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STUDY ON THE VALUE OF EUS AND EUS – FNA IN THE DIAGNOSIS OF PANCREATIC CANCER

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SUMMARY OF PHD THESIS

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THESIS INTRODUCTION

1. Background

Pancreatic cancer (PC) is a malignancy of pancreas cells, one of the leading causes of death in the world. The survivals rate at 1 year, 5 years and 10 years respectively of PC is below 20%, 5% and 1%. If the tumor is not removed, the average survival time would be less than 6 months. However, if PC is detected early (tumor size $\leq$ 2 cm) and the tumor is removed, the survival rate after 5 years would be higher (60%). Thus, diagnosis of early-stage PC is very significant in the treatment and prognosis for the patient's survival time. Endoscopic ultrasonography (EUS) with high-frequency ultrasound probe and high-resolution ultrasound transducers placing directly on the walls of the stomach and duodenum in the process of examination give clear and highly accurate images. So EUS can detect small lesions that other methods are unlikely to diagnose. Pancreatic cancer diagnosis is mainly based on the diagnostic imaging methods. However, these methods can not replace the cytology and histopathology. Diagnostic cytology, histopathology gives information on the nature of the tumor, which is an important evidence to confirm diagnosis and choose treatment plan. Endoscopic ultrasonography– Guided fine needle aspiration (EUS – FNA) is a less invasive procedure which have the lowest complication rate than the other methods. In the world, there are many researches about the value of EUS and EUS - FNA and these methods has become routine diagnosis of pancreatic lesions. In Vietnam, the research of the EUS value is still limited with not many patients and no researches on EUS - FNA in diagnosing PC was conducted. Therefore, we conducted research on this issue with two aims:

- To describe clinical and lab tests features of pancreatic cancer.
- To evaluate EUS and EUS – FNA value in diagnosis of PC.

2. The topicality of thesis

The pancreas is an organ which is located deep in the body; it is covered by the hollow organs so it's difficult to be checked. Pancreatic lesions were diagnosed mainly based on the diagnostic imaging methods. Despite there are many advances in techniques and diagnosis equipment, the diagnostic imaging methods (Ultrasound (US),

Computed Tomography (CT), Magnetic Resonance Imaging (MRI) ...) are difficult to detect small pancreatic lesions. On the other hand, diagnostic cytology and histopathology let us know the nature of tumor, especially in the stage that PC is unresectable because there is convincing evidences for using chemotherapy or radiotherapy. The EUS and EUS - FNA have been solved these problems.

In the world, there are many researches on the value of EUS and EUS - FNA in the diagnosis of PC. However, Vietnam doesn't have any research in this field. Thus, PC diagnosis on EUS and EUS - FNA in comparison with pathology after surgery is necessary, meaningful scientific and practical issue in our country.

3. Scientific contributions of thesis

This is one of the first studies in Vietnam to evaluate value of Endoscopic Ultrasonography (EUS) and Endoscopic Ultrasonography – Guided Fine Needle Aspiration (EUS-FNA) in diagnosis of pancreatic cancer in our country.

The study has shown that EUS and EUS - FNA is a relatively safe method in diagnosis of PC, with 73 EUS procedures and 94 times of EUS - FNA in 62 patients without any complications.

The value of EUS in diagnosis of PC: Sensitivity was 92.9%, specificity was 76.5% and accuracy was 89.0%.

The value of EUS in diagnosis of small size tumor of PC ($\leq$ 2 cm): sensitivity was 87.5%, and accuracy was 81.8%.

The value of EUS - FNA was 63.0% in sensitivity, 100% in specificity and 75.6% in .

Endoscopic ultrasonography and EUS – FNA have higher value than other diagnostic methods (US, CT/MRI) in diagnosis of PC.

EUS has higher value than other diagnostic methods (US, CT/MRI) in diagnosis of pancreatic cancer with small tumors size.

4. Thesis structure

The thesis has 138 pages including Background (2 pages), Literature Review (38 pages), Subjects and Methods of study (23 pages), Results (40 pages), Discussion (32 pages), Conclusion (2 pages), and Recommendation (1 page).

There are 49 tables, 6 figures, 8 images, and 6 diagrams, 188 references, and two appendices.

CHAPTER 1: LITERATURE REVIEW

1.1. Clinical manifestations

The clinical manifestations of PC depend on the size, location and invasion to other organs. The common symptoms of PC: Abdominal pain even appear even with small tumors (≤ 2 cm), jaundice and weight loss. Some other symptoms of PC include embolism, gastrointestinal bleeding, skin manifestations, epigastric or right upper quadrant mass, large gallbladder, ascites, lymph node metastasis, depression, psychosis.

1.2. Test methods in diagnosis of pancreatic cancer

1.2.1. Biomarker cancer

CA 19.9 is a glycolipid. The normal value level of CA 19.9 is less than or equal to 37 (U/ml).

1.2.2. The methods of diagnostic imaging in pancreatic cancer

1.2.2.1. Ultrasound in the diagnosis of pancreatic cancer

1.2.2.2. CT in the diagnosis of pancreatic cancer

1.2.2.3. MRI in the diagnosis of pancreatic cancer

1.2.2.4. Some other methods of diagnosis pancreatic cancer

ERCP, PET, Angiography, Pancreatic scintigraphy, Percutaneous Transhepatic Chongiography, US in the pancreatic duct, portal venous ultrasound etc.

1.3. Endoscopic ultrasonography in the diagnosis of PC

1.3.1. The concept, historical development EUS and EUS - FNA

EUS is a method using an ultrasound probe attaching into the distal end of the endoscope to examine. EUS technique is performed by ultrasound waves from 5MHz - 30 MHz frequency. In 1982, the first conference about EUS worldwide was held up in Stockholm - Sweden, the conference developed a consensus with indications and technique guidance of EUS. In 1992, Vilmann applied EUS - FNA for early diagnosis of pancreatic tumors for the first time. In 1997, Wiersema et al have demonstrated that diagnostic techniques using EUS - FNA was highly safe.

1.3.2. Indication of EUS in diagnosis of pancreatic cancer

America Society for Gastrointestinal Endoscopy recommends that EUS should be used to diagnose PC in the following cases:

- To have definitive diagnosis of pancreatic cancer when other imaging methods are unclear: US, CT, MRI etc.
- To evaluate the stages of pancreatic cancer.

- When patient has unresectable tumor that require to place stent by ERCP, EUS should be done before ERCP.

1.3.3. Endoscopic Ultrasonography in pancreatic cancer diagnosis

EUS pancreatic cancer findings

Tumor findings: Contour - The contour is from clear to relatively unclear. The contour at the area where it is clearly visualized is irregular. Interior - Presents from regular to relatively irregular hypoechoic. As the tumor grows, a hyperechoic lesion appears in the center.

Extratumoral findings: Intrapancreatic - The main pancreatic duct is highly dilated at the caudate in many cases. The duct is smooth or shows a beaded pattern, and is sharply dilated at the caudal part of the tumor. Extrapancreatic - Dilatation of the bile duct upstream of the tumor is observed. Invasion to the portal vein or other veins, arteries, and lymphadenopathy are observed. Tumor embolisms may also be observed.

Value of EUS in diagnosis of pancreatic cancer

EUS divided PC into stages according to AJCC (2010) and in the stages IA, IB, IIA and IIB , surgery could remove tumors. If the pancreatic tumor is small ($\leq$ 2 cm), the EUS will assess more accurately the T stage than the CT. Conversely, if pancreatic tumors are large, CT assesses more accurately the T stage than EUS.

EUS has sensitivity in detecting pancreatic tumors (91% - 98%) higher than CT (63% - 86%) and ultrasound (64% - 78%).

1.4. Endoscopic ultrasonography – Guided fine needle aspiration

1.4.1. Indication of EUS - FNA

a. To confirm diagnosis cancer before chemotherapy or radiation therapy.

b. To exclude other tumor types such as lymphoma, small-cell, metastasis, or neuroendocrine cancer that may require a different, management strategy.

c. To determine a diagnosis of cancer before surgery

d. To confirm the diagnosis in the case of other methods are unclear.

1.4.2. Needle selection and the number of insertions for EUS - FNA

There are 2 types of fine needle aspiration used including the 22G needle (0.64 mm in diameter) and 25G needle (0.5 mm in diameter).

The diagnostic value and complications rate when using two needles were similar.

The reports from 2000s showed that the number of insertions about 5-6 times had enough cells to diagnose PC. European Association of Gastroenterology recommends: At least 5 insertion during each suction aspiration is safe and provide sufficient cells for cytological diagnosis.

1.4.3. The value of EUS – FNA

We use 2 types of needle aspiration (22G and 25G) in EUS machine and Linear probe. The result of EUS-FNA in the diagnosis of PC depends on location, size of the tumors, experience of endoscopist and availability of histopathologist. According to Yoshinaga, EUS-FNA in the diagnosis of PC shows that the sensitivities is 78% - 95%, specificity is 75% - 100%, PPV is 98% - 100%, NPV is 46% - 80% and Acc is 78% - 95%.

1.4.4. Complication of EUS - FNA

According to some reports about complication rate of EUS – FNA in the world, the complication rate is less than 2%. Infections: 0% - 5.8%. Bleeding: 1.3% - 4%. Perforation: 0.03% - 0.07%. Pancreatitis: 0% - 2%, the average is 0.29%. Bile peritonitis is a rare complication. If complications occur, the possibly reason is the needle punctures into the bile duct or the gallbladder. Tumor seeding along a needle: This is a very rare complication after fine needle aspiration, in the literature there have been reports of events.

EUS - FNA unrelated to increased risk of death, this procedure is considered quite safe.

1.5. Study on EUS and EUS – FNA in Vietnam

In 1995, EUS technique was first applied at the Department of Gastroenterology - Bach Mai Hospital in Vietnam. In recent years, some hospitals were equipped EUS machine and EUS is used in the diagnosis of gastrointestinal tract disease and bile – pancreatic. In general, the initial study results demonstrated important role of EUS in the diagnosis of gastrointestinal and bile - pancreatic diseases but EUS has not been performed regularly in our country.

CHEAPER 2: SUBJECTS AND METHODOLOGY

2.1. Subjects

2.1.1. Study location and duration

Study location: Bach Mai Hospital, Hanoi Medical University Hospital and Viet Duc Hospital.

Study duration: From January, 2011 to April, 2016.

2.1.2. Inclusion criteria

The subjects were enrolled in this study with three criteria

- Patients' age: Over 18 years old.
- EUS suspects of pancreatic cancer.
- The cytological result of EUS - FNA was PC or histopathological tumor of pancreatic after surgery (benign or malignant) or in cases cytology and histopathology after surgery were not tumors, patients were followed up continuously in 1 year to confirm the diagnosis.

2.1.3. Exclusion criteria

Subjects were excluded from the study if having: Pyloric, duodenal bulb or duodenal stenosis. Pancreaticgastrostomy, pancreatoduodenectomy, pancreaticojejunostomy. Pseudocysts. Prothrombin time < 50%, INR > 1.5. Platelets <50,000 G/L.

2.1.4. EUS – FNA criteria

2.1.4.1. EUS – FNA indication criteria

Pancreatic lesions on EUS, an image of focal lesion in the pancreas have the following characteristics: Density on EUS is different with tissue around the pancreas, existing on many different sections of EUS. Contours can be clear or unclear, but they are enough to distinguish and measure on EUS.

2.1.4.2. EUS – FNA exclusion criteria

The patients did not agree or puncture path was not safe (vessel interposed in the path between the needle and target, bleeding diathesis, and risk of tumor seeding).

2.1.5. EUS criteria for diagnosis of pancreatic cancer

According to the criteria of the Japan Society of Ultrasonics in Medicine (2013), the following criterias are used:

Tumor findings: Internal tumor: Contour - The contour is from clear to relatively unclear. The contour at the area where it is clearly visualized is irregular. Interior - Plain hypoechoic signals are observed in a small-sized tumor (≤ 20 mm), but as the tumor grows, it develops a central hyperechoic area. *Extratumoral finding*: Intrapancreatic - Basically similar to US findings. When stenosis of the caudal main pancreatic duct is identified, it is accompanied by irregularity of the main pancreatic duct. Extrapancreatic - Irregular bile duct stenosis, occlusion, disruption of layer structures of blood vessels, invasion to the adjacent organs such as the stomach, duodenum, bile duct or spleen, or lymphadenopathy around the bile duct, portal vein and arteries are observed.

2.1.6. Cytology criteria for diagnosis of pancreatic cancer

According to Bellizzi and et al: Anisonucleosis, irregular nuclear contours, enlarged nuclei, loss of honeycomb pattern/nuclear overlap, cellular discohesion, chromatin clearing and clumping, prominent nucleoli, background necrosis, mitotic figure.

2.1.7. Histopathology criteria and classification of pancreatic cancer

Simplification of World Health Organization Classification for Cytology Practice: Ductal adenocarcinoma including variants, acinar cell carcinoma, pancreatic endocrine neoplasm, solid-pseudopapillary neoplasm, pancreatoblastoma, mucus-producing cystic neoplasms, intraductal papillary-mucinous neoplasm, mucinous cystic neoplasm, serous cystadenoma. Nonepithelial tumors and Metastases.

2.1.8. Final diagnostic criteria

* *Determine diagnosis of pancreatic cancer:* Pancreatic cancer evidence by EUS - FNA or the histopathologic specimen after surgery.

* *Determine diagnosis of benign pancreatic tumor:*

Identified by histopathology after surgery and classify tumors according to WHO (2000).

* *The cases are followed up to have final diagnostic*: Result of cytology is not cancer and histopathology after surgery is not tumor. The patients are followed up one year to confirm the diagnosis.

* *Confirmation criteria for not pancreatic cancer after follow up*: Patients is still stable, no metastasis.

2.2. Study methods

2.2.1. Study design

Prospective study to describe a diagnostic test.

2.2.2. Sample size

$$N(SN) = \frac{TP + FN}{P}, \quad TP + FN = Z^2 \frac{SN\,(1 - SN)}{W^2}$$

The sample size for EUS: SN = 0,96 (According to Palazzo), p = 0,85 (WHO), w = 0,05. Applying the formula, the sample size for EUS is 70 patients.

The sample size for EUS - FNA: SN = 0,86 (According to Yoshinaga), p = 0,85 (WHO), w = 0,1. Applying the formula, the sample size for EUS - FNA is 54 patients.

We have chosen 73 patients for EUS and 62 patients for EUS – FNA.

2.2.3. Study methods

2.2.3.1. Research diagram

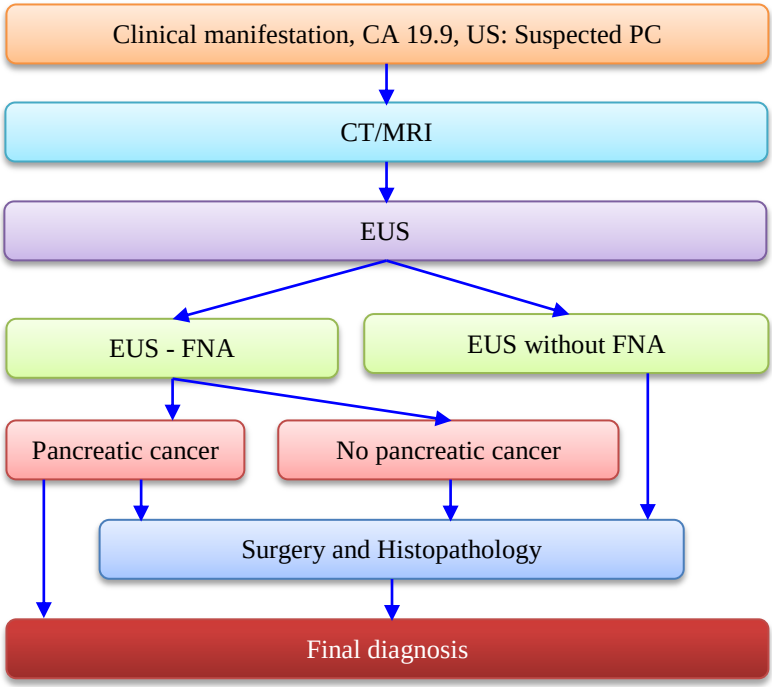

Figure 2.1. Algorithm for study design

2.2.3.2. Clinical examination and tests

Clinical examination was done and information was collected acccording to same medical record. Normal value of CA 19.9 is less than or equal to 37 (U/ml).

2.2.3.3. Abdominal ultrasound in diagnosis of pancreatic cancer

2.2.3.4. Abdominal CT in diagnosis of pancreatic cancer

2.2.3.5. Abdominal MRI in diagnosis of pancreatic cancer

2.2.3.6. Endoscopic ultrasonography and EUS – FNA

**** Study facilities***

EUS machines: Olympus GF - 20 and Fujifilm SU – 8000.

Linear probe with 5, 7.5, 10 and 12 MHz frequency.

Fine needle aspiration: 22G (Model GF-UM30P – Olympus).

Glass stems, tubers with formol 10%, absolute alcohol, syringes 10ml.

**** Assess results by EUS***

Internal tumor: Solid or cystic tumor, calcification. Tumor location: Head, body, tail of pancreas. Tumor number: One or many. Contour: Clear or unclear. Tumor size (cm): take the largest tumor size. Tumor structure: Hypoechoic, hyperechoic, heterogeneous echotexture.

Extratumoral, Intrapancreatic: Pancreatic parenchyma (normal or atrophy). MPD: Dilated or not. Calcification or not.

Extratumoral, Extrapancreatic: Invasive blood vessels, the adjacent organs. Bile duct, gallbladder: Dilated or not. Metastases: Lymphadenopathy, hepatic tumor, ascites or not.

**** Assess results by EUS - FNA***

There are 4 levels: Do not see the cells, less cells, benign cells and cancer.

2.2.3.7. Follow up and treat complications

2.2.3.8. Surgery

Histopathology after surgery is diagnosed at Histopathology and Cytology Center in Bach Mai hospital.

2.2.3.9 Follow up methods to determine the final diagnosis

The cases are not diagnosed pancreatic tumors (results of EUS - FNA and biopsy pancreatic are not pancreatic tumors): Patients are followed up and examined in 3rd, 6th, 9th month and 1 year later to confirm final diagnosis.

2.2.4. Data processing

Data was processed by SPSS 16.0 software on the computer, including algorithms: Chi- square, Youden Index (J) = max (Sn + Sp-1). Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (Acc).

2.2.5. Research ethics: The study complied all research ethics in medicine**.**

CHAPTER 3: STUDY RESULTS

3.1. Patients characteristics

3.1.1. Characteristics of age, gender

There were 56 PC patients (35 males, 21 females), the ratio of male/female was 1.7/1. The mean age was 60.6 ± 11.1 years old, the youngest was 20, the oldest was 79 years old.

3.1.2. Distribution characteristics of the disease by age group in pancreatic cancer

Age group under 40 had 1 patient with percentage of 1.8%. Age group 41 - 50 had 6 patients with percentage of 10.7%, 51- 60 age group had 19 patients with percentage of 33.9%, 61-70 age group had 21 patients with percentage of 37.5% and age group > 70 had 9 patients with percentage of 16.1%.

3.2. The clinical characteristics of pancreatic cancer

3.2.1. Symptoms of pancreatic cancer

The common symptoms of pancreatic cancer: Abdominal pain was 96.4%, fatigue was 87.5%, Anorexia was 87.5%, abdominal distension was 83.9% and weight loss was 73.2%.

3.2.2. Physical signs of pancreatic cancer

The percentage of patients with jaundice was 48.2%, dark urine was 48.2%, large gallbladder was 17.9%, hepatomegaly was 14.3%, abdominal tumors were 12.5% and diabetes was 14.3%.

3.3. Lab test characteristics of pancreatic cancer

3.3.1. CA 19.9

The mean level of CA 19.9 was 424.6 ± 578.4 (U/ml), the median of CA 19.9 was 193.6 CA (U/ml). CA 19.9 concentrations ≤ 37 (U/ml) had 16 patients accounting for 28.8%.

3.3.2. Characteristics of abdominal ultrasound

The mean tumor size was 3.7 ± 1.5 (cm). Hypoechoic structures rate was 73.5%. Tumor head was 67.3%. Tumor contour unclear was 91.8%. The irregular boundary was 53.1%.

Pancreatic parenchyma echotexture was 89.3%, dilated pancreatic duct was 48.2%, dilated bile duct was 55.4%, abdominal lymph nodes was 25%, liver metastases was 3.6%, no cases have ascites.

3.3.3. Characteristics of CT

The average tumor size was 3.9 ± 1.6 (cm). Hypoattenuating was 80.6%, little contrast was 72.2%, head pancreatic tumor was 69.3%, tumor contour unclear was 88.9%, and tumor boundary irregular was 52.8%.

Pancreatic parenchyma echotexture was 92.3%, dilated pancreatic duct was 59%, dilated bile duct was 48.7%, abdominal lymph nodes were 46.2% and no cases have ascites.

3.3.4. Characteristics of MRI

The average tumor size was 3.2 ± 1.5 (cm). Hypointense was 31.2%, little contrast was 87.5%. The head pancreatic tumor was 75%. Tumor contour unclear was 93.8%, tumor boundary irregular was 50% and solid tumor was 93.8%.

Pancreatic parenchyma echotexture was 88.2%, dilated pancreatic duct was 70.6%, dilated bile duct was 82.4%, abdominal lymph nodes were 41.2% and no cases have ascites.

3.3.5. Characteristics of Endoscopic Ultrasonography

The average tumor size was 3.4 ± 1.3 (cm) in which on 12 patients EUS detected tumor size ≤ 2 (cm) accounting for 21.8%, hypoechoic was 78.2%. Tumor head was 65.5%. Tumor contour unclear was 54.5%. The boundary irregular was 94.5% and soloid tumor was 92.7%.

Pancreatic parenchyma echotexture was 96.4%, dilated pancreatic duct was 58.9%, dilated bile duct was 55.4%, and abdominal lymph nodes were 48.2%.

Staging system of PC on EUS (AJCC 2010): Staging IA was 7.7%, IB was 13.5%, IIA was 21.1%, IIB was 40.4%, III was 15.4% and IV was 1.9%.

3.3.6. Characteristics of EUS – FNA

62 patients were performed by EUS - FNA include 94 times of puncture in which aspiration once was 30, twice was 32. Puncture into pancreatic head was 69.4%, body was 21.0% and tail pancreatic was 9.6%. Cytology results of cancer was 38 patients (61.3%).

3.4. Value of EUS in the diagnosis of pancreatic cancer

3.4.1. Value of EUS in the diagnosis of pancreatic cancer

EUS diagnostic value of pancreatic cancer on 73 patients for sensitivity was 92.9%, specificity was 76.5%, PPV was 92.9%, NPV was 76.5%, and Acc was 89.0%.

3.4.2. Value of EUS in the diagnostic PC with small tumor in size

There are 11 patients with tumors size ≤ 2 cm on the EUS. EUS diagnostic value with small size compared with histopathology after surgery for the sensitivity was 87.5%%, specificity was 66.6%, PPV was 87.5%, NPV was 66.6%, and Acc was 81.8%.

3.4.3. Value of EUS in the diagnosis of head pancreatic cancer

3.4.3.1. Value of dilated bile duct in the diagnosis of head pancreatic cancer

The risk of PC in patients with dilated biliary increased 5.5 times (OR = 5.5. 95% CI: 2.0 to 15.2) compared with no dilated biliary, the difference statistically significant with $p < 0.05$.

3.4.3.2. The value of "double sign" in diagnostic head pancreatic cancer

The risk head PC with "double sign" increased 3.5 times (OR = 3.5. 95% CI: 1.3 to 9.4) compared with those without "double sign", statistically significant difference with $p < 0.05$.

3.4.4. Value of EUS in the diagnosis of abdominal lymph nodes

Value of EUS in the diagnosis of abdominal lymph nodes compared with surgery: Sensitivity was 69.2%, specificity was 88.5%, PPV was 85.7%, NPV was 74.2%, and Acc was 78.9%.

3.4.5. Value of EUS in the diagnosis of vascular invasion

Value of EUS in the diagnosis of vascular invasion (CA, SMA or both) compared with surgery: Sensitivity was 60.0%, specificity was 97.9%, PPV was 75%, NPV was 95.8%, and Acc was 94.2%.

3.5. Value of EUS – FNA in the diagnosis of pancreatic cancer

41 patients who had histopathology after surgery and EUS - FNA. Value of EUS - FNA has compared with histopathology after surgery for sensitivity was 63.0%, specificity was 100%, PPV was 100%, NPV was 58.3%, and Acc was 75.6%.

3.6. Comparison EUS value to other methods in diagnostic PC

3.6.1. Comparison EUS value to other method in diagnostic PC

Table 3.1. Comparison diagnostic value of test methods.

Methods	n	Sn	Sp	PPV	NPV	Acc	J
EUS	73	92.9	76.5	92.9	76.5	89.0	0.694
EUS - FNA	41	63.0	100	100	58.3	75.6	0.630
CT/MRI	73	83.9	76.5	92.2	59.1	82.2	0.604
CA 19.9/100 (U/ml)	73	60.7	82.4	91.9	38.9	65.8	0.431
US	73	80.4	58.8	86.5	47.6	73.3	0.392

Comments: In the methods of diagnostic PC, value of EUS has the highest index J (0.694). Among the PC diagnostic methods, EUS - FNA specificity was 100%, and PPV was 100%.

3.6.2. Comparing EUS value and other tests with small tumor size

Table 3.2. Value of EUS, CT/MRI, SA in the diagnosis of small PC

Methods	n	Sn	Sp	PPV	NPV	Acc	J
EUS	11	87.5	66.6	87.5	66.6	81.8	0.541
CT/MRI	11	75.0	66.6	85.7	50.0	72.7	0.416
US	11	37.5	66.6	75.0	28.6	45.5	0.041

J index of EUS in the diagnosis of small PC is the highest (0.541).

3.6.3. Comparing tests value in diagnosis of abdominal lymph nodes

Table 3.3. Tests diagnostic value abdominal lymph nodes

Methods	n	Sn	Sp	PPV	NPV	Acc	J
EUS	52	69.2	88.5	85.7	74.2	78.9	0.577
CT/MRI	52	57.7	88.5	83.3	67.7	73.1	0.462
US	52	46.2	96.2	92.3	64.1	71.2	0.424

Comments: J index EUS is the highest (0.577).

3.6.4. Comparing tests value in diagnosis of vascular invasion

Table 3.4. Value of diagnosis of vascular invasion

Methods	n	Sn	Sp	PPV	NPV	Acc	J
EUS	52	60.0	97.9	75.0	95.8	94.2	0.579
CT/MRI	52	60.0	95.7	94.0	93.8	90.4	0.557
US	52	40.0	100	100	92.2	94.2	0.400

Comments: J index of EUS is the highest (0.579).

CHAPTER 4: DISCUSSIONS

4.1. The clinical characteristics of pancreatic cancer

In our study, the common symptoms of 56 PC patients: Abdominal pain, fatigue, Anorexia, abdominal distension and weight loss. These symptoms are main chief complaints of patients.

Table 4.1. Some clinical manifestations

Author	n	Clinical manifestation		
		Abdominal pain	Jaundice	Weight loss
Our study	56	96.4%	48.2%	73.2%
B.C.Huynh	111	69.4%	61.3%	24.3%
Porta	185	79.0%	56.0%	85.0%
D.T.Son	271	63.4%	77.5%	90.0%
N.T.Binh	42	78.6%	78.6%	81.0%
Alvarez	126	50.0%	43.0%	

4.2. Value of EUS in the diagnosis of pancreatic cancer

4.2.1. The number, size and location of the tumor

In case of PC which EUS failed to diagnose, it can be explained as follows: In this case, tumor was homogenous compared with surrounding pancreatic parenchyma so on EUS, it could not differentiate tumor structure and remaining pancreatic parenchyma.

Chronic pancreatitis and pancreatic cancer

Some difficulties in the differential diagnosis between chronic pancreatitis and PC may be due to the following reasons: Clinical manifestations some cases of chronic pancreatitis and PC are similar. Some PCs also have calcifications, pancreatic cysts and confuse necrotizing pancreatitis, PC often has chronic pancreatitis localized areas. Mujica et al recommends: surgery should be performed in suspected cases of pancreatic tumors in patients with chronic pancreatitis. In case of chronic pancreatitis with tumor lesions, we always have to be careful, considering whether or not accompanied by PC? Because the tumor lesions are often characterized assume similar cancer. This may also explain why among our 73 patients, but there were 12 patients with chronic pancreatitis with 16.9% ratio, a relatively high rate of misdiagnosis PC and chronic pancreatitis. The chronic pancreatitis has a very high risk of PC. Therefore, patients should be closely followed up to screen for the malignancy in chronic pancreatitis, especially when there was the lesion inflammation in the pancreas.

Notably, EUS has diagnosed 12 cases PC (21.8%) of small size (≤ 2 cm). This result demonstrates EUS is a imaging method that the ability to detect pancreatic tumors are quite small. Our study is similar to some other studies in the world: Yasuda I, Yasuda K and Gress.

Tumor location on EUS

Head of pancreatic tumor was 65.5%. The results of this study were similar to the results of our study that the majority of the pancreatic cancers are the pancreatic head tumors.

4.2.2. Pancreatic cancer echotexture

In clinical practice, there are several factors contributing to miss pancreatic tumors

Histological characteristics: In multi - center study, 20 cases of PC omitted, while 12 cases of EUS misdiagnosis was chronic pancreatitis.

Several other factors also increases false - negative values such as invasive carcinoma, acute pancreatitis (in the first 4 weeks), then the back pancreas (dorsal/ventral) hypertrophy often loudly so the evaluation EUS was difficult lesions. Most cases of pancreatitis reduced sensitivity of EUS in diagnostic PC. The pancreatitis (acute or chronic) changes the density of sound in normal pancreatic tissue, normal tissue becomes irregular hypoechoic and the lobe of the pancreas with an imaging similar mass lesions. When this situation appears, the contour of tumor becomes unclear or do not see, the abdomen pancreas (ventral) is normal (usually hypoechoic).

Lesion location: With hypoechoic natural surrounding normal pancreatic abdominal large decreases diagnostic sensitivity in small tumors such as uncinated process, pancreatic tail side are missed location for small tumor size. Missed lesions in position (due to incomplete examination) are more common than histopathology.

Some results of the study of the echotexture of pancreatic cancer

According to Tran Van Hop et al, the hypoechoic mass was 81.2% among PC. According to Le Thu Hoa et al, hypoechoic or heterogeneous tumors was 86.1%. According to Furukawa, hypoechoic in PC was 73.7%. D'Onofrio et al, lesions of PC was mainly hypoechoic.

The results of our study (hypoechoic in PC was 78.2%) is similar to findings of the authors in the world and Vietnam: The lesions in PC are mainly hypoechoic.

4.2.3. Value of EUS in the diagnostic abdominal lymphadenopathy

The results of our study: The sensitivity of the EUS (69.2%) is higher than CT/MRI (57.7%) and US (46.2%) in the diagnostic abdominal lymphadenopathy.

In the systematic review and meta - analysis of Gonzalo: Only one study said that EUS was better than CT in diagnosisd lymph nodes (93.1% versus 87.5%) but most studies agreed that CT and EUS have equal efficacy in the diagnosis of stage N of PC. According to Kulig et al, EUS's accurate diagnosis abdominal lymph nodes was 87.5%. According to Gress, EUS's diagnostic abdominal lymphadenopathy in sensitivity, specificity and diagnostic accuracy were approximately 85%, 100% and 89%. According to Iglesias et al in analysis of 11 studies involving 678 patients: EUS and CT accurate diagnosis of lymph node was 72% - 92%. According to Nawaz, analysis of 16

studies involving 512 patients showed: EUS diagnose abdominal lymphadenopathy of sensitivity was 69% (95%, CI: 51-82%), a specificity was 81% (95%, CI: 70 - 89%), PPV was 81% (95%, CI: 72-88%), NPV was 65% (95%, CI: 56-73%) and diagnostic accuracy was 83% (95%, CI: 79-86%).

4.2.4. Value of endoscopic ultrasound in the diagnostic invasive vascular

Invasive vascular assessment is one of the criteria for staging PC; thereby it helps to determine the treatment plan and prognosis. So far, the definition of invasive evaluation vascular has not yet to be agreed between the authors in the literature. Assessment invasive tumor on surrounding vascular can be performed by EUS: Observing tumor contact with the vascular or lose the boundary between the tumor and the blood vessels, intravascular tumor, embolization (thrombosis) or vascular wrap tumor. With these standards, EUS invasive diagnostic vascular with an accurate diagnosis is 100%, while CT is 80%. EUS sensitivity in the diagnosis of invasive vascular is from 73% to 90%.

In our study, the sensitivity of EUS in the vascular invasive diagnosis was 60%, CT/MRI was 60% and US was 40%. In the systematic review and meta-analysis of Iglesias et al, EUS in the vascular invasive diagnosis had a sensitivity of 42% - 91%, a specificity of 89% - 100% and diagnostic accuracy of 40% - 100%.

Value comparisons between CT/MRI and EUS in vascular invasive diagnosis: Some authors suggested that EUS vascular invasive accuracy diagnosis was better than CT. Some of other authors argue that CT is better than EUS and MRI (MRI have similar values EUS). The meta-analysis reports from 29 studies (1038 patients) showed that sensitivity of EUS vascular invasive diagnosis is about 73% and specificity of 90.2%. According to Nawaz (2013) (analysis of 25 studies involving 886 patients), EUS vascular invasive diagnosis: Sensitivity was 85% (95% CI: 76-91%), a specificity was 91% (95% CI: 85-94%), PPV was 87 % (95% CI: 81-92%), NPV was 87% (95% CI: 81-92%) and diagnostic accuracy was 94% (95% CI: 92-96%).

Through analysis of the results of research in the world in terms of value vascular invasive diagnosis showed that: Results of EUS in the diagnostic PC partly depends on the experience and skills of endoscopist. The advent of CT/MRI machines modern is vascular invasive diagnostic value of EUS, and CT/MRI are similar.

4.2.5. Value of EUS in diagnosis of pancreatic cancer

In the recent 25 years, EUS is the most advanced technique in gastroenterology field and has overcome the disadvantages of abdomen ultrasound. Even EUS can diagnose small lesions 2-3 mm in pancreas. Compared with US, CT, MRI, the EUS can observe pancreatic parenchyma the better. Some report from the 1990s shows: EUS in the diagnostic PC has higher sensitivity (98%) than other methods (CT is 80%, US is 75%). In the diagnosis of pancreatic tumors are smaller than 2 or 3 cm: US and CT have dropped 29% sensitivity. However, since the machine is CT multi probe diagnostic is sensitivity from 97% to 100%. In recent years, a new generation MRI in the diagnosis of PC has a sensitivity of 83% - 87% and a specificity of 81% - 100%.

As reported by the Gress et al, EUS accurate diagnosis is from 90% to 100%. If the tumor is small, EUS sensitivity is 100% compared with 66% of CT, EUS specificity is from 88% to 100%. According to the report's analysis Bipat et al (26 reports), diagnostic value of US, CT and MRI in the diagnostic PC, respectively: Sensitivity was 76% (95% CI: 69-82), 86% (95% CI: 81-89) and 74% (95% CI: 71-89); specificity was 75% (95% CI: 51-89), 79% (95% CI: 60-90) and 82% (95% CI: 67-92). The results of our study are similar Bipat and Gress's report.

Shrikhande et al showed that: EUS had a highest sensitivity and specificity in diagnosis highest of pancreatic tumor size $\leq$ 2cm. EUS findings with small tumor size: The Palazzo (n = 7) had a sensitivity of 100%, Yasuda (n = 7) had the sensitivity of 100%, Nakaizumi (n = 8) had a sensitivity of 88%, Legmann (n = 6) had a sensitivity of 100%, DeWitt (n = 12) had a sensitivity of 88.3%. The result of our research, EUS diagnosis of PC small tumor size ($\leq$ 2 cm) for a sensitivity of 87.5% and diagnostic accuracy (81.8%) is higher than the accuracy diagnosis CT/MRI (71.4%) and US (55.6%).

4.3. Value of EUS – FNA in the diagnostic pancreatic cancer

4.3.1. About technique

**** Advantage***

62 patients were performed by EUS - FNA, we found this technique has the following advantages:

During the procedure, the endoscopist always saw and controlled the path of the needle on the ultrasound screen. Therefore, the speci-

men can be obtained at the desired location. Due to this advantage (combined with Power Doppler), one can aspirate most of the lesions localized in the pancreas, including small lesions, while avoiding major blood vessels, necrotic lesions, pancreatic duct, calcification. So the results improved the accuracy of diagnosis, reduced complications and false negative values.

In this study, we have aspirated puncture in different locations of the pancreas (head, body and tail pancreas). Also we saw the tip of needle, defined boundaries lesions so we could determine the damaged area in the process of puncture and aspiration.

We performed 94 times puncture for 62 patients. Although, all puncture times are corrected tumor location but cytology results have 3 patients without pancreatic cells with only smear red blood cells, white blood cells and fewer of the gastrointestinal tract cells.

EUS - FNA is a highly safe technique. With 73 times ofEUS and 94 times of EUS - FNA, the patients have not had complications. There are some patients with post EUS - FNA have mild epigastric pain, but symptoms recovered after the first 24 hours. If compared with the complications of pancreatic biopsy that EUS - FNA complications is much lower (if there are complicationst, they are ofter milder). According to a report by the authors in the world shows that EUS is a relatively safe procedure. EUS is the technique safe and have a very low with rate of 0% - 0.4%, if any complications are mainly due to duodenal perforation. EUS - FNA has the rate of acute pancreatitis is 0% - 2%, perforation is 0.03%, infection is 1%, bleeding is 1.3% - 4%. As reported by the Association of Gastrointestinal Endoscopic Europe, EUS - FNA is a safe procedure with complication rate of approximately 1%; the common complications are infections, bleeding and acute pancreatitis. The complications of cyst EUS - FNA is rather than solid tumors. Incidence of complications after needle aspiration by 22G and 25G are similar. Wiersema and et al report: Complications of EUS - FNA was 0.5% (95%, CI: 0.1 to 0.8%) for solid tumors and 14% (95%, CI: 6-21%) for cysts. Eloubeidi et al follow up 4909 patients after solid tumors EUS - FNA (in 4 years at 19 centers) showed that complications occur in 14 pancreatitis was 0.29% (95%, CI:0.16 to 0.48). The cases hospitalized an average of 3 days of treatment and stability. Eloubeidi et al follow up 355 patients EUS - FNA: Complications (9 patients), rate was 2.54% (95%, CI: 1.17

to 4.76), acute pancreatitis was 0.56%; fever was 0.56% and no any bleeding, perforation or death. EUS - FNA have a lower incidence rate than CT biopsy (1% - 2% versus 5%). While the complications rate of pancreatic biopsy: The Tyng and et al, following complications rate of pancreatic biopsy was 8.7%. According to Amin et al, follow up 372 patients with pancreatic biopsy guided US and CT the complications were 4.6%.

EUS - FNA: Fine needle aspiration is small (needle diameter < 1 mm) so damage of pancreas is only minimum. Therefore, a patient is less painful and the risk of pancreatic fistula is lower than biopsy of pancreas.

EUS - FNA also allows shortening diagnosis of focal lesions in the pancreas. In these cases, in only 30 minutes to 1 hour we could have the results of cytological diagnosis. The time to get results of histopathological diagnosis takes a minimum of 72 hours. Thus, EUS - FNA has reduced the time of diagnosis. Thus, it helps to shorten the number of days in hospital and helps physicians to decide the next steps. Therefore, it creates effective economic benefits. Compared with pancreatic biopsy guided CT, with the EUS – FNA, patient and medical staffs are not contaminated radiation.

With such advantages, technical EUS - FNA is method considered priority in the diagnostic pancreatic cancer.

**** Disadvantages***

Besides the advantages mentioned above, the EUS- FNA also has disadvantages: EUS well as EUS - FNA is invasive technique and difficult to perform, cost of EUS and EUS- FNA remain high.

4.3.2. Several factors affect the success of EUS- FNA

**** Needle aspiration***

The purpose of the select needle aspiration is the desire to get the best diagnostic results, in order to avoid false negative maximum, and the complications of the procedure.

According to Lee et al, comparing the specimen sample quality after puncture by 22G and 25G needle showed that: The difference in the quality of samples 22G and 25G needles was not statistically significant.

According to Yusuf et al, studied 842 patients are diagnosed PC by EUS - FNA was divided into 2 groups: 22G needle aspiration (540 patients) and 25G (302 patients). The results showed that: diagnostic value of the 2 groups were similar; No complications occurred with 25G nee-

dle aspiration group, while in the 22G needle aspiration group, 2% of patients with pancreatitis. To explain, the author said that: Because 25G needles has diameter smaller 22G needles so 25G needle aspiration would be less injure than the 22G needle. However, differences complication rate of 2 groups had no statistical significance.

**** The number of passes***

According to LeBlanc et al (the number of passes EUS - FNA): If the one pass, the sensitivity was 17%, but if the 7 passes the sensitivity was 87%. Therefore, the authors recommend puncture at least 7 passes. Association Gastroenterology European recommends: At least 5 passes during each suction would be enough safety and accuracy of the method. Petrone et al: Number of puncture at least 5 - 7 passes would ensure adequate specimens to diagnose pancreatic cancer.

In this study, we chose the needle 22G and 5 -7 passes in a suction.

To solve the problem: Patients may need to puncture again or not? We conducted a preliminary assessment of specimens collected with the naked eye. The basis of this comment is based on the following observations: Specimens of pancreatic tumors are white or yellowish. When staging the slide shows this specimen chewy, not too finely as acne or pus, necrotic. So, if the slide is only just saw the blood or fluid, mucus or acne, we should puncture again.

In some cases the specimens obtained are wired, the specimens were put into a test tube with 10% formalin to do histopathological diagnosis. Some other cases, if the specimens more we wash the needle and for specimens into test tube for cell-block to strengthen, complement the results of cytological diagnosis.

**** Tumor size***

If the tumor size is bigger then the sensitivity of the aspiration is higher for PC. The results of our study showed that tumor stage T3 result in aspiration of cancer cells is the highest with ratio of 52.6%. This can be explained as follows: T3 stage is not too big tumor stage so that it is not necrotic tumors and tumors too small so it is accuracy puncture. Therefore, the results accurately aspirate is the most. With oversized or necrosis often in mass so needle aspiration should be able to necrosis. Therefore, diagnostic result is lower sensitivity and false negative value is higher.

**** Tumor structure***

Fine needle aspiration for solid tumors is higher sensitivity than cysts. Fine needle aspiration with hypoechoic structure is higher sensitivity than hyperechoic or heterogeneous. Because of area hyperechoic or heterogeneous are areas of fibrous or calcified then cytological result increase value of false negative and decrease sensitivity.

**** The path of the needle***

Choose the path of the needle affects complication and diagnostic value of the method. To minimize complications and false negative value of the method is in the process of aspiration must choose the path of the needle to avoid large blood vessels, solution, calcification. Distance from the digestive tract to injury aspiration should be as much safe as possible. Because, with the shortest possible distance (from the lesion to the gastrointestinal tract), the adjustment of the needle into the lesion better, and less damaging to the surrounding tissue as the puncture needle.

**** The patient age***

Pancreatic cancer is diagnosed mainly in elderly patients (≥ 60 years old) who have parenchyma with tend atrophy and fibrosis gradually with age, especially in patients with fibrosis chronic pancreatitis. Therefore, in older patients, the aspiration ability to get specimen of pancreas to be difficult.

**** The role of the physician***

The role of the endoscopist: Many reports showed that the experience and skill of the endosonographer was a factor affecting the results identified EUS and EUS-FNA. If endosonographer has more experience and good technique, the specimen obtained by EUS - FNA would be better. In our research, specimen of 3 patients are only erythrocytes, mucus without the pancreatic cells is the aspiration cases at the initial stage of research, the period that experienced our puncture was not much. We show that: EUS - FNA diagnosed PC at a later stage of the research is higher than the first phase study.

Although the cells by vacuum suction, vacuum suction pressure by the needle is always control in lesion, but because needle aspiration is small to take cells so difficult. So the specimen depends on the skill and experience of the endosonographer.

Aspiration needle is long and small together (1450 mm long, needle diameter < 1 mm). Therefore, to puncture the needle into the correct lesion, adjust the needle, the path of needle is always difficult.

To increase the sensitivity, reducing false negatives need to insert the needle into the correct position lesion to avoid ensure (blood vessel, necrosis lesion, pancreatic duct, pancreatic cysts ...) requires the endosonographer must be experienced and good skills. If the endosonographer has more experience, the success rate is higher.

The role of the pathologist: One-site interpretation of the pathologist increase the sensitivity, reduce the false NPV, and diagnostic duration.

If the pathologist has to dye and read the results together, the sensitivity increased from 10% to 15%. Assessment immediately cytological diagnosis does not only increasing accurate diagnosis but also reduces the number of section and complications of the procedure.

The success of EUS - FNA also depends on the experience of the pathologist. Unlike percutaneous pancreatic biopsy, specimen from EUS - FNA mixed epithelial cells of the GI tract. Therefore, easily mistaken epithelial cells of the gastrointestinal tract and pancreas cells.

Savoy and et al showed that: If EUS - FNA without on-site interpretation of the cytologist, the specificity was only 75%, but if the cytologist did together with endoscopist then specificity up to 100% and the diagnostic accuracy was 95%.

American Society Endoscopes recommended: Observe good lesion, select a reasonable needle size and technical EUS-FNA correct lesion will increase the accuracy of diagnosis and decreased complications of procedure.

4.3.3. Value of EUS – FNA in diagnosis pancreatic cancer

The reports in the world show that sensitivities for EUS-FNA varies widely, from 60% to 100%, with a mean of about 80%, while the specificity again approaches 100%.

The results of our research: The sensitivity of EUS - FNA is not high (63%) compared with some other authors, may be due to: Our experience is not much and without one-site interpretation of the pathologist.

CONCLUSIONS

The study was conducted from January, 2011 to April, 2015. 73 patients were enrolled study including 56 PCs. We have some conclusions:

1. The clinical, test characteristics of pancreatic cancer

1.1. *The clinical characteristics of pancreatic cancer*

The common symptoms of PC: Abdominal pain was 96.4%, fatigue was 87.5%, Anorexia was 87.5%, abdominal distension was 83.9% and weight loss was 73.2%.

1.2. *The test characteristics of pancreatic cancer*

The CA 19.9 characteristics of pancreatic cancer: The 71.2% of PC have CA 19.9 > 37 U/ml. The median value was 193.6 U/ml. CA 19.9 was 100 U/ml, clinical implications for diagnosis of PC.

The US characteristics of pancreatic cancer: Solid tumors were 93.3%, irregular contour was 91.8%, hypoechoic mass was 73.5%, dilated pancreatic duct was 52.1%, and dilated biliary was 55.4%.

The CT characteristics of pancreatic cancer: Irregular contour was 88.9%, hypoechoic mass was 80.6%, little contrast tumors were 72.2%, and dilated pancreatic duct was 59.0%.

The MRI characteristics of pancreatic cancer: Irregular contour was 93.8%, little contrast mas was 87.5%, dilated pancreatic duct was 70.6%, and dilated biliary was 82.4%.

The EUS characteristics of pancreatic cancer: Pancreatic head tumor was 65.5%, hypoechoic mass was 78.2%, irregular contour was 94.5%, irregular boundary was 54.5%, dilated pancreatic duct was 58.9%, and dilated biliary was 55.4%.

2. Value of EUS and EUS- FNA in diagnosis of pancreatic cancer

2.1. The safety of EUS and EUS - FNA

EUS and EUS - FNA in the diagnosis PC were the safe methods.

2.2. Value of EUS in the diagnosis of pancreatic cancer

Value of EUS in the diagnosis of pancreatic cancer: Sensitivity was 92.9%, specificity was 76.5%, and accuracy was 89.0%.

Value of EUS in the diagnosis of PC with small tumor size ($\leq$ 2 cm): Sensitivity was 87.5%, specificity was 66.6%, and accuracy was 81.8%.

EUS were higher value method than US, CT/MRI in the diagnostic pancreatic cancer and PC with small tumor size.

2.3. Value of EUS – FNA in the diagnosis of pancreatic cancer

Value of EUS – FNA in the diagnosis of PC: Sensitivity was 63.0%, specificity was 100%, and accuracy was 75.6%.

EUS - FNA were higher value method than US, CT/MRI in the diagnostic pancreatic cancer.

RECOMMENDATIONS

Through this study we would recommend:

1 - For patients with persistent signs of abdominal pain increasing, > 40 years of age, treatment was not relieved, US suspected pancreatic tumor, CA 19.9 > 100 U/ml, they should be transferred to specialized hospital for computed tomography or magnetic resonance and endoscopic ultrasound for early diagnosis of pancreatic cancer.

2 - EUS and EUS - FNA in the diagnosis of PC was relatively accurate and quite safe. This technique should be widely available to Internal Gastroenterologist, Surgeon and Oncologist for the diagnosis and treatment planning orientation for pancreatic cancer.

PUBLICATIONS

1. Nguyen Truong Son (2014). Preliminary Result of Endoscopic Ultrasonography – Guided Fine Needle Aspiration in the diagnostic pancreatic cancer. *Vietnam Association Gastroenterology Journal*, IX (37), 2416 - 21.
2. Nguyen Truong Son (2014). Initial comments role of endoscopic ultrasonography in the diagnostic pancreatic cancer. *Journal of practical medicine*, 8(928), 169 – 72.