrasound; Biopsy, Fine-Needle; Guidelines, Diagnosis.

Around 18% of the general population is affected by pancreatic cystic lesions (PL). Most are benign and few have potential for malignant transformation, but surveillance is required.[1] At the time of writing, three guidelines are available to help advise surgery (in case of malignancy) or further surveillance of the 2015 American Gastroenterological Association mucinous neoplasms (MNs) of the pancreas[2]: (AGA-2015), 2018 European Study Group (ESG-2018), and 2024 International Association of Pancreatology (IAP-2024), guidelines. All are controversial regarding the optimal form of surveillance and indications for surgery in MNs and branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs).[3,4] PLs are generally divided into benign, potentially malignant, and malignant. Imaging methods accurately characterize these lesions and provide appropriate screening; however, misdiagnosis is possible when one relies solely on magnetic resonance cholangiopancreatography (MRCP) or computed tomography (CT) findings.[5] Proper differentiation of PLs is challenging. Treatment decisions based on imaging alone can be unnecessarily invasive, costly, and harmful to the patient. The best strategy would be to first perform histological diagnosis of PLs, identify high-grade dysplasia (HGD) or carcinoma *in situ* (Cis) when present, and predict those in which cancer may develop. Diagnosis of intraductal papillary mucinous neoplasm (IPMN) is essential to determine the best form of treatment for this disease.[6] Morphologically, these neoplasms are divided into main pancreatic duct IPMN (MD-IPMN), BD-IPMN, or mixed (M-IPMN), with differences in prognosis.[7] Endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNA) allows collection of material for microhistological (McH) examination, biomarker measurement, and evaluation for the "string sign".[8,9] Malignant BD-IPMN is rare, suggesting that surveillance is sufficient to avoid the loss of pancreas function associated with resection of large portions of this gland. Current guidelines go to great lengths to identify signs of malignancy and avoid overtreatment, but the risk of failure remains non-negligible.[7] AGA guideline [5,10] applies exclusively to incidentalomas and suggests that PLs with at least two high-risk features are an indication for EUS-FNA. The IAP-2017[11]and ESG- 2018[5] guidelines advise EUS-FNA based on clinical and imaging red flags;[12] the ESG-2018 guideline further divides indications for surgery into absolute and relative. The IAP-2024 guideline, recently published and based on evidence,

From [1]Mackenzie Evangelical University Hospital, Curitiba [2]Digestive Endoscopy Service, Hospital Moriah, São Paulo [3] Endoscopy Service, A.C. Camargo Cancer Center, São Paulo [4] Surgical Service, Hospital 9 de Julho, São Paulo [5]Pathology Service, Hospital Moriah, São Paulo [6] Department of Surgery and Anatomy, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto (USP), Ribeirão Preto [7] Department of Diagnostic Imaging, Universidade Federal de São Paulo, São Paulo, Brazil.
Address correspondence to: JC Ardengh, MD, PhD, (e-mail: jardengh@gmail.com).

proposes a new management algorithm, no longer using EUS-FNA with cytology due to its low results (28.7%) in the classificatory diagnostic.[13] On the other hands the authors believe EUS-FNA is important in the evaluation of undiagnosed PLs, as there are no reliable clinical features that would allow accurate diagnosis in the majority of patients and guideline criteria are often applied to patients without prior diagnostic classification.[14] Within this context, the present study sought to compare the sensitivity, specificity, accuracy, positive and negative predictive values, and performance of current guidelines to indicate surgery versus surveillance for incidental MNs.

MATERIALS AND METHODS

Study design and patient selection

This is a retrospective, single-center study, with prospective data collection carried out at the Digestive Endoscopy Service of Hospital Moriah (São Paulo, Brazil) and the Medical Research Institute (IPEM) of Hospital Evangélico Mackenzie (Curitiba, Brazil) between 2010 and 2021. The study was approved by the Human Research Ethics Committee of Faculdade Evangélica Mackenzie do Paraná (Curitiba, Brazil) (Certificate of Submission for Ethical Appreciation: 65594422.30000.0103). We included patients with PLs identified by abdominal US, CT, or MRCP performed for diseases unrelated to the gastrointestinal tract and whose imaging findings were inconclusive. Patients who underwent EUS-FNA and/or tissue acquisition (EUS-TA) who exhibited PL growth ≥5 mm, elevated CA 19-9, history of pancreatic cancer in a first-degree relative or pancreatitis during follow-up, as well as those in whom the optimal management strategy going forward was unclear and those who underwent surgery and had a diagnosis of MN on histological examination of the surgical specimen, were eligible. We excluded those whose final diagnosis was not MN, those with dyspeptic symptoms or abdominal pain related to the gastrointestinal tract, those who underwent EUS alone (without FNA), and those with known coagulation disorders who would be at inordinate risk of bleeding during the procedure. Once the diagnosis had been established by EUS-FNA and/or EUS-TA with McH, we applied each of the guidelines' criteria to identify MNs consistent with cancer and/or exhibiting imaging or clinical red flags and then compared the performance of each of the guidelines.

Variables analyzed

Sex, age, PL characteristics on MRI/MRCP, and EUS, cyst size, multiplicity, number, location, presence of mural nodule, thick wall, maximum MD size, and presence of lymphadenopathy were noted. In patients who underwent surgery, we noted the type of procedure and the surgical pathology result. If surgical resection was not indicated after EUS- FNA, patients were monitored with at least one control MRI/MRCP 12 months later, the results of which were evaluated by staff physicians at the center.

Application of guidelines

Once data had been collected, the criteria set of each of the guidelines (AGA-2015, ESG-2018, and IAP-2024) were applied. The AGA-2015 guideline suggests that MRI/MRCP must demonstrate at least 2 "high-risk features" (cyst size ≥ 30 mm, MD diameter between 5 and 9 mm, and presence of an associated solid component) for EUS-FNA to be considered. The ESG-2018 guideline lists the following as relative indications for surgery: cyst growth rate >5 mm per year, CA 19-9 level >37 ng/mL, MD diameter between 5 and 9.9 mm, cyst size >40 mm, enhancing mural nodule <5 mm, new-onset diabetes mellitus, and acute pancreatitis. In the IAP-2024 guidelines, the primary imaging methods are MRI/MRCP and multidetector computerized tomography (MDCT), that require at least one of the "high-risk stigmata" or high-grade dysplasia (HGD) or invasive carcinoma (IC) identified on EUS-FNA, such as obstructive jaundice in a patient with a PL located in the pancreatic head; the presence of an enhancing mural nodule >5 mm or a solid component; a MD >10 mm; or suspicious or positive cytology results detected via EUS-FNA, which can be used for further investigation. Additionally, any of the following "worrisome features" are included as criteria: acute pancreatitis; elevated serum levels of CA19-9; newly diagnosed diabetes; lesion size >30 mm; a thickened and enhancing cyst wall; enhancing mural nodules <5 mm; a MD diameter between 5 and 9 mm; an abrupt change in the diameter of the MD with distal pancreatic atrophy; lymphadenopathy; and rapid cyst growth, defined as greater than 2.5 mm per year. Finally, any of the following additional factors are considered: recurrent episodes of acute pancreatitis, the presence of one or multiple "worrisome features" that increase the likelihood of HGD/IC, and young patients in good surgical condition. For each guideline, we applied all criteria and calculated sensitivity, specificity, positive and negative predictive values, accuracy, and likelihood ratios.

Endoscopic Ultrasound-guided fine needle aspiration (EUS-FNA) or tissue acquisition (EUS-TA)

All procedures were performed using a Fujinon EG 580-UT or EG 580-UT2 linear echoendoscope (FUJIFILM Medical Systems, Wayne, NJ, USA). We used conventional EchoTip 19G or 22G (EchoTip® Ultra Endoscopic Ultrasound Needle, Cook Medical, Bloomington, IN, USA), as well as the new ProCore® 20G model

(EchoTip® Ultra Endoscopic Ultrasound Needle, Cook Medical, Bloomington, IN, USA). Lesions in the head of the pancreas and/or unciform process were approached transduodenally, whereas a transgastric approach was used for PLs in the body and tail.

Microhistology (McH)

The specimens obtained by EUS-FNA or EUS-TA were placed in 10% formaldehyde for 6 to 24 hours and subjected to routine histopathological processing, with a single pathologist (FEV) analyzing the results.

Statistical analysis

For statistical analysis, the DTComPair package[15] was implemented in *R* version 4.2 for Mac iOS to calculate and compare the sensitivities, specificities, positive and negative predictive values, and positive and negative likelihood ratios of the AGA-2015, IAP-2017, and ESG-2018 guideline criteria to predict malignancy on final diagnosis. Fagan nomograms were calculated for all tests using the prevalence of malignancy on final diagnosis. This statistical technique is one of several ways to use probabilistic reasoning in daily clinical practice. The Fagan nomogram is a graphical method for estimating how much the result of a diagnostic test changes the probability that the patient has a disease (post-test probability) given the prevalence of this disease found in the literature. To supplement our analyses and facilitate interpretation of the results, test consequence graphics[16] considering a hypothetical cohort of 1000 cases were plotted.

RESULTS

Sample profile

During the study period, 560 patients with PLs were assessed. A diagnosis of MN was established in 251 (45%). Among them, 140 (56%) were asymptomatic, with a mean age of 64.7 years (range, 25– 85 years); most (61%) were female. Of these, 40 (28%) had a final diagnosis of mucinous cystadenoma [33 (82.5%) benign and 7 (17.5%) malignant] and 100 (72%) of IPMN [91 (91%) benign and 9 (9%) malignant]. Forty-two of the 140 (30%) had MNs with *"high-risk stigmata"* and 16/140 (11%) were malignant (9 IPMN and 7 MN). Twenty-five patients (18%) presented with the following concerning findings during the surveillance period (i.e., before EUS-FNA): 9 (6%) with an increase in CA 19-9 alone, 9 (6%) with suspected MD involvement and dilatation, 5 (4%) with cyst growth >2.5 mm in the last year, and 2 (1%) with elevated CA 19-9 plus cyst growth >2.5 mm in the last year of follow-up. These features were part of the indication for EUS-FNA and/or EUS-TA for these patients.

Morphological characteristics of PLs identified by EUS

The mean size of PLs identified by EUS was 2.4 cm (0.4–10.5 cm). The MD was enlarged in 24/140 patients (17%); in all cases, dilatation was identified by MRCP and EUS. Mural nodules were identified in 8/140 patients (6%), 1 (12.5%) by MRCP and 7 (87.5%) by EUS; 5/140 (62.5%) were Doppler-positive. Eleven of 140 (8%) had well-defined thickening of the cyst wall, all identified by EUS (11/11); 3 (2%) patients had an abrupt change in MD caliber, all identified concomitantly by MRCP and EUS; and 12/140 (9%) had a peripheral solid mass, with EUS identifying 12/12 (100%) and MRCP 2/12 (16%) of these. All patients underwent FNA. The mean number of punctures was 1.5 per patient (range, 1-4). FNA was performed with a 19G or 22G needle in 74 (53%) of the patients, while tissue acquisition with the ProCore® 20G needle was performed in 66 (47%). After analyzing all data and based on the findings of EUS-FNA or other clinical and radiological features, 69 patients (49%) underwent pancreatic surgery; the remaining 71 (51%) were referred for surveillance (repeat pancreatic imaging) based on the diagnosis obtained by EUS-FNA and/or EUS-TA.

Analysis of application of the AGA-2015, ESG-2018, and IAP-2024 guidelines

All patients were assessed according to the AGA-2015, ESG-2018, and IAP-2024 guidelines. The IAP-2024 had significantly higher sensitivity than the AGA-2015 (p=0.002) and ESG-2018 (p=0.025) guidelines. The AGA-2015 and ESG-2018 guidelines had similar specificities (p=0.083), which were significantly higher than that of IAP-2024 (p<0.001). Again, the AGA-2015 and ESG-2018 guidelines had similar positive predictive values (p=0.132), which were significantly higher than those found for the IAP-2024 criteria (p<0.001). There were no statistically significant differences in negative predictive values between the AGA-2015 and IAP-2024 guidelines (p=0.081), AGA-2015 *vs* ESG-2018 (p=0.050), or IAP-2024 *vs* ESG-2018 (p=0.529). The positive likelihood ratio of AGA-2015 was significantly higher than that of IAP- 2024 (p=0.006). The positive likelihood ratio of ESG-2018 was also significantly higher than that of the IAP-2024 guidelines (p<0.001). No statistically significant differences were found between AGA-2015 and ESG-2018 in this respect (p=0.203). Regarding negative likelihood ratios, no statistically significant differences were found in comparison of AGA-2015 *vs* IAP- 2024 (p=0.105), AGA-2015 *vs* ESG-2018 (p=0.054), or IAP-2024 *vs* ESG-2018 (p = 0.542). Table 1 shows the sensitivity, specificity, positive (PPV) and negative predictive values (NPV), and positive and negative likelihood ratios for each of the guidelines when applied to asymptomatic patients for the detection of malignancies (Figure 1). Considering a malignancy

prevalence of 30% in asymptomatic patients, the AGA- 2015, ESG-2018, and IAP-2024 guidelines showed a positive and negative post-test probability of 94% and 20%, 85% and 18%, and 55% and 17%, respectively (Figure 2).

TABLE 1. Sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios for the three guidelines when applied to asymptomatic patients.

Statistics	AGA-2015	ESG-2018	IAP-2024
Sensitivity	0.41 (0.26, 0.56) ‡¥	0.54 (0.38, 0.69) ‡	0.67 (0.52, 0.81) †¥
Specificity	0.99 (0.97, 1.00) ‡	0.96 (0.92, 0.99) ‡	0.76 (0.68, 0.85) †¥
PPV	0.94 (0.83, 1.00) ‡	0.84 (0.70, 0.98) ‡	0.52 (0.38, 0.66) †¥
NPV	0.81 (0.74, 0.88)	0.84 (0.78, 0.91)	0.86 (0.78, 0.93)
LR+	41.4 (5.69, 301.9) ‡	13.6 (4.98, 37.1) ‡	2.81 (1.85, 4.24) †¥
LR-	0.60 (0.46, 0.77)	0.48 (0.34, 0.68)	0.44 (0.28, 0.69)

† = difference in relation to AGA-2015; ‡ = difference in relation to IAP-2024; ¥ = difference in relation to ESG-2018; AGA = American Gastroenterological Association; ESG = European Study Group; IAP = International Association of Pancreatology; PPV = positive predictive value; NPV = negative predictive value; LR+ = likelihood ratio positive; LR- = likelihood ratio negative.

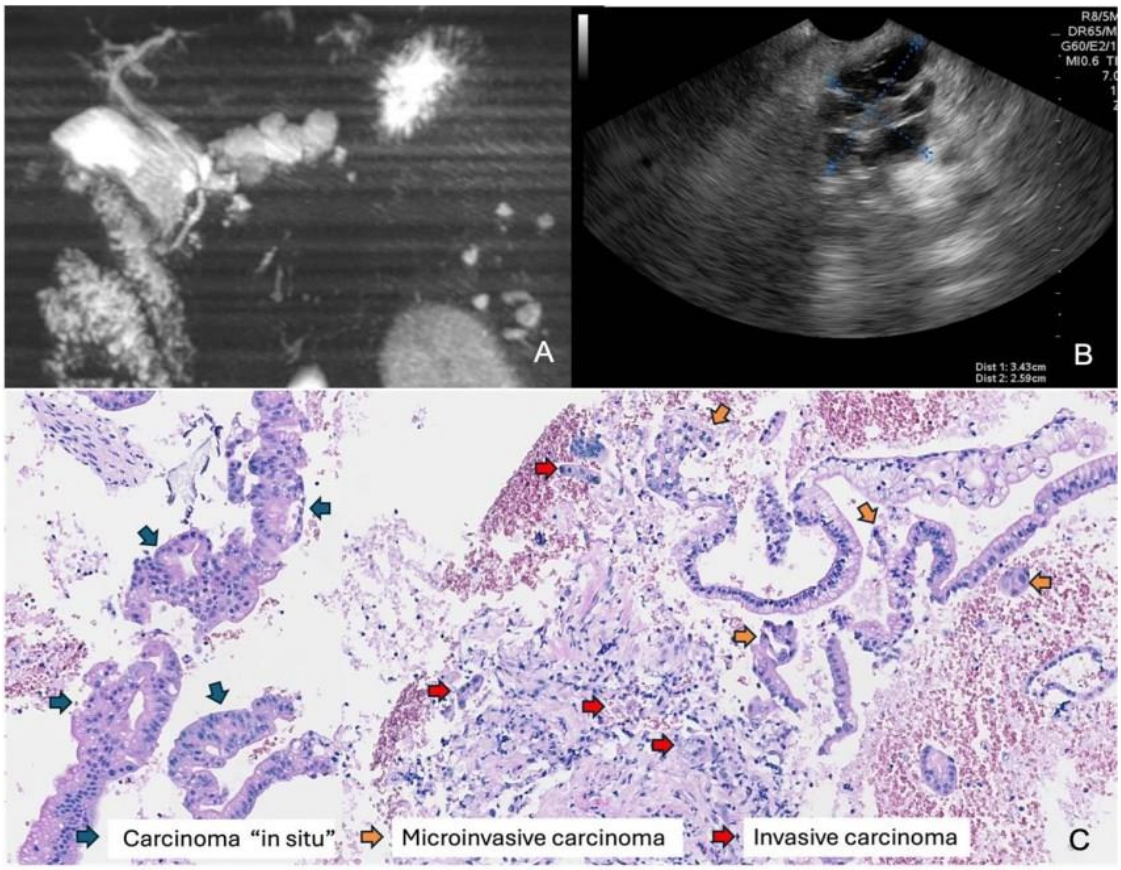

Figure 1: 78 y-old asymptomatic woman. MRI performed during a check-up revealed multiple coalescent pancreatic cysts without worrisome features. Two years after starting follow-up, an MRI showed an increase in the coalescent cysts, and an EUS-FNA was indicated in other service. The cytology result was inconclusive, and the biochemical analysis revealed glucose < 40 mg/dL, CEA of 34.7, and amylase of 534 U/L. One year later, a follow- up MRI (A) showed an increase in the cystic. EUS-TA (B) was performed, and McH analysis revealed well-differentiated invasive adenocarcinoma associated with IPMN in situ (green arrows), microinvasive (orange arrows), and invasive (red arrows) carcinoma.

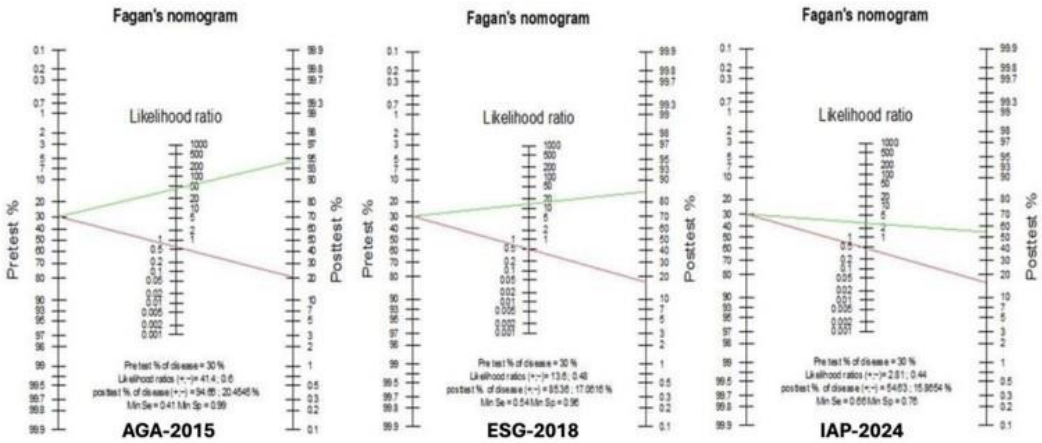

Figure 2. Fagan nomogram illustrating post-test probability (considering a prevalence of 30% for asymptomatic patients) with the AGA-2015, IAP-2017, and ESG-2018 guidelines.

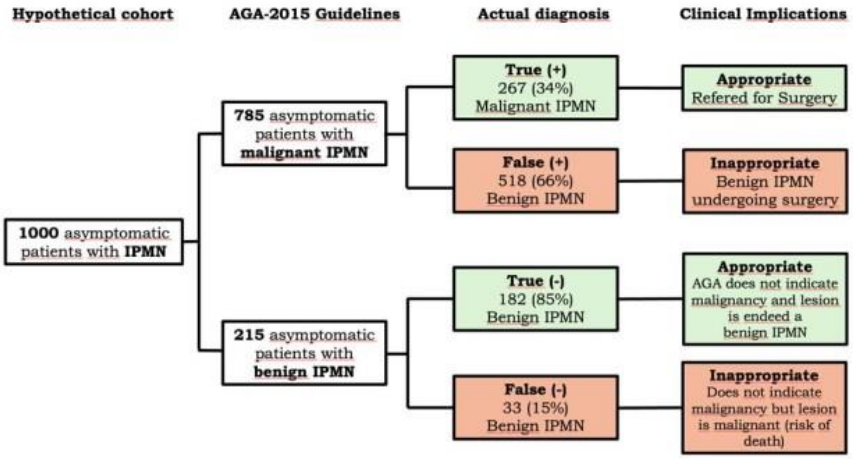

Figure 3. Test consequence graphic for the AGA-2015 guidelines in asymptomatic patients (hypothetical cohort of 1000 patients).

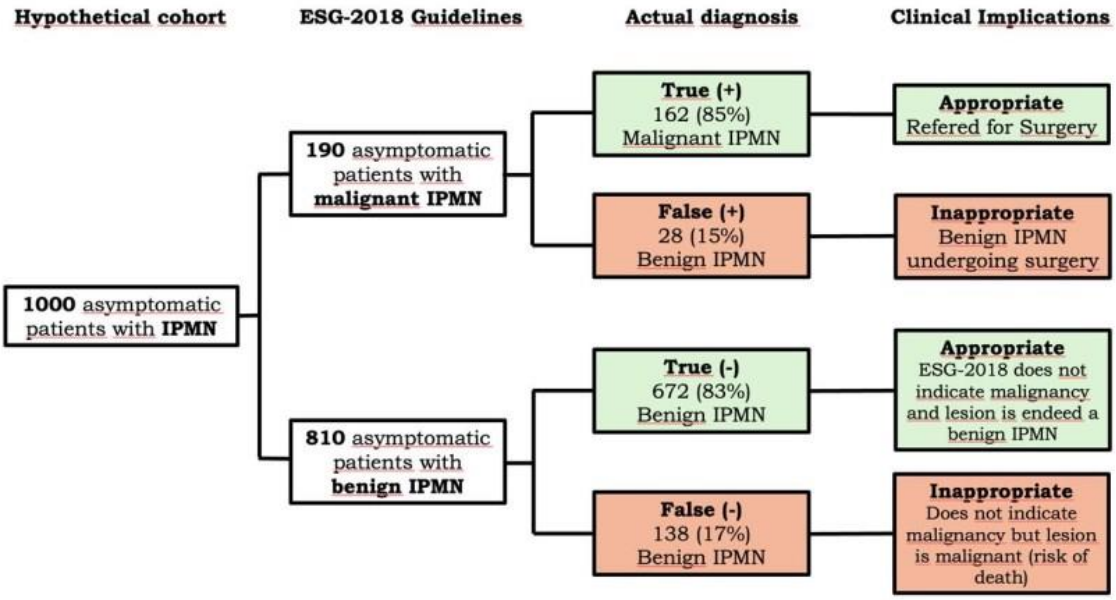

Figure 4. Test consequence graphic for the ESG-2018 guidelines in asymptomatic patients (hypothetical cohort of 1000 patients).

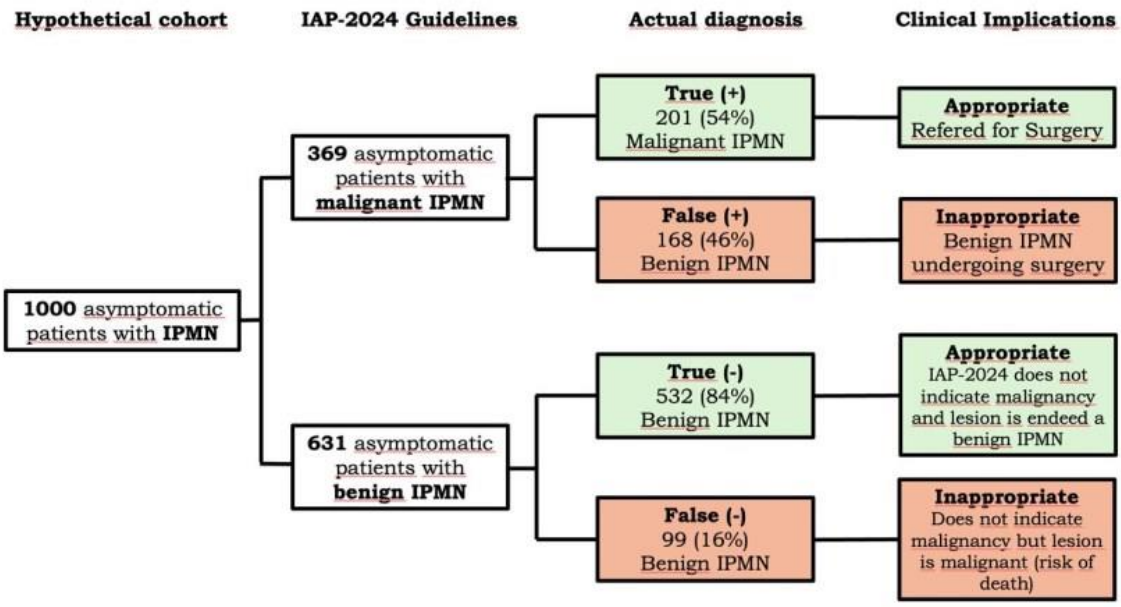

Figure 5. Test consequence graphic for the IAP-2024 guidelines n asymptomatic patients (hypothetical cohort of 1000 patients).

To supplement our analyses and facilitate interpretation of the results presented above, we plotted test consequence graphics (considering a hypothetical cohort of 1000 patients) of the performance of the AGA-2015, ESG-2018, and IAP-2024 guidelines in advising surgery or surveillance based on the results of the current study cohort. Therefore, the application of the AGA-2015, ESG-2018, and IAP-2024 guidelines, following the diagnosis obtained through EUS-FNA/TA, would indicate unnecessary surgeries and fail to treat malignant IPMNs erroneously classified as benign in 66% and 15%, 15% and 17%, and 46% and 16% of cases, respectively (Figures 3, 4, and 5).

DISCUSSION

There is no question that patients with MD-IPMN and M-IPMN should undergo surgery, as should those with BD-IPMN with worrisome features, *high-risk stigmata* or invasive carcinoma.[3,11] The risk of malignant transformation in MNs <4.0 cm is low.[17] The AGA-2015 guideline suggests that PLs with at least 2 high-risk signs should undergo EUS- FNA.[5,18] The IAP-2017 guideline suggests that the presence of "worrisome features" in PLs identified by MRCP should indicate EUS-FNA.[11] Finally, the ESG-2018 guidelines divide surgical indications into absolute and relative based on imaging and/or clinical findings.[12] AGA-2015 includes asymptomatic PLs except MD-IPMN, ESG-2018 includes all PLs, and IAP-2017 and IAP-2024[13] focuses mainly on IPMNs.[19] However, all guidelines disagree on the optimal strategy for monitoring MNs and on the indications for surgical treatment, since diagnosis is based on MRI/MRCP or MDCT without proper histological confirmation.[20,21] They all advise surveillance for patients who do not undergo surgery, even without a histological diagnosis. One interesting concept introduced by the AGA-2015 guideline is discontinuation of surveillance after 5 years.[17] Forty-one percent of patients in our sample had malignant MNs (n=16) or high-risk stigmata (n=42). Application of the AGA-2015, ESG-2018, and IAP-2024 criteria would have advised surgery unnecessarily in 66%, 15%, and 46% of patients with incidental MNs, respectively. These findings show that the AGA-2015 guideline, despite its conservative approach,[22] would have led two-thirds of patients to overtreatment. This strategy places undue stress on patients and families, overburdens the health system and payers, can prompt litigation in cases of misdiagnosis and may even lead to more serious consequences, such as morbidity and mortality resulting from unnecessary pancreatic surgery. In this study, the AGA-2015, ESG-2018, and IAP-2024 criteria failed to identify 15%, 17%, and 16% of high-risk and/or malignant MNs, respectively. Lekkerkerker et al.[22] studied 115 patients undergoing surgery. The final histopathological diagnosis was compared to the initial indication for surgery as established by the guidelines. The preoperative diagnosis was found to be correct in 72% of cases. For IPMNs, resection was justified in 59%, 54% and 53% of patients who would have had surgery based on AGA-2015, IAP-2017, and ESG-2018 criteria respectively; in our sample, this was the case in 34%, 54% (IAP- 2024), and 85%, respectively. The authors concluded that, although fewer patients undergo unnecessary surgery with the AGA-2015 criteria, the risk of missing malignancy or HGD with this guideline appears high when surgery is indicated without histological evidence,[22] a

finding corroborated by the present study, which showed a lower risk of advising unnecessary surgery when the histological diagnosis is known beforehand. Some studies have shown that malignancy occurs in up to 33% of MNs and 61.6% of MD-IPMNs.[23-25] In our cohort (asymptomatic), 11.4% were malignant. EUS-FNA is therefore an important tool to avoid misdiagnosis.[8] It is highly cost-effective as a diagnostic test for the surveillance of single and/or multiple asymptomatic PLs <1 cm. This was recently confirmed when we used needles for EUS-TA in PLs of any nature, where the correct diagnosis in 58 operated patients was 90%.[9] Furthermore, it is considered useful in differentiating PLs and diagnosing MD involvement in IPMNs, as well as for risk stratification.[17,26] A multicenter study suggested that EUS alone without FNA to visualize PLs and characterize them in detail had an accuracy of 50%.[27] Another study compared the AGA-2015 and IAP-2012 guidelines and found a sensitivity, specificity, and accuracy of 17.6% vs. 35.3% (p=0.03), 94.5% vs. 66.1% (p<0.001), and 76.2% vs. 58.7% (p=0.002), respectively.[28] Our study found that AGA-2015 had greater specificity compared to the other guidelines. The IAP-2024 guideline showed the best sensitivity for advising surgery, and all three guidelines had only modest sensitivity. The ESG-2018 and AGA-2015 guidelines had superior specificity, and all missed similar numbers of malignant PLs. ESG-2018 proved to be more accurate when applied to asymptomatic patients with MNs once a diagnosis had been obtained by EUS-FNA, compared application of guidelines based on imaging findings alone. According to Lee et al., the AGA-2015 and IAP-2012 guidelines missed 25% and 18.8% of malignant cysts, respectively (p=1.00), while in our study they missed 15% and 16% – lower absolute numbers.[28] For referral to surgery, both guidelines have modest sensitivity and specificity and miss a similar percentage of malignant lesions.[28] Our strategy of applying the guidelines only after EUS-FNA/TA had been performed increased sensitivity and specificity but missed similar – although numerically lower – percentages of malignant PLs. The AGA-2015 criteria lead to a 60% rate of unnecessary surgery and recommend surveillance accurately in 95% of asymptomatic patients.[10] These data are consistent with the present study, in which 66% of AGA-2015-advised surgeries were unnecessary even when the criteria were applied after EUS-FNA. In a study of 115 patients with IPMN (75), resection was justified in 54%, 53%, and 59% based on the IAP-2017, ESG-2018, or AGA-2015 guidelines, respectively. AGA-2015 prevented resection in 28%, compared to 11% and 9% when the IAP-2017 and ESG-2018 criteria were applied. However, 12% of HGD or malignant lesions would have been missed with the AGA-2015 criteria compared to IAP-2017 or ESG- 2018. Although fewer patients would undergo unnecessary surgery based on the AGA-2015 criteria, the risk of missing malignancy or HGD with this guideline appears considerably higher.[22] All guidelines attempt to stratify patients as high risk, those with worrisome or concerning characteristics, and low risk. Recent data demonstrate that current consensus guidelines for surgical resection of IPMN may not adequately stratify patients at risk for HGD or invasive cancer,29 despite the use of EUS-FNA as set out in the IAP-2024 guideline.[13] In this guideline, EUS-FNA associated with cytology is no longer indicated due to its low results in the classificatory diagnosis. This is due to the use of cytology in the preparation of the material obtained and not the microhistology, which is why the authors believe that EUS- FNA or EUS-TA associated with McH is a fundamental tool for evaluating PLs,[9] as the classificatory diagnosis of PLs, before applying the guideline, offers us better results in relation to the applicability of the guidelines and the surgical management.[14] This could be evaluated in the present study: in a hypothetical cohort, application of the AGA-2015, ESG-2018, and IAP-2024 guidelines after McH diagnosis of specimens obtained by EUS-FNA would indicate surgery appropriately in 34%, 85%, and 54%, of patients with malignant MNs or *high-risk stigmata*, while 66%, 15%, and 46%, would undergo unnecessary surgery and 15%, 17%, and 16%, of those with cancer patients would be missed entirely by the guidelines, respectively. On the other hand, 85%, 83%, and 84% would be adequately referred for surveillance according to the AGA-2015, ESG-2018, and IAP-2024 guidelines, respectively. Our study provides a relevant contribution to the body of evidence on this topic; however, it is not without limitations. A critical issue would be molecular and/or immunohistochemical analysis to identify expression of p53, MUC5AC, MUC1, MUC2, and MUC6, which constitute the epithelial molecular profile for prediction of malignancy. McH analysis of wall fragments improved our results, even without molecular and histopathological examination of the entire specimen in approximately half of the patients. Recently 145 patients with PLs underwent EUS-TA, the mean size was 2.3 cm, with 81 patients (77.9%) having a PLs < 3.0 cm. The sensitivity, specificity, positive and negative predictive values, and accuracy for identifying malignant PLs were 92%, 99.2%, 95.8%, 98.3%, and 97.9%. The AE rate was 2.7%, with no deaths in this cohort, with a high accuracy and technical success with a low AE rate for PL diagnosis.[9] Diagnostic accuracy for MNs must be based on a combination of two or more variables.[30] In our statistical analysis, we used tests widely applied in screening and diagnosis research on asymptomatic individuals; however, as in all probabilistic data, only population averages were taken into account, not specific and/or individual patient characteristics. The limitations of this study include its retrospective nature, the lengthy data collection period, the short follow-up time (12

months), the use of two different guided biopsy techniques (FNA and TA), and, since the study was conducted at a single reference center with a high volume of cases, it can be inferred that local management and referral practices may also have been a limiting factor. In the authors' opinion, when conventional imaging modalities such as MDCT, and MRI/MRCP are inconclusive, performing EUS-FNA or TA even before applying guideline criteria appears to be an appropriate course of action for adopting the optimal therapeutic strategy in asymptomatic MNs, as it helps avoid unnecessary surgery and refer patients appropriately and safely for surveillance. Finally, the ESG-2018 proved most accurate in guiding further management of incidental MNs once the diagnosis had been established by EUS-FNA.

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