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Original Article

The Application of EUS-guided FNA in the Diagnosis of Pancreatic Neoplasms in the Elderly☆

Hsiang-Hung Lin [1, 2, 3], Chen-Wang Chang [1, 2, 3], Pao-Shu Wu [3, 4], Cheng-Hsin Chu [1, 3], Shou-Chuan Shih [1, 2, 3], Ming-Jen Chen [1, 2, 3 *]

[1] *Division of Gastroenterology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei Branch,* [2] *Department of Nursing, MacKay Junior College of Medicine, Nursing and Management, Taipei,* [3] *Department of Medicine, MacKay Medical College, New Taipei City,* [4] *Department of Pathology, MacKay Memorial Hospital, Taipei Branch, Taipei, Taiwan*

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SUMMARY

Background: Endoscopic ultrasound guided fine needle aspiration has become a standard procedure in diagnosis of pancreatic neoplasms with a high diagnosis yield. However, the clinical application focusing on the elderly population is scanty.
Methods: Consecutive procedures for EUS-FNA diagnosis of pancreatic neoplasms at a tertiary referral center from March 2014 to December 2015 were analyzed retrospectively. The procedures were divided into two groups according to their age, the control group consisted of patients ≤60 years old and the elderly groups consisted of patients >60 years old. The primary outcome is the accuracy of the diagnosis in the two groups. The secondary outcome is the safety during the procedure.
Results: A total of 28 EUS-FNA procedures were performed. The mean age of the control group was 48.7 years (n = 14) versus 70.2 years (n = 14) for the elderly cohort. Diagnostic accuracy of the EUS-FNA procedure in detecting malignant (true positive) and benign (true negative) lesions were higher in the control group (nonelderly: 85.7% vs. elderly: 50%; P = 0.046). There were two mild acute pancreatitis associated to the EUS-FNA procedures in the control group.
Conclusion: Although EUS-FNA is safe and well tolerated in the elderly patients, our study showed a lower EUS-FNA diagnosis accuracy in this group. Focal fibrotic changes in the pancreas associated with the elderly patients resembled that of chronic pancreatitis microscopically.

1. Introduction

Pancreatic cancer is a disaster cancer disease with a poor prognosis and mainly occurs after 60 years of age. The 5-year survival rate for the pancreatic cancer is only at about 8% and the current progression in treatment modality have been relatively slow in comparison to most other cancers. A major reason for the poor prognosis is because of more than half of the pancreatic cancer patients were diagnosed in the advanced stage[1]. Pancreatic cancer is the fourth leading cause of cancer death in United States and the eighth in Taiwan. There is an increased trend of death caused by pancreatic cancer in Taiwan, tallying mortality rate 8.3 persons per one hundred thousand of the population in 2015[2].

Preoperative diagnosis of pancreatic lesions remains a challenge despite current advancement in imaging technologies. Endoscopic ultrasound (EUS) allows for excellent imaging and analysis of the pancreas and EUS-guided fine needle aspiration (EUS-FNA) permit needle advanced into the lesion precisely and obtain the tissue under real-time guidance. The tissue obtained from the FNA can provide for cytopathologic analysis. EUS has the benefit of being a relative less invasive, well-tolerated procedure.

☆ Conflicts of interest statement: I certify that all my affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties). All authors have no financial interests related to the material in the manuscript.

* Correspondence to: Ming-Jen Chen, Division of Gastroenterology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei Branch, Taipei, Taiwan.
E-mail address: mingjen.ch@msa.hinet.net (M.-J. Chen).

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Studies suggest that the yield of EUS-FNA is high in patients with pancreatic cancer. The pooled sensitivity and specificity of EUS-FNA were 92% (95% CI = 91–93%) and 96% (95% CI = 93–98%), respectively[3]. For the most part, EUS-FNA were generally both safe and effective when elderly patients are chosen appropriately. EUS-FNA has become a standard procedure in diagnosis of pancreatic neoplasms with a high diagnosis yield. However, clinical application focusing on the elderly population is scanty.

2. Patients and methods

All patients with suspected pancreatic neoplasms that were identified on a Computed Tomography (CT) scan or a Magnetic Resonance Imaging (MRI) scan referred for EUS-FNA were eligible to participate in this study. A total of twenty-eight EUS-FNA procedures were performed between March 2014 and December 2015 at a tertiary referral center. Procedures were performed on an inpatient basis. The patients were divided into two groups according their age, the control group consisted of patients ≤60 years old and the elderly groups consisted of patients >60 years old. The demographics, EUS indications, procedural information (instruments, passes, size, tumor location, interventions), cytopathological result, accuracy and complications, followed-up period were analyzed. The cytology samples were reported as positive, suspicious for malignancy, atypical, or negative on the official pathology report. The criteria for final diagnosis of benign and malignant lesions are defined as follow. Diagnosis was malignancy if meeting one or more of the following criteria: (1). Malignant cells in the surgical specimen of the lesion or metastases. (2). Unresectable during operation. (3). Progression of disease or development of metastases upon follow-up imaging. (4). Clinical evidence of pancreatic cancer or confirmed cancer-related death when follow-up with patient's primary care physician. Classified as benign if meeting one or more of the following criteria: (1). No malignancy in surgical pathology and/or exploration. (2). Follow-up CT or ultrasound after five months showed a normal pancreas, stable mass or no metastases. The primary outcome is the accuracy of diagnosis in the two groups. The secondary outcome is the safety during the procedure. The Institutional Review Board at Mackay Memorial Hospital approved this retrospective study (16MMHIS131e).

3. Equipment and procedure

Standard EUS was performed by using a curvilinear echoendoscope (Olympus GF-UCT260). A 22- gauge FNA needle (Olympus EZ Shot 2 Aspiration Needles; Olympus or Expect™; Boston Scientific) was used to obtain tissue. Prior to the procedure, in all cases, written informed consent was obtained from the patient. Procedures were performed with patients in the left lateral decubitus position. Midazolam 5 mg and Fentanyl 0.1 mg or meperidine 50 mg were used for moderate conscious sedation in most of the procedures. Sedation was administered by the endoscopist who performing EUS-FNA. The type of sedation was chosen based on comorbidities and previous experience with sedation. Monitoring of patients during the procedures was included continuous pulse oximetry and blood pressure assessment every 5 minutes.

All of the EUS related procedures were performed by an endosonographer (HHL). Prior to the EUS-FNA, color Doppler examinations were performed to exclude interposed vascular structures. All pancreatic head and uncinate neoplasms were accessed via the duodenum, while pancreatic body and tail neoplasms were accessed via the stomach. During individual EUS-FNA passes, by using the “up-down” dial of the echoendoscope, the needle was moved back and forth, four times at four different areas within the lesion, described in previous studies as fanning technique[4]. Immediate cytopathologic evaluation (ICE) was not available and the samples were prepared by endosonographer himself. The stylet was introduced into the needle, and the extruded material was placed either onto glass slides for primary inspection; if one or more small-core biopsy cylinders were acquired, these were collected by catheter needle and placed into formalin for histologic analysis (Figure 1A–D). The remaining partially liquid material was either placed in saline solution or smeared onto glass slides for cell block or cytologic analysis.

3.1. Statistical analysis

Demographic data (including age, gender), EUS indications, procedural information (instruments, passes, size, tumor location, interventions), cytopathological result, accuracy and complications, followed-up period were retrospectively analyzed. Statistical analysis was performed between two cohorts using the Statistical Package for the Social Science, version 18.0. Tests were two-tailed with significance level of 0.05. Descriptive statistics for continuous were calculated and were reported as mean ± standard deviation (SD). For categorical variables were described using frequency distributions and were reported as n (%). P values were based on Chi-Square test for categorical variables and Mann-Whitney *U* test for quantitative variables.

4. Results

4.1. Demography and clinical characteristics of patients

A total of twenty-eight EUS-FNA procedures were performed in twenty-eight patients. The mean age of the control group was 48.7 years (range 32–60 years); 64.2% of male, n = 14 versus 70.2 years (range 63–87 years; 50% of male, n = 14) for the elderly cohort. The final diagnosis classifying as malignancy was 24 of 28 patients (85.71%), whereas as benign disease was in 4 patients (14.28%). The overall accuracy was 71.4%. No statistically significant differences among the two groups with regard to gender, location, passes or size of the masses were found (Table 1).

4.2. Endoscopic finding and outcomes measures

Indications for EUS-FNA were to evaluate solid pancreatic neoplasms (n = 24) or pancreatic cystic lesion (n = 4). A neoplasm with a suspicious, atypical or malignant FNA reading with the final diagnosis of benign neoplasm was considered “false positive”. Meanwhile, a neoplasm with a negative FNA reading for malignancy but with a final diagnosis of malignant neoplasm was classified as “false negative”. Patients with atypical or suspicious cytology were considered true positive if the final diagnosis was malignancy.

Among 24 patients with malignancy diagnosis, cytopathological evaluation revealed positive of malignancy (n = 8), suspicious of malignancy (n = 4), atypical (n = 3), negative of malignancy (n = 9). Among 4 patients with benign diagnosis, cytopathological evaluation revealed all negative of malignancy. The cytologic classifications of FNA results are outlined in Table 2. The overall accuracy was 71.4%.

For the primary outcome, diagnostic accuracy of the EUS-FNA procedure in detecting malignant (true positive) and benign (true negative) lesions were higher in the nonelderly cohorts (nonelderly: 85.7%; elderly: 50%; P = 0.046) (Table 1). For the secondary outcome, complications related to the EUS-FNA procedure were defined as pancreatitis, moderate or severe bleeding, perforation, infection, abdominal pain, hemodynamic or respiratory compromise during or after the procedure and any event leading to post

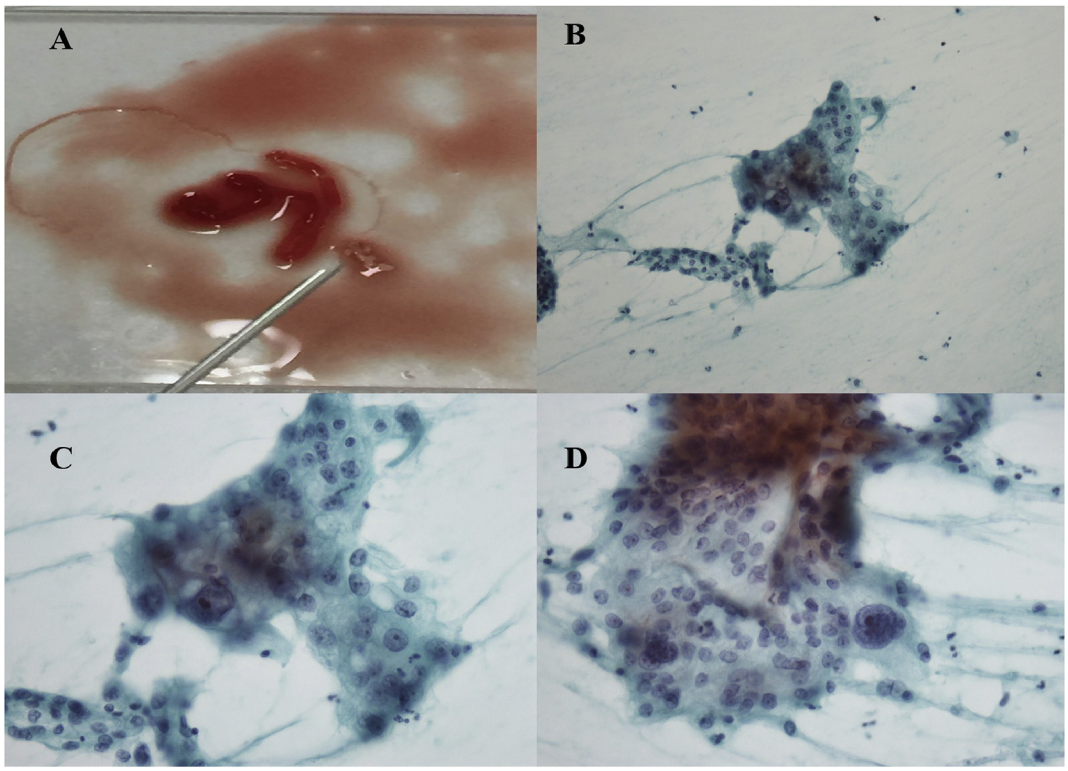

Figure 1. (A) Extruded material showed some small-core biopsy cylinders acquired, these were collected by catheter needle. (B and C) Cytology smear (Papanicolaou stain) showing clusters of tumor cells with large size, prominent and enlarged nucleoli arranged in vague acinar growth pattern, compared with the benign acinar and ductal cells in the background (×200 and ×400 respectively). (D) Occasionally showing single tumor giant cell with large nucleoli.

Table 1
The clinical presentation, tumor morphology and diagnostic accuracy according to the age.

	Nonelderly	Elderly	P value
Numbers of procedure	14	14	–
Mean age (range), years	48.7 (32–60)	70.2 (63–87)	–
Male/Female, n/n	9/5	7/7	0.45
Tumor size, cm	3.12	3.19	1.0
Location of mass, head/others, n/n	7/7	7/7	1.0
Chronic pancreatitis, n	2	2	1.0
FNA pass, mean	4.42	4.92	0.21
Complication, n	2	0	0.14
Mean FU period, months	7.7	5.3	0.27
Malignancy, n (%)	11 (78.6)	13 (92.9)	0.28
Accuracy, %	85.7	50	0.046

Table 2
Pancreatic FNA cytology in patients with pancreatic mass.

Cytologic classification	Benign lesion (n = 4)	Malignant lesion (n = 24)
Positive	0	8
Suspicious	0	4
Atypical	0	3
Negative	4	9

EUS-FNA procedure hospital admission or death. There were no statistical differences in complication rates found between two cohorts (Table 1). There were only two mild acute pancreatitis complication associated with the twenty-eight EUS-FNA procedures, both in the nonelderly cohort, requiring additional admission for observation for no more than 3 days.

5. Discussion

Given the increasing aging population, gastroenterologists or endoscopists are respected to perform more advanced diagnostic or therapeutic procedures for GI neoplasms in the extremes of ages. The current study illustrates the experience of endoscopic ultrasound at a tertiary referral center evaluating pancreatic neoplasms in the elderly. Prior studies have generally found these procedures to be safe and effective, and the complications not higher than those in younger patients[5–7]. To our best knowledge, our observation is the first study of EUS-FNA in elderly cohort for pancreatic neoplasms.

Our study showed a lower EUS-FNA accuracy in the elderly (nonelderly: 85.7%; elderly: 50%; P = 0.043). Changes in the pancreas along with age increase have been described for decades. The ageing pancreas seem to demonstrate abnormal findings similar to those seen in chronic pancreatitis when viewed by endoscopic ultrasound imaging[8]. A prospectively study evaluate 120 patients referred for EUS for an indication unrelated to pancreaticobiliary disease. Twenty eight percent of the all patients and 39% of patient older than 60 years-old had at least one parenchymal and/or ductular abnormality similar to those finding in patients with chronic pancreatitis, with a trend of increasing abnormality with age. Hyperechoic stranding or lobulations were more common finding than the calculi, ductal narrowing, and ductal dilatation[9]. Microscopically, fibrotic changes are the hallmark of comparable chronic pancreatitis. Previous study evaluated 89 postmortem specimens from persons without any known pancreatic disease, were divided into two age classes (younger or older than 60 years). Fibrotic changes in the pancreas were more common in individuals older than 60 years. Fibrotic foci were commonly associated with ductal papillary hyperplasia in ducts draining fibrotic lobuli. The

pattern of fibrosis was termed "patchy lobular fibrosis in the elderly" (PLFE)[10]. Diagnosis pancreatic cancer in the setting of chronic pancreatitis is clinical challenge. A lower sensitivity for EUS-FNA was observed in patients with chronic pancreatitis than in those without chronic pancreatitis (73.9% vs. 91.3%; $P = 0.02$)[11]. In our observational study, when the patients were divided into two groups according to 60 years old, the EUS-FNA accuracy is lower in the elderly may be due to the increase in focal fibrosis which resembled that of chronic pancreatitis microscopically.

Due to the rigidity and stiffness of the scope tip that carries the ultrasound transducer, the complication rates of echoendoscope are higher than that of standard endoscope[12]. Add to the fact that the echoendoscope had larger diameter compared to regular gastroscopes or duodenoscopes, the mean EUS examination time was also much longer than that needed for standard endoscope[13]. A systemic review identified 51 articles with a total of 10,941 patients found overall rate of EUS-FNA-specific morbidity was 0.98%. The most common complications were acute pancreatitis (36/8246; 0.44%), and post-procedural pain (37/10,941; 0.34%). Infectious complications, bleeding, gastrointestinal perforations and bile leaks were less common. The EUS-FNA related mortality was reported as 0.02%[14].

There were few data focus on feasible and safety of EUS in the elderly. One retrospective study analyzed complications in the 400 EUS procedures, among 21% were FNA procedures. The complication rate was not statistically differences among elderly and non-elderly cohort[6]. But the study evaluated pancreatic pathology (27%) and suspected esophageal pathology (27%), there were no sub group analysis for pancreatic cancer alone. Another retrospective study analyzed 265 EUS procedures, included 35.8% FNA procedure with a mean age of 83.8 years. No complication occurred related to sedation, EUS, or EUS-FNA. But only 65.2% EUS-FNA results were consistent with clinical suspicion of malignancy[5], which was relative low compared with previous study.

A retrospective study also revealed the safety of combined ERCP/EUS in one session in the elderly patients. Although elderly patients (>65 years-old) had higher Comorbidity Index scores compared to non-elderly patients, there were no statistically significant differences in adverse event[7].

To our best knowledge, our observation is the first study of EUS-FNA in elderly cohort for pancreatic neoplasms. In our data, there was two mild acute pancreatitis complication associated with the twenty-eight EUS-FNA procedures, both in the nonelderly cohort (age are 47 and 50 years respectively). The complications resolved after additional admission by no more than 3 days. One retrospective study report post-ERCP pancreatitis was significantly less frequent in the elderly cohort (>80 years) (0.9% vs 5.3%; $P < 0.05$)[15]. The possible explanation may be found in the change in pancreatic histology related with age increase. These include proliferation of ductal epithelial cells with stratified squamous epithelium replacing normal ductal epithelium, fatty infiltration, and fibrosis. These factors may have caused elderly patients to be less responsive to pancreatic trauma[16]. The same theory may also explain why EUS-FNA related pancreatitis may be lower in elderly patients.

In conclusion, although EUS-FNA is safe and well tolerated for most elderly patients, our study showed a lower EUS-FNA accuracy in this group. This may be due to the increase in focal fibrosis associated with the elderly patients which resembled that of chronic pancreatitis microscopically. EUS-FNA accuracy is lower in the setting of chronic pancreatitis or similar microscopic backgrounds.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. 2016;66(1):7–30.
2. Statistics of causes of death in Taiwan, 2015. Available at: http://www.mohw.gov.tw/news/572256044. Accessed 5 August 2016.
3. Chen J, Yang R, Lu Y, et al. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. *J Cancer Res Clin Oncol*. 2012;138(9):1433–1441.
4. Bang JY, Magee SH, Ramesh J, et al. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. *Endoscopy*. 2013;45(6):445–450.
5. Attila T, Faigel DO. Endoscopic ultrasound in patients over 80 years old. *Dig Dis Sci*. 2011;56(10):3065–3071.
6. Benson ME, Byrne S, Brust D, et al. EUS and ERCP complication rates are not increased in elderly patients. *Dig Dis Sci*. 2010;55(11):3278–3283.
7. Iles-Shih L, Hilden K, Adler DG. Combined ERCP and EUS in one session is safe in elderly patients when compared to non-elderly patients: outcomes in 206 combined procedures. *Dig Dis Sci*. 2012;57(7):1949–1953.
8. Chantarojanasiri T, Hirooka Y, Ratanachu-ek T, et al. Evolution of pancreas in aging: degenerative variation or early changes of disease? *J Med Ultrason (2001)*. 2015;42(2):177–183.
9. Rajan E, Clain JE, Levy MJ, et al. Age-related changes in the pancreas identified by EUS: a prospective evaluation. *Gastrointest Endosc*. 2005;61(3):401–406.
10. Detlefsen S, Sipos B, Feyerabend B, et al. Pancreatic fibrosis associated with age and ductal papillary hyperplasia. *Virchows Archiv*. 2005;447(5):800–805.
11. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. *Gastrointest Endosc*. 2005;62(5):728–736.
12. Razavi F, Gross S, Katz S. Endoscopy in the elderly: risks, benefits, and yield of common endoscopic procedures. *Clin Geriatr Med*. 2014;30(1):133–147.
13. Jenssen C, Alvarez-Sánchez MV, Napoléon B, et al. Diagnostic endoscopic ultrasonography: assessment of safety and prevention of complications. *World J Gastroenterol*. 2012;18(34):4659–4676.
14. Wang KX, Ben QW, Jin ZD, et al. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. *Gastrointest Endosc*. 2011;73(2):283–290.
15. Finkelmeier F, Tal A, Ajouaou M, et al. ERCP in elderly patients: increased risk of sedation adverse events but low frequency of post-ERCP pancreatitis. *Gastrointest Endosc*. 2015;82(6):1051–1059.
16. Lukens FJ, Howell DA, Upender S, et al. ERCP in the very elderly: outcomes among patients older than eighty. *Dig Dis Sci*. 2010;55(3):847–851.