COLUMBIA UNIVERSITY
College of Physicians and Surgeons

Tamas A. Gonda, M.D.
Assistant Professor of Medicine
Director of Endoscopic Research
Division of Digestive and Liver Diseases
Director of Gastroenterology Services
The Pancreas Center
161 Ft. Washington Ave. Suite 850A
New York, NY 10032-3784

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Dear Editor,

We would like to thank the reviewers for their comments and suggestion regarding our manuscript entitled "Overview and Comparison of Guidelines for Management of Pancreatic Cystic Neoplasms". Below we provide line-by-line responses and made corresponding adjustments in the manuscript. We have also revised the manuscript based on suggestions of the Editor and have made these changes in the resubmission.

We hope you will be able to consider the revised manuscript for publication.

Sincerely,

The Authors

Responses to Reviewers

Response to Review#1

1. *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.*

   We have added the modality of surveillance for the European guidelines.

2. *In the ACG recommendations, please clarify if it is correct that no diagnosis of the cysts neoplasm is needed in order to follow the recommended algorisms?*

   The ACG guidelines were formulated for patients with identification of any type of pancreatic cyst or lesion concerning for pancreatic cyst.

3. *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, itdo 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.

This section has been revised to clarify how these numbers were obtained and calculated. We recognize that molecular markers and histologic diagnosis using microforceps will influence cyst evaluation and discuss these as possible future areas to include in the guidelines.

4. *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).*

   Positive cytology has been clarified in our article
   Table X has been changed to Table 1.

Response to Review #2

We appreciate the comments that suggestions and have made substantial changes to the manuscript. Our goal was to provide a practical overview of the current guidelines and therefore we did not highlight novel evaluation and treatment strategies. However, these aspects are now discussed more broadly in the discussion.

Response to Review# 3

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*

   This has been corrected.

2. *Regarding Fukuoka's guidelines, in the subchapter "Approach to Initial Risk Stratification" we read "Worrisome features include cyst ≥3 cm, enhancing mural nodules <5 cm". Please, correct with <5 mm.*

   This has been corrected.

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."

We have clarified that in younger patients, although this is controversial, the Fukuoka guidelines suggest resection for >2 cm cysts. This has been revised in the text.

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.*

   Table “1” was listed in error. It is table 2 that highlights the differences in surveillance based on cyst size and age (with >80 having surveillance every 2 years). This has been corrected.

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"*

   We have corrected this by clarifying, “referral to multidisciplinary group and consideration of EUS/FNA”

6. *In the chapter "Differences in Performance of Guidelines" ….*

   We truly appreciated your thorough review of this section and several suggestions. We have revised the text to reflect the different methodologies used in these studies and revised Table 3 to include additional suggested by the Reviewer.

7. *In addition, some other works, not considered in this paper, could be evaluated….*

   We have expanded the studies cited in this section and have added these to Table 3.