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Review article

International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

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ABSTRACT

The international consensus guidelines for management of intraductal papillary mucinous neoplasm and mucinous cystic neoplasm of the pancreas established in 2006 have increased awareness and improved the management of these entities. During the subsequent 5 years, a considerable amount of information has been added to the literature. Based on a consensus symposium held during the 14th meeting of the International Association of Pancreatology in Fukuoka, Japan, in 2010, the working group has generated new guidelines. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. To simplify the entire guidelines, we have adopted a statement format that differs from the 2006 guidelines, although the headings are similar to the previous guidelines, i.e., classification, investigation, indications for and methods of resection and other treatments, histological aspects, and methods of follow-up. The present guidelines include recent information and recommendations based on our current understanding, and highlight issues that remain controversial and areas where further research is required.

1. Introduction

Since the publication of the international consensus guidelines for management of intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) of the pancreas in 2006 [1], these entities have been drawing increasing attention. As a consequence, a considerable amount of information has been added to the literature during the subsequent 5 years. In particular, new information has been obtained regarding endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of the cyst contents, the indications for resection of branch duct IPMN (BD-IPMN) have changed from rather early resection to more deliberate observation, and some reports have documented the occurrence of concomitant pancreatic ductal adenocarcinoma (PDAC) in patients with BD-IPMN. All this new knowledge makes an update of the guidelines imperative. During the 14th meeting of the International Association of Pancreatology (IAP) held in Fukuoka, Japan, in 2010, we arranged a symposium where recent progress in preoperative diagnosis and management was presented. All the speakers in the symposium, including eight initial members and six

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new members of the working group, have generated new guidelines based on an elaborate list of items to be addressed. Since the levels of evidence for all items addressed in these guidelines are low, being 4 or 5, we still have to designate them "consensus", rather than "evidence-based", guidelines. We have made a series of recommendations for all items in Table 1. However, since the grades of the recommendations are low, we have avoided repetition of grade C in almost all of the items.

All the authors contributed equally to the guidelines. M. Tanaka chaired and C. Fernandez-del Castillo co-chaired this working group of the IAP, and these two authors played a major role in the preparation of the manuscript. The remaining authors are listed in alphabetical order.

Table 1
Summary of recommendations.

1. Classification
   1a. The threshold of MPD dilation, segmental or diffuse, for characterization of MD-IPMN has been lowered to >5 mm without other causes of obstruction, thereby increasing the sensitivity for radiologic diagnosis without losing specificity. MPD dilation of 5–9 mm is considered a "*worrisome feature*", while an MPD diameter of ≥10 mm is one of the "*high-risk stigmata*".
   1b. The definition of "malignancy" of IPMNs and MCNs has been variable, hampering comparisons of data. We recommend abandoning the term carcinoma in situ in favor of high-grade dysplasia, reserving the descriptor of malignancy for invasive carcinoma, as outlined in the recent WHO classification.

2. Investigation
   2a. CT or MRI with MRCP is recommended for a cyst of ≥1 cm to check for "*high-risk stigmata*", including enhanced solid component and MPD size of ≥10 mm, or "*worrisome features*", including cyst of ≥3 cm, thickened enhanced cyst walls, non-enhanced mural nodules, MPD size of 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy. All cysts with "*worrisome features*" and cysts of >3 cm without "*worrisome features*" should undergo EUS, and all cysts with "*high-risk stigmata*" should be resected. If no "*worrisome features*" are present, no further initial work-up is recommended, although surveillance is still required.
   2b. MDCT and MRCP are most useful for distinguishing BD-IPMN from other cysts by showing multiplicity and a connection to the MPD.
   2c. Cyst fluid analysis is still investigational, but is recommended for evaluation of small BD-IPMNs without "*worrisome features*" in centers with expertise in EUS-FNA and cytological interpretation.
   2d. Routine ERCP for sampling of fluid or brushings in IPMN is not recommended, and should only be used in the context of research.
   2e. Distinction of BD-IPMN from a small oligocystic SCN is challenging and may require EUS-FNA with cyst fluid CEA determination.

3. Indications for Resection
   3a. Resection is recommended in all surgically fit patients with MD-IPMN. If the margin is positive for high-grade dysplasia, additional resection should be attempted to obtain at least moderate-grade dysplasia.
   3b. The indications for resection of BD-IPMN are more conservative. "*Worrisome features*" as well as "*high-risk stigmata*" are proposed. A BD-IPMN of >3 cm without "*high-risk stigmata*" can be observed without immediate resection.
   3c. Surgical resection is recommended for all surgically fit patients with MCN. For MCNs of <4 cm without mural nodules, laparoscopic resection as well as parenchyma-sparing resections and distal pancreatectomy with spleen preservation should be considered.

4. Methods of Resection and Other Treatments
   4a. Pancreatectomy with lymph node dissection remains the standard treatment for invasive and non-invasive MCNs and IPMNs. Focal non-anatomic resections or anatomic resections without lymphadenectomy or splenectomy may be considered for those without suspicion of malignancy, but carry a risk of possible leakage of mucin, and higher incidences of pancreatic fistulae and recurrence. Low-grade and possibly high-grade dysplasia of IPMN and MCN may be good candidates for laparoscopic surgery.
   4b. EUS-guided ethanol ablation cannot be recommended for patients with BD-IPMN or MCN outside of a closely monitored research protocol.
   4c. Multifocal BD-IPMNs carry a similar risk of malignancy to unifocal BD-IPMN. Segmental resection can be performed to remove the IPMNs at the highest oncological risk. The threshold for total pancreatectomy should perhaps be lowered in patients with a strong family history of PDAC and multifocal BD-IPMNs, but the data supporting this idea are incomplete.

Table 1 (*continued*)

5. Histological Aspects
   5a. The type of invasive carcinoma, colloid versus tubular, has major prognostic implications and should be part of the reporting of IPMNs, with colloid carcinomas being characterized by "intestinal" differentiation and a better prognosis than tubular carcinomas.
   5b. Instead of "minimally invasive carcinoma" derived from IPMN or MCN, it would be more appropriate to stage invasive carcinomas with the conventional staging protocols and further substage the T1 category into T1a (≤0.5 cm), T1b (>0.5 cm and ≤1 cm), and T1c (1–2 cm).
   5c. The histologic subtypes of IPMN have clinicopathologic significance. The gastric type is typically low grade, with only a small percentage developing into carcinoma. However, if a carcinoma does develop, it is usually of the tubular type and aggressive. Large intestinal-type IPMNs can have invasive carcinoma of the colloid type with indolent behavior.
   5d. If clear high-grade dysplasia or invasive carcinoma is present at the margin by frozen section analysis, further resection is warranted. All patients should be informed preoperatively about the possibility of total pancreatectomy. Moderate-grade or low-grade dysplasia may not require any further therapy.
   5e. Pathologists should make every attempt to classify the lesion as MD-IPMN or BD-IPMN, being careful to identify the MPD as precisely as possible when processing the specimen.
   5f. A distinction between PDAC derived from an IPMN and PDAC concomitant with an IPMN is proposed with regard to the topological relationship and histological transition, although the distinction sometimes remains undetermined.

6. Methods of follow-up
   6a. Patients without "*high-risk stigmata*" should undergo MRI/MRCP (or CT) after a short interval (3–6 months) to establish the stability, and then annual history/physical examination, MRI/MRCP (or CT) and serologic marker surveillance. Short interval surveillance (3–9 months) should be considered for patients whose IPMN progresses toward "*high-risk stigmata*" and patients with a family history of hereditary PDAC. Some investigators continue surveillance at short intervals owing to concern over the development of distinct PDAC.
   6b. Non-invasive MCNs require no surveillance after resection. IPMNs need surveillance based on the resection margin status. If there are no residual lesions, repeat examinations at 2 and 5 years may be reasonable. The aspect of whether a margin with moderate-grade dysplasia increases recurrence is unknown. For patients with low-grade or moderate-grade dysplasia at the margin, we suggest history/physical examination and MRCP surveillance at least twice a year. The follow-up strategy of invasive IPMN should be identical to that for PDAC.
   6c. In patients with two or more affected first-degree relatives, the risk rapidly escalates and merits aggressive surveillance by MRI/MRCP (or CT) and EUS. "*Worrisome features*" are of more concern. If present, patients should be considered for resection if they are surgically fit. If absent, patients should be followed by MRI/MRCP (or CT) at 3-month intervals and EUS annually for the first 2 years. Patients with a rapidly growing BD-IPMN and patients who develop "*worrisome features*" should be strongly considered for resection. The interval of surveillance after 2 years of no change can be lengthened to 6 months, but no longer in view of the relatively high incidence of PDAC reported for BD-IPMN.
   6d. There are no screening recommendations for detecting extrapancreatic malignancies in patients with IPMN on surveillance and after resection, but consideration of extrapancreatic neoplasms should be made based on the frequency of these malignancies in the general population of the country or region.

2. Classification

2.1. Criteria for distinction of BD-IPMN and main duct IPMN (MD-IPMN)

IPMNs can be classified into three types, i.e., MD-IPMN, BD-IPMN, and mixed type, based on imaging studies and/or the histology (Fig. 1) [1]. MD-IPMN is characterized by segmental or diffuse dilation of the main pancreatic duct (MPD) of >5 mm without other causes of obstruction. According to recent reports, a low threshold for MPD dilation (5 mm) can be adopted, which increases the sensitivity for radiologic diagnosis of MD-IPMN without losing specificity [2–10]. In the revised guidelines, MPD