Value of pancreatic cyst fluid SPINK1 and glucose in differentiating potentially malignant cysts from those of benign nature: A prospective cohort study

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Abstract

Background: Diagnosis of malignant pancreatic cystic lesions (PCLs) is challenging as there is no investigation that offers both high diagnostic sensitivity and specificity for a definite diagnosis. Accurate diagnosis of cyst type is vital in order to not miss opportunities for early treatment of potentially malignant lesions and to avoid unnecessary surgeries. Serine protease inhibitor Kazal type I (SPINK1) and glucose are promising cyst fluid markers for differentiation of mucinous from non-mucinous cysts. We aim to validate the value of SPINK1 and glucose in detecting potentially malignant PCLs.

Methods: A prospective study was conducted on 80 patients presenting with PCLs. Endoscopic ultrasound (EUS) evaluation of detailed cyst morphology and EUS with fine needle aspiration (FNA) were done. Fluid analysis for carcinoembryonic antigen (CEA), glucose and SPINK1 and cytopathology were done. We compared these data with the final diagnosis based on cytopathological and postoperative histopathological examination.

Results: Cyst fluid SPINK1 was significantly higher in malignant or potentially malignant cysts compared to benign cysts (0.91 vs 0.47 ng/ml; P = 0.001). Also, glucose was significantly lower in malignant or potentially malignant cysts compared to benign cysts (21.5 vs 68.5 mg/dl; P = 0.0001). Glucose and SPINK1 had the best sensitivity and specificity for differentiating mucinous from non-mucinous cysts with 84.78% and 73.53% (AUC 0.76; 95% CI [0.65–0.88]; cutoff value = 42 mg/dl), and 70.59% and 65.22% (AUC 0.72; 95% CI [0.64–0.86]; cutoff value = 0.58 ug/L) respectively. CEA level >192 ng/ml, high SPINK1 level and lymph node enlargement were the independent predictors of malignant cysts.

Conclusion: Cyst fluid SPINK1 and glucose are promising diagnostic markers for the diagnosis of potentially malignant PCLs.

Keywords: CEA, cystic fluid glucose, EUS-FNA, pancreatic cystic lesions, SPINK1

INTRODUCTION

Pancreatic cystic lesions (PCLs) are being increasingly detected, often accidentally, on abdominal imaging performed for non-pancreatic indications. They have wide differential diagnoses, ranging from absolutely benign to...
malignant.[9] Hence, proper diagnosis is essential to guide the management plan and help to prevent pancreatic adenocarcinoma. However, the current standard of management lacks sufficient accuracy.[10]

Endoscopic ultrasound (EUS) offers a high diagnostic performance in delineating malignant features and enables EUS with fine needle aspiration (FNA) (EUS-FNA) for cytology.[4] However, the diagnostic yield of cytology is limited, with a pooled sensitivity of 63% and specificity of 88%.[9] Carcinoembryonic antigen (CEA), the most widely used cyst tumor marker, can differentiate mucinous from non-mucinous cysts with a diagnostic accuracy of 80%; however, low values do not exclude malignancy and surveillance is possibly a better resort.[6,7]

Cyst fluid glucose represents a simple and cheap biomarker for detection of mucinous cysts with 90% accuracy, as reported in a recent study.[8] At a cutoff value of 66 mg/dl, it could accurately differentiate non-mucinous from pre-malignant mucinous cysts with 94% sensitivity and 64% specificity (AUC 0.88).[9]

Serine protease inhibitor Kazal type 1 (SPINK1) is a polypeptide encoded by the SPINK1 gene and synthesized by several cell lines and tumors.[10] It has been used as a marker for various cancers such as ovarian, bladder and renal cancers.[11,12] SPINK1 measurement in pancreatic cyst fluid is a good marker to distinguish benign from potentially malignant PCLs with 85% sensitivity and 85% specificity at a cutoff value of 118 mg/L.[13]

In this study, we aimed to validate the value of glucose and SPINK1 to differentiate mucinous from non-mucinous pancreatic cysts.

PATIENTS AND METHODS

This prospective study was conducted in Kasr Al-Ainy hospitals in the period from June 2018 to August 2020. It assessed patients presenting with pancreatic cystic lesions ≥10 mm in diameter and who were referred for EUS-FNA. Patients unfit for endoscopy (e.g., those with severe cardiovascular disease), those who had contraindications to EUS-FNA such as coagulopathy, and patients with stenosis or obstruction of esophagus were excluded. EUS was performed in 80 patients; all of them were included in the study. All procedures followed were conducted with appropriate approval by the Ethics Committee of Cairo University in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.[14] Informed consent was obtained from all patients before being included in the study.

All cases were subjected to history taking, full clinical examination and laboratory investigations (CBC, INR and total bilirubin). EUS was performed, and data regarding cyst location, size, number, detailed morphology and pancreatic duct diameter were collected. EUS was done under deep sedation using Pentax echoendoscope EG-3870UTK connected to Hitachi Avius Machine (Tokyo, Japan). EUS-FNA was done using a 22- or 19-gauge echotip needle (Cook medical company, NY). Cyst fluid sample was submitted for testing for mucin stain, amylase, glucose level, carcinoembryonic antigen (CEA), cytopathology and SPINK1 using ELISA kits (Chongqing Biospes Co., Ltd). Cysts were considered malignant when any of the following were present: cytopathological detection of malignancy, presence of metastasis, presence of mural nodules that progress in size within six months and postoperative pathological diagnosis of malignancy, if available. Cysts were considered benign when proved negative for malignancy via cytopathological examination and were followed up for at least six months without change in size, detection of mural nodules, metastasis, or occurrence of obstructive jaundice.

Statistical analysis

Data were coded and entered using the statistical package STATA version 15. They were summarized using mean, standard deviation, median for continuous variables and using frequency and percentage for categorical data. Comparisons between the two groups of patients were done using independent sample t test or Mann–Whitney U test, as appropriate. Logistic regression was done to study predictors of malignant cysts. Receiver operating characteristic (ROC) curves were constructed to assess the discriminatory power of the study biomarkers in diagnosing malignant lesions. P values less than 0.05 were considered as statistically significant. Multivariate regression model was built using forward selection and backwards elimination. Relevant predictors that revealed significant P value (<0.05) in the univariate analysis were included in the model.

RESULTS

A total of 80 pancreatic cyst samples were collected. The mean age of patients was 49 ± 11.75 years; 45 were females (56.25%). Sixty eight, patients (85%) presented with abdominal pain, 11 (13.75%) had abdominal swelling, 3 (3.75%) had weight loss, 6 (7.5%) had jaundice and
2 (2.5%) had history of fever. In 12 patients (15%) pancreatic cysts were incidentally detected on imaging for unrelated symptoms.

### Pancreatic cyst characteristics

Most of the cysts were single (70 patients, 87.5%), located in the body of 37.5% of the patients. Mural nodules were detected in 23 cysts (28.75%). The median size of the mural nodules was 8 mm (7–11 mm). Twelve patients had enlarged peripancreatic lymph nodes; they were mostly small and reactive, except in 4 patients where they appeared malignant. Dilatation of pancreatic duct was detected in 4 patients, as shown in Table 1.

Cyst fluid amylase was high (>250 U/L) in 4 patients (5%). Median level of cyst fluid CEA was 90 (8.39–2750) ng/ml. Median SPINK1 in cyst fluid was 0.56 (0.35–0.97) ng/ml. Median glucose level was 50 mg/dl, as shown in Table 1.

According to EUS examination, and cytopathological and biochemical analysis, the most common type was pseudocysts followed by mucinous cystadenomas. Table 1 shows the final cyst diagnosis. Fifteen patients underwent surgery for various indications (7 IPMN, 3 pancreatic adenocarcinomas, 3 pseudocysts, 1 mucinous cystadenoma, 1 serous cystadenoma). We followed all non-operated cysts, whether mucinous or non-mucinous, for at least 18 months with no change in the size of the cysts, and there was no development of high risk stigmata or metastasis.

Cysts were classified into non-mucinous (mostly benign cysts) and mucinous cysts (malignant or potentially malignant cysts). Malignant or potentially malignant cysts (34; 42.5%) included intraductal papillary mucinous neoplasms (IPMN) with low- and high-grade dysplasia, mucinous cystadenoma, mucinous cystadenocarcinoma and pancreatic adenocarcinoma with cystic breakdown. Benign cysts (46; 57.5%) included serous cystadenomas, pseudocysts and cystic lymphangioma.

### Comparison between mucinous and non-mucinous cysts

Mucinous cysts were mostly of complex nature, more likely to contain intramural nodules and enlarged peripancreatic lymph nodes compared to benign cysts (P < 0.001). There was no statistical difference regarding the cyst size and the presence of intramural doppler signals between the two groups. Pancreatic duct dilatation was only found in potentially malignant cysts, as shown in Table 2.

Cyst fluid biochemical analysis revealed that, mucinous cysts were more likely to have positive mucin stain and elevated CEA levels (P < 0.0001, P = 0.001 respectively). Cyst fluid SPINK1 was significantly higher in mucinous than in non-mucinous cysts (0.91 vs 0.47, P = 0.001). Glucose was lower in mucinous compared to non-mucinous cysts (21.5 vs 68.5, P = 0.0001).

### Accuracy of CEA, SPINK1 and glucose

ROC curves revealed that area under the curve (AUC) was comparable for CEA, glucose and SPINK1 (0.75, 0.76 and 0.72, respectively). Cyst fluid glucose had the highest sensitivity, specificity and accuracy (84.8%, 73.5% and 80%, respectively) as shown in Table 3.

The best sensitivity and specificity for CEA in predicting mucinous cysts were at a threshold of 21.62 ng/ml (80% and

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**Table 1: Baseline characteristics of pancreatic cysts**

| Type of pancreatic cyst and number of loculations | Number | Percentage |
|--------------------------------------------------|--------|------------|
| Simple                                           | 35     | 37.75%     |
| Complex                                          | 45     | 56.25%     |
| Unilocular                                       | 36     | 45%        |
| Bilocular                                        | 1      | 1.25%      |
| Multilocular                                     | 43     | 53.75%     |

| Characteristics of cyst contents                 | Number | Percentage |
|--------------------------------------------------|--------|------------|
| Fluid content                                    |        |            |
| Turbid                                           | 25     | 31.25%     |
| Thick                                            | 42     | 52.5%      |
| Mural nodules                                    | 23     | 28.75%     |
| Calcification                                    | 7      | 8.75%      |
| Enlarged lymph nodes                             | 12     | 15%        |
| Pancreatic duct dilation                         | 4      | 5%         |
| Doppler signal                                   | 2      | 2.5%       |

| Cytological diagnosis of pancreatic cysts        | Number | Percentage |
|--------------------------------------------------|--------|------------|
| Pseudocysts                                      | 29     | (36.25%)   |
| Mucinous cystadenoma                             | 16     | 1          |
| Serous cystadenomas                              | 13     | (16.25%)   |
| IPMNs with high-grade dysplasia                  | 8      | (10%)      |
| IPMNs with low-grade dysplasia                   | 6      | (7.5%)     |
| Pancreatic adenocarcinomas                       | 3      | (3.75%)    |
| with cystic breakdown                            |        |            |
| Cystic lymphangiomas                             | 3      | (3.75%)    |
| Mucinous cystadenocarcinoma                      | 1      | (1.25%)    |
| Duplication cyst with multiple                    | 1      | (1.25%)    |
| pancreatic retention cysts                       |        |            |

| Biochemical analysis of cyst fluid                | Median | Range            |
|--------------------------------------------------|--------|-----------------|
| CEA (ng/m)                                       | 90     | (8.78–1560)     |
| PNK1 (ng/ml)                                     | 0.56   | (0.35-0.97)     |
| Glucose (mg/dl)                                  | 50     | (10-84)         |
| CEA (ng/ml)                                      | 90     | (8.78–1560)     |
| Amylase (U/L)                                    | 515    | (0-1185)        |

*High amylase level > 250 U/L*
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60%, respectively) (AUC 0.75; 95% CI [0.61–0.89]; LR+ = 2.0000, LR− = 0.33) with overall accuracy of 71.11%, as shown in Figure 1. At a threshold of ≥42 mg/dl, glucose excluded mucinous cysts with sensitivity of 80%, specificity of 73.53% and overall accuracy of 80% (AUC 0.76; 95% CI [0.65–0.88]; LR+ = 3.20, LR− = 0.207), as shown in Figure 2.

SPINK1 level ≥ 0.58 ug/L, in any cyst size, had a sensitivity of 70.59% and specificity of 65.22% detection of mucinous cysts with overall accuracy of 67.50% (AUC 0.72; 95% CI [0.64–0.86]; LR+ = 2.0294, LR− = 0.451), as shown in Figure 3. In the subcohort of small pancreatic cysts (<3 cm in size), the best sensitivity and specificity were at a cutoff value 0.95 ug/L (60% and 100%, respectively). For cysts larger than 3 cm, a cutoff value of 0.58 mg/L had the best sensitivity and specificity (72.41% and 64.29%, respectively) with overall accuracy of 67.61% (AUC 0.73; LR+ = 2.0276, LR− = 0.4291).

Predictors of malignant or potentially malignant cysts

In univariate logistic regression analysis, the presence of complex cysts, mural nodules and lymph node enlargement were shown to be highly predictive of mucinous cysts, as shown in Table 4. Pancreatic duct dilation was only associated with malignant cysts. Mucin stain was positive in 30/34 of mucinous cysts. An increase in cyst fluid CEA and SPINK1, increased the probability of having a mucinous cyst. Low glucose level was significantly related to malignant cyst nature, as shown in Table 4.
In multivariate analysis, CEA level >192 ng/ml, high SPINK1 level and lymph node enlargement were the independent predictors of malignant cysts, as shown in Table 4.

**DISCUSSION**

The management of PCLs is a common problem in clinical practice. Mucinous pancreatic cysts may harbor or develop invasive malignancy. Pancreatic ductal adenocarcinoma (PDAC) is a deadly cancer, with an overall survival of less than 8%. Thus, accurate classification of PCLs is crucial in the prevention and early detection of pancreatic cancer. Due to limitations in diagnostic accuracy with the current diagnostic modalities, there remains a growing research interest in discovering novel cyst fluid biomarkers that may improve the diagnostic accuracy. The present study was designed to determine the value of cyst fluid SPINK1 and glucose level in detecting cysts with malignancy.

Mucin staining has been used for mucinous cyst differentiation with sensitivity and specificity of 80% and 40%, respectively. In our study, positive mucin stain was significantly more frequent in potentially malignant cysts ($P < 0.0001$). Another two studies have shown higher sensitivity and specificity (85.45% and 86.05%, and 85% and 95%, respectively) with PPV of 72.31% and 92%. Glucose was markedly consumed in malignant or potentially malignant cysts that was significantly lower than the glucose level of benign cysts (21.5 vs 68.5, $P = 0.0001$). At <42 mg/dL, glucose diagnosed mucinous pancreatic cysts with 80% overall accuracy (84.78% sensitivity and 73.5% specificity). Carr et al. found that median cyst fluid glucose was lower in mucinous versus non-mucinous cysts (19 vs 96 mg/dL; $P < 0.0001$). With a threshold of ≤50 mg/dL, cyst fluid glucose was 92% sensitive, 87% specific, and 90% accurate in diagnosing mucinous pancreatic cysts.

| Table 3: Diagnostic accuracy of cyst fluid CEA, glucose and SPINK1 |
|--------------------------|-------|-------|-------|-------|-------|----------------|----------------|
| Cut off                  | AUC   | Sensitivity | Specificity | Accuracy | Positive LR | Negative LR | 95% CI          |
| CEA (ng/ml)              | ≥21.62| 0.75     | 80%      | 60%      | 71.11%     | 2.00        | 0.33           | 0.61-0.89      |
| Glucose (mg/dl)          | ≤42   | 0.76     | 84.78%   | 73.53%   | 80%        | 3.20        | 0.207          | 0.65-0.88      |
| SPINK1 (ug/L)            | ≥0.58 | 0.72     | 70.59%   | 65.33%   | 67.5%      | 2.0294      | 0.451          | 0.64-0.86      |

The most widely used pancreatic cyst fluid biomarker is CEA. In our study, median cystic CEA level was 84.65 ng/ml in malignant PCLs which is significantly higher than the levels in benign PCLs which was 2.86 ng/ml ($P = 0.0002$). At the standard threshold value of >192 ng/mL, CEA can differentiate mucinous from non-mucinous cysts with an accuracy of 77%, according to a large multi-institutional study of 1861 patients. In our study, CEA >113 ng/mL had an accuracy of 68.75% with high specificity at 86.96%, but sensitivity was low at 44.12%. Thus, an alternative threshold of ≥21.62 ng/mL was chosen to maximize the diagnostic performance (sensitivity, specificity and accuracy was 69%, 60% and 71.11%, respectively). This threshold value is similar to that chosen by Carr et al.; CEA ≥26 ng/mL had relatively higher sensitivity, specificity and accuracy of 85%, 85% and 86%, respectively. However, CEA alone is not accurate enough for routine identification of mucinous cysts.

Cyst fluid glucose represents a simple and cheap biomarker for detection of mucinous cysts, that requires a small amount of fluid with a relatively lower cost than CEA. Our findings confirm the previously reported high diagnostic performance of glucose. Glucose was markedly consumed in malignant or potentially malignant cysts that was significantly lower than the glucose level of benign cysts (21.5 vs 68.5, $P = 0.0001$). At <42 mg/dL, glucose diagnosed mucinous pancreatic cysts with 80% overall accuracy (84.78% sensitivity and 73.5% specificity). Carr et al. found that median cyst fluid glucose was lower in mucinous versus non-mucinous cysts (19 vs 96 mg/dL; $P < 0.0001$). With a threshold of ≤50 mg/dL, cyst fluid glucose was 92% sensitive, 87% specific, and 90% accurate in diagnosing mucinous pancreatic cysts.
In our study, cyst fluid glucose performed better than cyst CEA level in detection of mucinous cysts; glucose was 80% accurate compared to 71.11% for CEA. However, AUC for glucose and CEA were similar, that is, 0.76 and 0.75 respectively.

Räty et al. were the first to evaluate the role of cyst fluid SPINK1 in differentiating potentially malignant from benign PCLs. They found that the patients with a malignant or potentially malignant cystic lesion had significantly higher SPINK1 levels than those with a benign lesion (1609 ± 418 vs 46 ± 21 ug/L; P = 0.0001). The authors concluded that SPINK1 was a promising marker and better than other markers (e.g., CEA and CA 19–9).

Our study supports the evidence for these previous observations. We found that the median level of SPINK1 was significantly higher in malignant or potentially malignant cysts compared to benign cysts (0.91 [0.41–1.45] vs 0.47 [0.3–0.72], P = 0.001). The best sensitivity (70.59%) and specificity (65.22%) of SPINK1 to differentiate potentially malignant from probably benign cysts were at a cutoff value of 0.58 ug/L (AUC 0.72; LR+ = 2.0294, LR− = 0.451). We found that in small pancreatic cysts (less than 3 cm in size), the best sensitivity (60%) and specificity (100%) to differentiate potentially malignant from benign cysts were at a cutoff value of 0.95 ug/L (LR+ = 2.0276, LR− = 0.4291). For cysts larger than 3 cm, a cutoff value of 0.58 mg/L had the best sensitivity (72.41%) and specificity (64.29%) with overall accuracy of 67.61% (LR+ = 2.0276, LR− = 0.4291; AUC 0.73).

The cyst fluid SPINK1 measurements in our study are lower than those in previous studies. This may be due to the different laboratory techniques used. In our study, we used ELISA technique (SPINK1 ELISA kits, Chongqing Biospes Co., Ltd), while in the studies by Räty et al. in 2004 and Raty et al. in 2013, SPINK1 levels were quantitated with a time-resolved immunofluorometric assay (TR-IFMA) which is characterized by lower detection limits and greater specificity and reproducibility.

In our study, CEA >192 ng/ml, high SPINK1 and low glucose measurements in cyst fluid were highly predictive of malignancy in univariate analysis. Of these three markers measured in cyst fluid, only CEA and SPINK1 were independent predictors of malignancy. This suggests that these markers could be helpful in differentiating potentially malignant cysts from benign cysts.

Our study should be viewed in the context of some limitations that include the lack of a gold standard postoperative histopathological diagnosis to all of the PCLs and a lack of some important markers such as cyst fluid DNA analysis that could have added more diagnostic benefit. Further studies addressing new markers are awaited. Also, this sample of patients were mostly symptomatic, which may not represent other clinicians’ experience as many patients are asymptomatic when presenting for medical attention.

In conclusion, this study has shown that EUS examination of cyst morphology along with cytological analysis and cyst fluid analysis for CEA, glucose and SPNK1 improve the differentiation between different types of pancreatic cysts. We suggest that SPINK1 and glucose measurements may be good additional tests to disease history and imaging, to detect cysts that possibly should be resected. Cyst fluid glucose level at cutoff value of 42 mg/dl had the highest sensitivity (84.78%), specificity (73.5%) and accuracy (80%) for differentiating potentially malignant cysts from benign cysts. However, the area under curve was similar for all the three markers, CEA, glucose and SPINK1. Larger comparative studies are still needed to confirm these results.

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**Conflicts of interest**
There are no conflicts of interest.

**REFERENCES**

1. De Jong K, Nio CY, Hermans JJ, Dijkstra MG, Gouma DJ, Van Eijck CH, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. Clin Gastroenterol Hepatol 2010;8:806–11.

2. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG clinical guideline: Diagnosis and management of pancreatic cysts. Am J Gastroenterol 2018;113:464–79.

3. Law JK, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, et al. A systematic review of solid-pseudopapillary neoplasms: Are these rare lesions? Pancreas 2014;43:331–7.

4. Salvia R, Malleo G, Marchegiani G, Pennacchio S, Pailla S, Paini M, et al. pancreatic resections for cystic neoplasms: From the surgeon's presumption to the pathologist’s reality. Surgery 2012;152:5135–42.

5. Thosani N, Thosani S, Qiao W, Fleming JB, Bhutani MS, Guha S. Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: A systematic review and meta-analysis. Dig Dis Sci 2010;55:2756–66.

6. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, et al. Diagnosis of pancreatic cystic neoplasms: A report of the cooperative Pancreatic Cyst Study. Gastroenterology 2004;126:1330–6.

7. Suzuki R, Thosani N, Annangi S, Guha S, Bhutani MS. Diagnostic yield of EUS-FNA based cytology distinguishing malignant and benign IPMNs: A systematic review and meta-analysis. Pancreatology 2014;14:380–4.

8. Carr RA, Yip-Schneider MT, Simpson RE, Doyle S, Schneider JG,
Wu H, et al. Pancreatic cyst fluid glucose: Rapid, inexpensive, and accurate diagnosis of mucinous pancreatic cysts. Surgery 2018;163:600-6.

9. Park WG, Wu M, Bowen R, Zheng M, Fitch WL, Pai RK, et al. Metabolomic-derived novel cyst fluid biomarkers for pancreatic cysts: Glucose and kynurenine. Gastrointest Endosc 2013;78:295–302.

10. Stenman UH, Koivunen E, Irkonen O. Biology and function of tumour associated trypsin inhibitor. Scand J Clin Lab Invest Suppl 1991;207:5-9.

11. Lukkonen A, Lintula S, von Boguslawski K, Carpén O, Ljungberg B, Landberg G, et al. Tumour-associated trypsin inhibitor in normal and malignant renal tissue and in serum of renal-cell carcinoma patients. Int J Cancer 1999;83:486-90.

12. Stenman UH. Tumor-associated trypsin inhibitor. Clin Chem 2002;48:1206-9.

13. Räty S, Sand J, Laukkaninen J, Vasama K, Bassi C, Salvia R, et al. Cyst fluid SPINK1 may help to differentiate benign and potentially malignant cystic pancreatic lesions. Pancreatology 2013;13:530-3.

14. Williams JR. The Declaration of Helsinki and public health. Bull World Health Organ 2008;86:650-2.

15. Khalid A, Brugge W. ACG Practice Guidelines for the Diagnosis and Management of Neoplastic Pancreatic Cysts. Am J Gastroenterol 2007;102:2339-49.

16. Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015;148:824-48.

17. Choi SH, Park SH, Kim KW, Lee JY, Lee SS. Progression of unrectsected intraductal papillary mucinous neoplasms of the pancreas to cancer: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2017;15:1509–20.

18. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. 2016. Available from: https://seer.cancer.gov/. [Last accessed 2016 Sep 07].

19. Lennon AM, Wolfgang CL, Canto MI, Klein AP, Herman JM, Goggins M, et al. The early detection of pancreatic cancer: What will it take to diagnose and treat curable pancreatic neoplasia? Cancer Res 2014;74:3381-9.

20. Morris-Stiff G, Lentz G, Chalikonda S, Johnson M, Bisceotti G, Stevens T, et al. Pancreatic cyst aspiration analysis for cystic neoplasms: Mucin or carcinoembryonic antigen—which is better? Surgery 2010;148:638–44.

21. Okasha HE, Behiry M, Ramadan N, Ezzat R, Yamany A, El-Kholi S, et al. Endoscopic ultrasound-guided fine needle aspiration in diagnosis of cystic pancreatic lesions. Arab J Gastroenterol 2019;20:86-90.

22. Okasha HH, Ashry M, Imam HMK, Ezzat R, Naguib M, Farag AH, et al. Role of endoscopic ultrasound-guided fine needle aspiration and ultrasound-guided fine-needle aspiration in diagnosis of cystic pancreatic lesions. Endosc Ultrasound 2015;4:132–6.

23. Gaddam S, Ge PS, Keach JW, Mullady D, Fukami N, Edmundowicz SA, et al. Suboptimal accuracy of carcinoembryonic antigen in differentiation of mucinous and nonmucinous pancreatic cysts: Results of a large multicenter study. Gastrointest Endosc 2015;82:1060-9.

24. Brugge WR. Cyst fluid: Moving beyond the carcinoembryonic antigen. Gastrointest Endosc 2015;82:1070–1.

25. Zikos T, Pham K, Bowen R, Chen AM, Banerjee S, Friedland S, et al. Cyst fluid glucose is rapidly feasible and accurate in diagnosing mucinous pancreatic cysts. Am J Gastroenterol 2015;110:909-14.

26. Räty S, Sand J, Alfthan H, Haglund G, Nordback I. Cyst fluid Tumour-associated trypsin inhibitor may be helpful in the differentiation of cystic pancreatic lesions. J Gastrointest Surg 2004;8:569-74.

27. Sheng SL, Bao SH, Huang G, Wang LM. Development of time-resolved immunofluorometric assays for vascular endothelial growth factor and application on plasma of patients with gastric tumours. Clin Exp Immunol 2008;151:459-66.