

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 48204

**Title:** Overview and comparison of guidelines for management of pancreatic cystic neoplasms

**Reviewer's code:** 02542641

**Reviewer's country:** Italy

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-04-21 18:22

**Reviewer performed review:** 2019-04-27 07:54

**Review time:** 5 Days and 13 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

Dr Gonda et al. have done a great job of revising the guidelines on cystic pancreatic lesions by comparing four of the most widely used guidelines in the world. The authors tried to highlight, for the reader's use, the main characteristics and peculiarities



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of each guideline, underlining similarities and differences. The same authors then tried to evaluate a series of studies to validate and compare these guidelines to evaluate the performance of each of them. The work is well written and in correct English. However, a number of points need to be highlight for an overall assessment of the work:

- 1) In the chapter entitled "Approach to Initial Risk Stratification" we read: "Relative indications for surgery are summarized in Table X", but table X does not exist.
- 2) Regarding Fukuoka's guidelines, in the subchapter "Approach to Initial Risk Stratification" we read "Worrisome features include cyst  $\geq 3$  cm, enhancing mural nodules  $< 5$  cm". Please, correct with  $< 5$  mm.
- 3) In the same chapter we read "However, the guidelines recommend strong consideration of resection for cysts  $> 3$  cm in diameter"; this is not correct. The revised Fukuoka guidelines suggest evaluating the resection of cysts above 2 cm in young subjects who would have a high cumulative risk of degeneration: "Although still controversial, younger patients ( $< 65$  years) with a cyst size of  $> 2$  cm may be candidates for resection owing to the cumulative risk of invasive carcinoma and HGD". It is not written anywhere in the work to send patient for surgery just if the cysts is above 3 cm in diameter. Indeed in Fukuoka Guidelines regarding this point, we can read: "Although cyst size is associated with an increased risk of harboring HGD and invasive cancer, there is no cut-off to quantify the risk, and in general, cyst size alone is not an appropriate parameter to indicate surgery given its poor predictive value for invasive carcinoma and HGD."
- 4) In the chapter entitled "Comparison of Guidelines and their Performance" you can read: "The ACR white paper is the only set of guidelines that tailors its approach to the age of the patient (Table 1)": but in table 1 there is no referral to age.
- 5) In the chapter "Differences in Approach to Initial Surveillance" we read as follows: "Positive cytology was considered in the European, Fukuoka, and ACG guidelines, and these patients were referred to surgery in the European and Fukuoka guidelines, while the ACG recommended EUS/FNA". This

is not correct; it would not make sense to repeat the EUS-FNA in the case of positive cytology. In fact, the ACG recommends, in case of positive cytology, re-evaluation by the multidisciplinary team. In fact, in the ACG guidelines one can read as follows: "Concerning cytology. Cytology has a low sensitivity of 64.8% (95% CI, 0.44-0.82), but has excellent specificity of 90.6% (95% CI, 0.81-0.96) for pancreatic cancer. The presence of high grade dysplasia or pancreatic cancer warrants urgent referral to a multidisciplinary pancreatic group". 6) In the chapter "Differences in Performance of Guidelines" we reads as follows: "In several multicenter study comparing the performances of the AGA and Fukuoka guidelines across 4 patient cohorts, the sensitivity of the AGA guidelines ranged from 7% to 73% (7%, 28%, 56 %, and 73%), and the specificity ranged from 63-93% (63%, 80%, 88%, and 93%). The AGA guidelines were determined to have an accuracy ranging from 75% to 93%. The sensitivity of the Fukuoka guidelines ranged from 28% to 81% (28%, 58%, 73%, and 81%), and specificity ranged from 34% to 88% (34%, 45%, 79%, and 88%). The accuracy ranged from 49% to 84% (Xu, Yin et al. 2017). What are these "several multicenter study"? Why are there no numbered references connected with bibliography sources? The articles cited in Table 3 do not seem to compare either the same guidelines or the same surgical indications of different guidelines in the different works: The work by Xu et al. deals with assessing the different ability of the guidelines of Fukuoka, AGA and the American Society of Radiology to assess the presence of "high-grade dysplasia (HGD) or cancer in resected cysts" on the basis of surgical indication. For Fukuoka guidelines surgical indication were cyst size >3cm in asymptomatic, surgically fit patient OR Mural nodule on EUS OR Dilation of pancreatic duct > 5mm ORs suspicious or positive cytology for malignant cells. The authors have interpreted the guidelines of Fukuoka, by putting together worrisome features, such as 30 mm cysts and dilation of the main pancreatic duct > 5 mm, which, really, are not absolute surgical indications, but only indications to perform

a EUS-FNA, and absolute indications to surgery such as positive cytology on cystic fluid. For AGA the surgical indication were: two of the following features present concurrently: -cyst size >3cm -dilated pancreatic duct -mural nodule confirmed on EUS OR positive cytology on FNA. The work by Sighinolfi et al. is a comparison of Sendai, Fukuoka and AGA guidelines for predicting advanced pancreatic cystic cancer. Indication for surgery for Sendai Guidelines were presence of a mural nodule, dilated main pancreatic duct greater than 6 mm, abnormal cytology ("malignancy" or "atypical"), associated symptoms, or a cyst size greater than 3 cm. Surgical indication for Fukuoka guidelines were: obstructive jaundice with a cystic lesion at the pancreas head, enhancing solid component within the cyst, or a main pancreatic duct greater than 10 mm or patients who had EUS for worrisome features showing a mural nodule, main duct involvement, and/or abnormal cytology. You can see that, differently from the article from Xu et al., in this article, regarding Fukuoka guidelines, there is no indication for surgery in patients with only cyst size >30 mm. For AGA the surgical indication were (1) abnormal cytology by EUS ("malignancy" or "atypical"), (2)  $\geq 5$  mm for main duct dilation in conjunction with a solid component by cross-sectional imaging, or (3) EUS identification of a mural nodule or main duct involvement. In study by Sighinolfi et al. >3 cm cyst were not considered between the features that have to be evaluated for surgical indication for AGA guidelines, unlike the study by XU et al. The work by Ma et al., on the other hand, had the aims to evaluate the performance of only Fukuoka and AGA "high risk criteria". The FG "high-risk" features were jaundice, enhancing solid component, and PDD  $\geq 10$  mm (with differences respect to the study by Singhinolfi because there are no reference to EUS in patients with worrisome features) and the AGA "high risk" features were solid component with pancreatic duct dilation (PDD) and concerning features on EUS-FNA to identify high-grade dysplasia and invasive cancer. As is easily understood, these works and the values of sensitivity, specificity, VPP and



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VPN are not comparable because they analyze different indications for surgery for the same guidelines, making comparison difficult or impossible. 7) In addition, some other works, not considered in this paper, could be evaluate. For example, the work by Singhi (Singhi AD et al. American Gastroenterological Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: a clinicopathologic study of 225 patients with supporting molecular data. *Gastrointest Endosc.* 2016;83:1107-1117 e1102) shows that the AGA guidelines would have missed 38% of all cases of advanced malignancy (including cystic PNET) and 45% of the intraductal IPMNs with adenocarcinoma or high-grade dysplasia, and 43% of patients selected by the AGA guidelines in this study would have undergone unnecessary surgery. Another interesting study that could to be considered was published in 2016 (Lekkerkerker SJ, Besselink MG, Busch OR, et al. Comparing 3 guidelines on the management of surgically removed pancreatic cysts with regard to pathological outcome. *Gastrointest Endosc.* 2016). The study of 115 patients with confirmed surgical resection data comparing the AGA guidelines with the revised ICG and European guidelines reports respective PPVs of 59 versus 54 versus 53% and NPVs of 81 versus 100 versus 100%. In this particular study, application of the AGA guidelines recommended unnecessary surgery in 22 of 53 patients (41.5%). So, while all guidelines result in overtreatment of patients, in this particular study only the AGA guidelines resulted in 12% of pancreatic cysts with advanced neoplasia being missed compared with either the revised ICG or the European guidelines. In essence, the revision work done by Gonda is interesting, but the discussion should be re-evaluated with greater attention to what has been evaluated in the different works, with a critical re-evaluation of the individual works and the possibility or not to compare them. Furthermore, the discussion should be expanded, including other pertinent and significant works. In addition, the bibliographic numeration in the text connected with the correct bibliography references should be



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added in all section of the article, and a general correction of small errors and inaccuracies throughout the text and the correct referrals to the tables and figures is desirable.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ Y] No

##### ***BPG Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ Y] No

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 48204

**Title:** Overview and comparison of guidelines for management of pancreatic cystic neoplasms

**Reviewer's code:** 03262781

**Reviewer's country:** Italy

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-05-22 19:37

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input checked="" type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

In this review Authors provide a summary of the recommendations of different guidelines for pancreatic cystic lesions. Despite this paper can be useful for physicians who are not expert in the field, the manuscript only summarizes the Guidelines content.



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It might be much more interesting if some critical point or novelty by more recent studies were discussed. The manuscript is presented in a sort of “first draft” with some typos, some missing paragraphs, and references not properly included.

#### **INITIAL REVIEW OF THE MANUSCRIPT**

##### ***Google Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No

##### ***BPG Search:***

- ☐ The same title
- ☐ Duplicate publication
- ☐ Plagiarism
- ☐ No



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology

**Manuscript NO:** 48204

**Title:** Overview and comparison of guidelines for management of pancreatic cystic neoplasms

**Reviewer's code:** 03026941

**Reviewer's country:** Denmark

**Science editor:** Ruo-Yu Ma

**Reviewer accepted review:** 2019-05-21 13:53

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**Review time:** 13 Days and 23 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
			<input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS

To the authors, It was a pleasure reading your paper. I find the topic very interesting; however, I have a few comments and concerns that I would like to share with you. In the European guideline, you state that patients should undergo surveillance at certain

time intervals. However, you do not state by which modality. Please add that to the description. In the ACG recommendations, please clarify if it is correct that no diagnosis of the cystis neoplasm is needed in order to follow the recommended algorithms? Page 18, line 1-9: It is great that you present these numbers. But you might want to add, how these are calculated? If they are based on surgery with histopathology as gold standard, they might be skewed. This fact is off course inevitable; however, it do represent an important source of possible bias. I suggest that you briefly discuss in what direction the current and future guidelines will take and the perspectives of improved diagnosis with the use of genetic testing (Springer et al, A Combination of Molecular Markers and Clinical Features Improve the Classification of Pancreatic Cysts. Gastroenterology, 2015). and/or EUS-guided microbipsies (Kovacevic B et al, Endoscopy 2018). The latter might even add knowledge of histological subtypes of IPMN and grade of dysplasia, which possibly change the current approach. Minor comments: Please clarify how “positive cytology” is defined. Page 6, line 1: Please correct Table X to Table 1 (if that is what it refers to).

## **INITIAL REVIEW OF THE MANUSCRIPT**

### ***Google Search:***

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- ☐ No

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- ☐ The same title
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[ ] Plagiarism

[ Y ] No