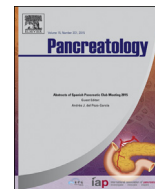




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Review article

Quality assessment of the guidelines on cystic neoplasms of the pancreas

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ABSTRACT

Background: Though cystic pancreatic neoplasms (CPNs) are being increasingly detected, their evaluation and management are still debated and have lead to publication of multiple guidelines for diagnostic work-up, indications for resection, and non-operative management with follow-up strategies of CPNs.

Aims: To analyze available guidelines in order to evaluate their overall quality and clinical applicability, indications for surgical resection and its extent, modalities and timing of follow-up when non-operative management is indicated.

Methods: After a systematic search of the English literature, we selected eight guidelines for assessment according to the Appraisal of Guidelines, Research and Evaluation in Europe (AGREE) II instrument.

Results: One guideline received the lower AGREE score regarding the “scope and purpose”, “rigor of development” and “clarity and presentation” domains, whereas one received the best score for “stakeholder involvement” domain. No differences were found among different guidelines regarding the “applicability”. The overall quality assessment score showed that only two guidelines were significantly lower than the others. According to the practical utilization recommendation score, four guidelines were considered as having full applicability in clinical practice.

Conclusion: Existing guidelines provide adequate guidance, at least with the present knowledge, for the management of cystic pancreatic lesions; however, not any one was satisfactory to all aspects related to the management of CPN. An update of the existing guidelines should be considered if and when more evidence-based data are available.

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Introduction

Cystic pancreatic neoplasms (CPNs) are being increasingly detected because of the widespread use of cross-sectional imaging techniques, mainly in elderly and asymptomatic patients [1–3]. Non-inflammatory pancreatic cysts are found in approximately 10% of individuals 70 years old or older, the majority of which are

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thought to be branch-duct intraductal papillary mucinous neoplasms (IPMNs) [4]. Although there is an increased awareness of CPNs among clinicians, their natural history is still unknown, and their evaluation and management are debated [5,6].

In the last decade different guidelines have been published to provide recommendations for diagnostic work-up, indications for resection, and non-operative management with follow-up strategies of CPNs [7,8]. However, several controversial issues and areas of uncertainty that need to be clarified.

Our goals were to analyze published guidelines on the diagnosis and management of CPNs for a) overall quality and applicability in the clinical setting; b) indications for surgical resection and its extent; c) modalities and timing of follow-up, when non-operative management is indicated; in no way we would like to create new recommendations or assign a gold medal to available guidelines.

Methods

The working group

The working group for reviewing the guidelines on cystic lesion of the pancreas included; i) nine experts in this field (M. Falconi, S. Chari, K. Conlon, SW. Kim, P. Levy, M. Tanaka, J. Werner, C. Wolfgang, C. Fernandez-del Castillo) with right of vote at any single step of the process (appraisers); ii) two methodologists (S. Crippa, R. Pezzilli) who coordinated the entire process and iii) three external reviewers (M. Del Chiaro, C. McKay, R. Salvia). The latter two groups did not have voting right. In the first phase, the methodological group defined the following methodology: a) definition of clinical questions and evaluation of the recommendations for each clinical question among the various guidelines; b) selection and quality assessment of the guidelines. The group had online meetings in order to assess the quality of the existing guidelines and had weekly contacts by e-mail to discuss the steps of the evaluation methods [9].

Definition of clinical questions and evaluation of the recommendations on selected guidelines

Among 25 questions proposed by the methodologists, seventeen were selected by the experts and considered important from a clinical point of view; questions were also shared with all the participants. The remaining eight questions were excluded because no sufficient data were present in literature as well as in the available guidelines. They focused on indication for surgical resection and its extent providing that the patient was fit for treatment, whereas three questions held the modalities and timing of follow-up for those patients fit for surgery for whom a non-operative management was indicated. Once the quality assessment process finished, all the statements present in each selected guideline for each single question were reported in a dedicated file which thereafter was submitted to the voters for their final judgment.

Selection and quality assessment of the guidelines

The entire process of guidelines assessment was carried out according to the ADAPTE method [10]. In brief, the tool 3 (declaration of conflict of interest), tool 11 (Sample Currency Survey of Guideline Developers), tool 14 (Scientific Validity of Guidelines – Consistency between Evidence, Its Interpretation, and Recommendations), tool 17 (Table for Reporting on Results of Update Process) were filled by the appraisers. Regarding the consensus guidelines, they give recommendations without evidence levels and recommendation grade to be used in clinical practice.

For scoring the selected guidelines, the working group rated the global quality of the guidelines by using the Appraisal of Guidelines, Research and Evaluation in Europe II (AGREE) instrument updated on September 2013 [11]. The AGREE II consists of 23 key items organized within 6 domains followed by 2 global rating items (“Overall Assessment”). Each domain captures a unique dimension of guideline quality as follows: Domain 1. *Scope and Purpose* concerns the overall aim of the guideline, the specific health questions, and the target population (items 1–3); Domain 2. *Stakeholder Involvement* focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (items 4–6); Domain 3. *Rigour of Development* relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them (items 7–14); Domain 4. *Clarity of Presentation* deals with the language, structure, and format of the guidelines (items 15–17); Domain 5. *Applicability* pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline (items 18–21); Domain 6. *Editorial Independence* concerns with the formulation of recommendations not being unduly biased with competing interests (items 22–23). *Overall assessment* includes i) the rating of the overall quality of the guideline and ii) whether the guideline would be recommended for use in practice. Each of the AGREE II items and the two global rating items are rated on a 7-point scale (1–strongly disagree to 7–strongly agree). Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. Although the domain scores are useful for comparing guidelines and will inform whether a guideline should be recommended for use, there is no minimum domain scores or patterns of scores across domains to differentiate between high quality and poor quality guidelines. The minimum and maximum standardized domain scores calculated according to the AGREE formula (Standardized domain score (0–100): Obtained score – Minimum possible score/Maximum possible score – Minimum possible score) for each domain are the following: 27–189 for Scope and Purpose, 27–189 for Stakeholder involvement, 72–504 for Rigor of development, 27–189 for Clarity and Presentation, 36–252 for Applicability, 18–126 for Editorial independence.

When recommendations concerning the same topic were present in two or more guidelines, the recommendation of the more recent guidelines was selected [9]. The percentage of agreement/disagreement equal to or less than 50% expresses a gray area that require further studies.

For the finalization phase of the evaluation process, the entire evaluation process was revised by three independent external expert reviewers.

Ethics

There were no economic resources for both project management and administrative support; the panel members accepted no honoraria. The working group included physicians normally involved in the management of patients with cystic lesions of the pancreas. According to the ADAPTE tool 3 no economic or other related conflict of interest were disclosed by the participants except for the participation to one or more guidelines development (11 of the 14 participants). It should be underlined that the conflict of interest is a set of circumstances that results in a risk for professional judgment or actions regarding the primary interest (i.e. protection of patients). In the present work, the conflict of interest regarding the protection of patients with cystic lesions is not influenced by a secondary interest (i.e. financial gain, advancement,

etc.); thus, we believe that in our case there are no secondary interests disclosed by participants nor by the methodologists and the question resulted not relevant in this setting.

Statistical methods

Once the guidelines were selected, nine appraisers of the working group made their judgment on the 23 key items of the AGREE-II instrument. The six standardized domain scores (0–100) were then calculated according to the AGREE policy [11]. Homogeneity of the six domains among the eight selected guidelines was tested by one-way ANOVA and homogeneous subsets within each domain were evaluated by means of the Duncan post hoc test.

Results

Literature search and guidelines inclusion

All papers published from 2000 to 2014 using the term “cystic lesions of the pancreas” with the following limits “**Humans, Practice Guideline**” were searched in PubMed, in the Cochrane Library and other databases (Science Direct, Scopus, Web of Science) for publications on this topic. Regarding Medline/PubMed the search was not carried out with MESH terms because these are a “young” disease and there are no medical subject headings (MESH) terms in Medline/PubMed database to identify them; in addition, IPMNs of the pancreas are indicated as cystic lesion in the descriptor of the medical databases explored. A total of 10 papers were found [7,8,12–19]. Two papers were not considered because they did not fit with the aims of this study [15,16]. Thus, 8 guidelines published from 2004 to 2014 which fulfilled the inclusion criteria were selected [7,8,12–14,17–19] and each of these publications was independently and thoroughly reviewed by the panel of experts. All the guidelines were released from scientific societies such as surgical, medical, endoscopic or pathological associations.

Guidelines assessment

The “rough” and standardized domain scores are detailed in Table 1 and Fig. 1. More recent guidelines appeared to have higher scores across all domains; however, regarding the *Rigor of Development* all guidelines had scores lower than the minimum AGREE standardized score. The Italian Consensus Guidelines received the best score for Stakeholder involvement [19] whereas the Society for Surgery of the Alimentary Tract (SSAT) guideline [14] received the lower score regarding the Scope and Purpose, Rigor of Development and Clarity and Presentation. No differences were found among different guidelines regarding their Applicability. Fig. 1 reports the overall assessment of the selected guidelines. The overall

Table 2

AGREE: overall quality assessment score. Data are reported as mean $\pm$ SD. Homogeneity subset within the guidelines was evaluated by means of the Duncan post-hoc one-way analysis of variance. The values of the guidelines included in the subset with the highest score are shown in bold.

Guideline	Mean $\pm$ SD (Score from 1 to 7)
SSAT 2007 [14]	2.3 $\pm$ 1.3
ASGE 2005 [13]	3.8 $\pm$ 1.3
Hruban 2004 [12]	4.4 $\pm$ 1.7
Canto 2013 [18]	5.1 $\pm$ 1.4
Tanaka 2012 [17]	5.3 $\pm$ 0.7
Del Chiaro 2013 [8]	5.6 $\pm$ 1.2
Tanaka 2006 [7]	6.0 $\pm$ 0.9
Buscarini 2014 [19]	6.0 $\pm$ 1.0
Overall	4.8 $\pm$ 1.6
P value	<0.001

quality assessment score showed that only two guidelines [13,14] were significantly lower than the others (Table 2). According to practical utilization recommendation score (Fig. 2), four guidelines were considered as having full applicability in clinical practice [8,17–19] (Fig. 2). For the IAP guidelines, the updated version of 2012 [17] replaced the old version of 2006 [7]. Of note only two guidelines report the evidence levels and the grade of recommendation [8,19].

Clinical questions and evaluation of the recommendations on selected guidelines

Topic 1. Indication for surgical resection and its extent providing that the patient is fit for treatment

Question 1. Which cystic lesions must be unequivocally surgically resected?

Answer. Resection is recommended in all surgically fit patients with main duct (MD)-IPMN. The indications for resection of branch duct (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. Surgical resection is recommended for all surgically fit patients with mucinous cystic neoplasms (MCNs). Although still controversial, younger patients (<65 years) with cyst size (BD-IPMN) of >2 cm may be candidates for resection owing to the cumulative risk of malignancy [17] (*Percent of agreement: 41.7*).

Question 2. Is there a cut-off for main pancreatic duct dilation which represents an indication for surgery?

Answer. Main pancreatic duct (MPD) dilation of 5–9 mm should be considered as one of the “worrisome features”, similar to the

Table 1

Domain scores of the AGREE instrument evaluated by nine appraisers. Data are reported as mean $\pm$ SD. Homogeneity subsets within each domain were evaluated by means of the Duncan post-hoc one-way analysis of variance. The values of the guidelines included in the subset with the highest score are shown in bold.

	Scope and purpose	Stakeholder involvement	Rigor of development	Clarity and presentation	Applicability	Editorial independence
Minimum and maximum score	27–189	27–189	72–504	27–189	36–252	18–126
Hruban 2004 [12]	51.3 $\pm$ 5.9	37.0 $\pm$ 9.5	31.0 $\pm$ 5.9	39.0 $\pm$ 9.6	34.5 $\pm$ 7.7	37.5 $\pm$ 5.2
ASGE 2005 [13]	47.3 $\pm$ 6.1	32.3 $\pm$ 7.4	30.4 $\pm$ 5.3	38.0 $\pm$ 2.0	29.8 $\pm$ 5.1	31.5 $\pm$ 2.1
Tanaka 2006 [7]	56.7 $\pm$ 2.5	40.3 $\pm$ 11.6	36.6 $\pm$ 5.1	47.3 $\pm$ 1.2	38.8 $\pm$ 7.6	38.5 $\pm$ 17.7
SSAT 2007 [14]	40.7 $\pm$ 1.0	31.7 $\pm$ 12.9	20.7 $\pm$ 4.4	31.0 $\pm$ 2.6	24.8 $\pm$ 2.8	27.5 $\pm$ 7.8
Tanaka 2012 [17]	56.3 $\pm$ 2.1	40.0 $\pm$ 12.0	39.9 $\pm$ 1.7	52.0 $\pm$ 1.0	38.3 $\pm$ 8.0	42.0 $\pm$ 15.6
Canto 2013 [18]	57.0 $\pm$ 2.6	46.7 $\pm$ 4.6	44.0 $\pm$ 7.8	45.3 $\pm$ 1.5	38.0 $\pm$ 4.6	55.0 $\pm$ 4.2
Del Chiaro 2013 [8]	57.3 $\pm$ 3.8	40.3 $\pm$ 12.3	41.1 $\pm$ 9.9	51.3 $\pm$ 5.5	39.3 $\pm$ 6.8	51.0 $\pm$ 0.0
Buscarini 2014 [19]	59.0 $\pm$ 1.7	51.0 $\pm$ 10.6	52.4 $\pm$ 7.1	53.0 $\pm$ 2.6	45.3 $\pm$ 8.2	54.5 $\pm$ 4.9
P value	<0.001	0.008	<0.001	<0.001	0.088	0.002

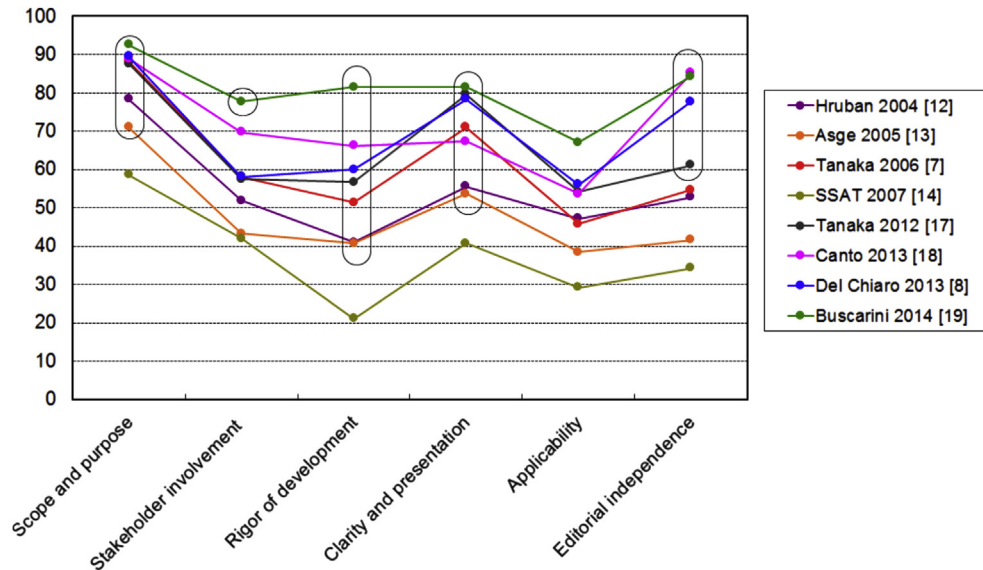


Fig. 1. AGREE: standardized domain scores for each guideline (the subsets with the higher statistically significant score in respect to the others for each domain are identified by filled boxes).

case for BD-IPMN, with a recommendation of evaluation but no immediate resection; for MPD of 5–9 mm and presence of any one of thickened enhancing walls, intraductal mucin or mural nodules, resection is indicated. MPD ≥ 10 mm is considered as a “high-risk stigmata” and represents an indication for resection [17] (Percent of agreement: 60.0).

Question 3. Is a vascularized nodule an indication for surgery?

Answer. Enhanced solid component is considered as a “high-risk stigmata” and represents an indication for resection in patients fit for surgery [17] (Percent of agreement: 53.8).

Question 4. Is a non-vascularized nodule an indication for surgery?

Answer. Non-enhancing mural nodule is considered as a “worrisome feature” that requires further investigation. All cysts with “worrisome features” and cysts of >3 cm without “worrisome features” should undergo endoscopic ultrasound (EUS). The differential diagnosis (of a non-enhancing mural nodule) includes a mucin plug. Mucin plugs can move with change in the patient's

position, may be dislodged on cyst lavage and do not have Doppler flow. Features of a true tumor nodule include lack of mobility, presence of Doppler flow and fine needle aspiration (FNA) of nodule showing atypical cells. If a true tumor nodule is confirmed, surgical resection is indicated [17] (Percent of agreement: 66.7). It should be underlined that in all guidelines the size of mural nodule compatible with malignancy has not reported but it should be visible at the imaging techniques and greater enough to be biopsied and pathologically analyzed.

Question 5. Is the presence of a symptom(s) an indication for surgery?

Answer. Obstructive jaundice in a patient with cystic lesion of the head of the pancreas is considered as “high-risk stigmata” and represents a mandatory indication for resection. Pancreatitis is considered as a “worrisome feature” and may be an indication for surgery for relief of symptoms [17] (Percent of agreement: 36.4).

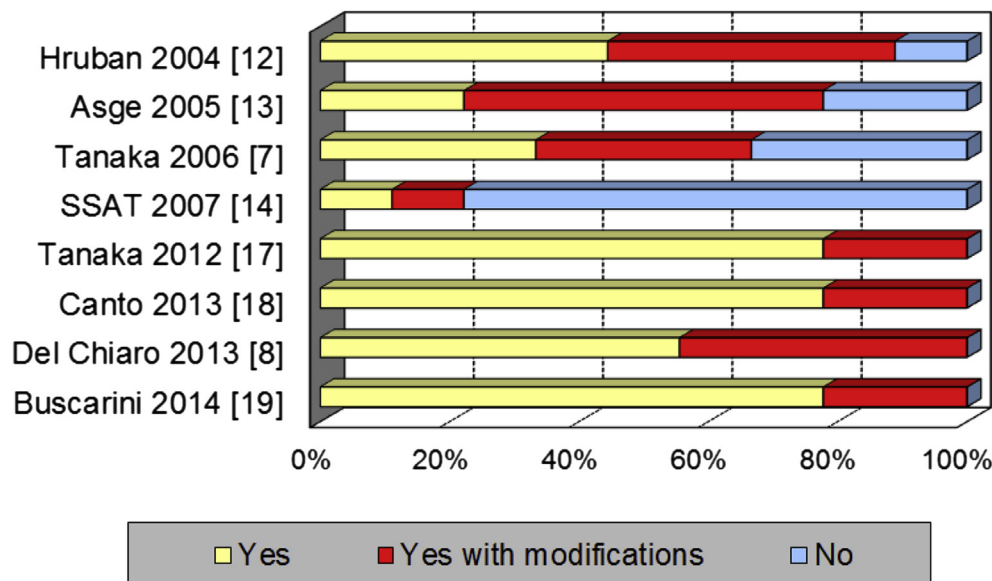


Fig. 2. Recommendation for use of the guidelines in practice.

Question 6. Does size of the lesion at diagnosis represent an indication for surgery?

Answer. For BD-IPMNs dimension correlates with the risk of malignancy; but there is no safe lower size limit that completely excludes malignancy. Asymptomatic BD-IPMNs without dimensional progression or other risk factor (e.g. mural nodules, MPD dilatation >6 mm) can be followed until the lesion has reached a size of 4 cm in diameter. For the remaining cystic lesions of the pancreas, size at presentation does not represent an indication for surgery [8] (Percent of agreement: 36.4).

Question 7. Does an increase of size over time represent an indication for surgery?

Answer. For BD-IPMNs, rapidly increasing size (cysts growing faster than 2 mm/year) is considered a relative indication for pancreatic resection [8] (Percent of agreement: 50.0).

Question 8. Does the patient's age at diagnosis represent an indication for surgery?

Answer. Patients unfit for surgery for comorbidities and advanced age have been excluded. Surgery should be considered in young patients with "suspicious" morphological features [19] (Percent of agreement: 41.7). We should underline that in the various guideline both young age and advanced age have not been defined.

Question 9. Are high serum levels of tumor markers an indication for surgery?

Answer. In the setting of patients with suspicious morphological features, elevated serum CA 19.9 levels can be useful and add weight to decision to operate [19]. SerumCA19.9 determination provides additional information within the diagnostic work-up since a positive result is associated with the presence of an invasive carcinoma with a specificity ranging from 79 to 100%; conversely, a negative result does not exclude the presence of a malignancy (sensitivity 37–80%) [19]. (Percent of agreement: 83.3).

Question 10. Are high intracystic levels of tumor markers an indication for surgery?

Answer. Intracystic CEA and CA 19-9 are not accurate in differentiating malignant from non-malignant CPNs. Increased CEA levels in the cystic fluid are helpful in distinguishing mucinous from non-mucinous CPNs [19] (Percent of agreement: 54.5). It should be pointed out that for the assessment of cut-off values of CEA is mandatory to establish a reference standard in order to properly classify true positive and true negative cases. Most of the data available regarding the accuracy of this marker derive from retrospective studies which employed the histology obtained after surgery as the gold standard. Thus, the interpretation should be cautious when the data come from retrospective series and refer to patients without clear morphological indications for surgery. Laboratories which intend to carry out marker assays on the cystic fluid should collaborate with clinicians in order to establish their own cut-off value on the basis of patient outcome [19].

Question 11. Is the presence of a cytological atypia alone an indication for surgery?

Answer. Cytological examination is useful in the differential diagnosis between benign and malignant CPNs. The presence of cells with high grade dysplasia is the best cytological marker of malignancy [19] (Percent of agreement: 50.0).

Question 12. Is a family history of pancreatic cancer an indication for surgery?

Answer. No. Patients with one affected first degree relative can be followed using the same criteria for patients without a family history. For individuals with two or more affected first-degree relatives, the risk rapidly escalates and merits more aggressive surveillance, but does not necessarily imply a recommendation for resection [17] (Percent of agreement: 45.5).

Question 13. What are the indications for limited resection for a lesion localized in the pancreatic body-tail (i.e. middle pancreatectomy, enucleation, spleen-preserving distal pancreatectomy)?

Answer. Limited resections or even focal non-anatomic resections (enucleation, resection of the uncinate process) may be considered for MCN or BD-IPMN without clinical, radiologic, cytopathological, or serologic suspicion of malignancy. MCNs <4 cm in size without mural nodules have a low likelihood of malignancy. In this setting parenchyma-sparing resections (i.e. middle pancreatectomy) or distal pancreatectomy with spleen preservation as well as laparoscopic procedures should be considered. Conversion to a standard resection with lymphadenectomy should occur if intra-operative findings raise concern for malignancy or frozen-section pathology reveals high-grade dysplasia or invasive disease. When the final pathology reveals invasion or positive margin for high-grade dysplasia undetected on frozen sections, a reoperation should be performed in surgically fit patients [8] (Percent of agreement: 50.0).

Question 14. What are the criteria for a limited resection for a pancreatic head lesion?

Answer. Limited resections or even focal non-anatomic resections (enucleation, resection of the uncinate process) may be considered for MCN or BD-IPMN without clinical, radiologic, cytopathological, or serologic suspicion of malignancy. Conversion to a standard resection with lymphadenectomy should occur if intra-operative findings raise concern for malignancy or frozen-section pathology reveals high-grade dysplasia or invasive disease. When the final pathology reveals invasion or positive margin for high-grade dysplasia undetected on frozen sections, a reoperation should be performed in surgically fit patients [17] (Percent of agreement: 85.7).

Question 15. What are the criteria for duodenal preserving pancreatic head resection?

Answer. No answer on this topic is present in any of the guidelines.

Question 16. What are the indications for an upfront total pancreatectomy?

Answer. In patients fit for surgery with diffuse/multifocal disease, based on the site and extent of IPMN, total pancreatectomy with lymph node dissection should be considered. In patients with multifocal BD-IPMNs and a strong family history of PDAC, the threshold for total pancreatectomy should be lowered because of the increased prevalence of higher-grade lesions [17] (Percent of agreement: 70.0).

Question 17. What are the indications for an extension of a planned partial pancreatectomy up to a total pancreatectomy?

Answer. If clear high-grade dysplasia or invasive carcinoma is present at the margin, further resection is warranted [17] (Percent of agreement: 72.7).

Topic 2. Modalities and timing of follow-up for those patients fit for surgery for whom a non-operative management is indicated

Question 1. What is the best imaging technique for the follow-up of cystic lesions?

Answer. The imaging test of choice for follow-up is magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) [19] (Percent of agreement: 36.4).

Question 2. What are the criteria that influence and eventually modify the diagnostic modality?

Answer. Patients with 1) cyst size ≥ 3 cm, 2) any "worrisome feature", 3) with two or more affected first-degree relatives merit aggressive surveillance by MRI/MRCP (or computed tomography, CT) and EUS [17] (Percent of agreement: 62.5).

Question 3. What are the criteria that influence and eventually modify the timing of follow-up.

Answer. Cyst size represents a major criterion that influences the timing of follow-up. If surgically fit, patients with “high-risk stigmata” detected on surveillance should undergo resection. Shorter interval surveillance (3–9 months) should be considered in patients whose IPMN progresses toward these indicators or patients who already have “high-risk stigmata” and, for reasons of operative risk or personal preference, have chosen heightened surveillance over resection. The issue of whether a rapid growth rate is correlated with an increased risk of malignancy remains unclear, but shorter interval surveillance is recommended in such patients [17] (*Percent of agreement: 100.0*).

Discussion

The management of CPNs has constantly changed over the past two decades from aggressive surgical resection to a more selective approach [3,20,21]. Nevertheless, there is clear evidence for the need of surgical resection for most of the mucin-producing cystic tumors, especially all main-duct IPMNs, and MCNs [22]. With regard to branch-duct IPMNs the treatment has to be diversified according to risk criteria. As a consequence, many of these cystic lesions are nowadays managed conservatively [23].

Many efforts have been done to improve the knowledge of CPNs of the pancreas. Unfortunately high level of evidence is largely missing because prospective or large-cohort studies are lacking, and most of the evidence that support guidelines and recommendations come from case series, retrospective studies and experts' opinions (level III/IV evidence or low quality evidence using the GRADE criteria). Moreover, the conservative strategy began only about a decade ago, and we still lack a clear view on the long term consequences of this strategy on large number of patients. As a consequence, the selected guidelines can offer only weak recommendations, while firm conclusions are generally lacking. In addition, most of these guidelines focus only on specific issues and do not cover broad features of cystic lesions, making a direct comparison among guidelines difficult. Finally, from a methodological point of view, it can be noted that only the most recent guidelines apply properly the rules of the evidence based medicine including levels of evidence scores as well as grades of recommendations [8,19] and should be also underlined that all guidelines had scores lower than the minimum AGREE standardized score regarding the *Rigor of Development*; this aspect need to be taken into account when the guidelines will be updated.

In the clinical setting the acceptability of the four selected guidelines is well recognized worldwide without significant differences among them. The score of overall quality seems to reflect more the “familiarity” of the reviewers with the more longstanding guidelines and the recognition of different nuances of risk (i.e. high-risk stigmata, worrisome feature, different timing of follow-up according to size and risk factors) rather than true disagreements.

It is evident that future studies must take into account important practical factors such as patient's fitness for surgery, life expectancy, number of pancreatic adenocarcinomas prevented by follow-up strategy, number of saved lives, risk of loss to follow-up due to weariness, risk and type of surgery and even the cost of treatment and investigations at diagnosis and follow-up. By reviewing the results of the present work, it is clear that these topics in fact represent the major areas of debate. Of note, only one question, namely the criteria that influence and eventually modify the timing of follow-up, received the maximum agreement among reviewers in this paper. On the other hand it is somehow impressive that six crucial questions (1. whether cystic lesions must be unequivocally surgically resected, 2. if the

presence of a symptom(s) is an indication for surgery, 3. if the size of the lesion at diagnosis represents an indication for surgery, 4. whether the patient's age at diagnosis represent an indication for surgery, 5. If the family history of pancreatic cancer is an indication for surgery, 6. what is the best imaging technique for the follow-up of cystic lesions) had an agreement of less than 50% among the nine experts. This degree of disagreement amongst experienced physicians is somewhat surprising but reflects the lack of robust evidence based data that currently exists and points to the need for future prospective multi-institutional studies in this field.

From a “political” point of view, the present work underscores how many guidelines have been published on nearly the same topics from different countries, different specialties (surgeons, internists, geneticists, radiologists and so on). This raises the question whether we really need so many guidelines whose conclusions are very similar as exemplified during the last joint IAP-EPC meeting in Southampton, where the present work was presented. The process and publication of so many guidelines result in a waste of time and resources. Are there so many “cultural” or local differences in medical approach of pancreatic diseases that justify those redundancies? Guidelines should now be organized at an international level with well-balanced representation from different countries, continents, societies and specialties including gastroenterologists, surgeons, radiologists, and pathologists. International guidelines should be triggered when sufficient new evidence based data are available.

In conclusion, our recommendations after this deep review of the available guidelines is that the scientific community does not need new guidelines but, as soon as more evidence-based data is available, an update of the existing ones should be done. Moreover, when an update is planned, more attention should be paid to all aspects of an evidence based medicine approach as suggested by SIGN, NICE or by the Oxford criteria [24–26]. In addition it can be recommended to those researchers who are involved in the field of CPNs to plan the nearby future multicenter collaborative studies in order to clarify black holes and gray areas which are still present in the available guidelines.

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All the authors contributed equally to the this work. M. Falconi chaired and C. Fernandez-del Castillo co-chaired the working group. S. Crippa and R. Pezzilli chaired the methodology aspects of the work and played a major role in the preparation of the manuscript and did not vote; the remaining authors are listed in alphabetical order and actively participated as voting members at all the steps of the process. All the authors critically reviewed the manuscript for important intellectual content and approved this final version.

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