Role of ultrasound guided fine needle biopsy, EUS and serum CA19-9 level in diagnosis of Pancreatic Masses

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Abstract:Objective: Pancreatic Cancer is a very aggressive tumor with an extremely poor prognosis. Early diagnosis, accurate preoperative staging and better adjuvant treatment remain a challenge. Abdominal ultrasound, abdominal CT, EUS and ERCP are common tools used for imaging of pancreatic cancer. Fine needle aspiration has made significant contribution to the diagnosis of cancer pancreas. The aim of the present work was to evaluate the role of ultrasound guided fine needle aspiration cytology (FNAC) in the diagnosis of pancreatic masses and in the differentiation of cancer pancreas from benign lesions. In addition to that, the level of serum CA19-9 was measured to assess its accuracy in differentiating cancerous from benign lesions. **Methods:** This cross section descriptive study included 40 patients with pancreatic lesions. They were subjected to full clinical examination, laboratory tests (including serum level CA19-9), abdominal ultrasound, percutaneous sonar guided FNAC of pancreatic lesions, endosonography and surgical interference (was done to 32 patients). **Results:** Thirty three patients proved to have pancreatic malignancy while seven patients proved to have pancreatitis. Ultrasonography (US) showed a sensitivity of 70%, specificity of 86% and accuracy of 73% for malignancy detection. Adding CA19-9 to ultrasound raised to sensitivity to 94%, specificity remained 86% and accuracy to 93%. Adding FNAC to US raised the sensitivity to 85%, specificity remained 86% and accuracy to 91%. EUS showed a sensitivity of 90%, specificity of 100% and accuracy of 91%. Adding CA19-19 to EUS showed a sensitivity of 94%, specificity of 100% and accuracy of 91%. Adding FNAC to EUS showed a sensitivity of 97%, specificity of 86% and accuracy of 97%. **Conclusion:** The combination of EUS, serum CA 19-9 level and Sonar guided fine needle aspiration showed accuracy of 97% in diagnosis of pancreatic lesions. These investigatory tools are cheap and available and thus may be an excellent alternative to EUS guided fine needle aspiration which is expensive and available in only few centers.
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1. Introduction

Pancreatic cancer is a very aggressive tumor with an extremely poor prognosis; less than 20% of affected patients survive the first year and only 4% are alive 5 years after diagnosis(**Gudjonsson** et al 1987)(11).More recent studies have found improved five and seven year survival rates of 19% and 11% respectively in selected surgical patients. Yet, despite this improvement, pancreatic cancer is the fourth leading cause of death due to cancer in both men and women (**Ahmed** et al.,2000)(2)

Early diagnosis, accurate preoperative staging and better adjuvant treatment remain a challenge (**Blumeke** et al 1995).[3]At present, the common tools used or imaging of pancreatic cancer are CT., abdominal ultrasound, endoscopic ultrasonography (EUS) and ERCP. Ultrasonography is used for initial imaging evaluation of patients with suspected pancreatic disease. However, ultrasound imaging may not be abnormal until the tumor is large and unresectable. In many occasions, the differentiation of cancer from chronic pancreatitis is challenging exposing the patient to either delay in diagnosis or aggressive intervention.

Ultrasound guided fine needle aspiration (US-FNA) has made significant contribution to the preoperative and intraoperative diagnosis of cancer patients since it is sensitive, rapid, cost effective and relatively atraumatic method for evaluating cancer pancreas. The histopathological diagnosis permits the identification of patients with malignancies other than pancreatic adenocarcinoma or benign masses in which surgery can frequently be avoided.

Endoscopic ultrasound [EUS] was introduced in the early 1980s. Today, EUS is the most accurate modality for local staging of gastrointestinal cancers. It accurately stages pancreatic masses and EUS guided fine needle aspiration biopsy has been proposed as a complementary technique to obtain tissue diagnosis with an accuracy of 85%. Its accuracy rates for staging superior to those achieved by CT scan and MRI [**Ahmed *et al.*,2000**](2).CA19-9 is the most useful marker in patients with suspected pancreatic cancer [**Shahangian *et al.*,1989**](15). Its

level correlates with the tumor burden and level of cancer expression and thus is often normal in patients with small tumors. CA19-9 represents the least expensive of the noninvasive methods for determining the success of surgical procedures and the behavior of the disease during radio chemotherapy.

The aim of the present work is to evaluate the role of EUS, serum CA19-9 level and US-FNA in the diagnosis of pancreatic masses and in the differentiation of cancer pancreas from chronic pancreatitis.

2. Subjects and Methods

This study was conducted on forty patients presenting to Kasr Al Aini hospital, Internal Medicine Department, El Ebrashi Unit for gastroenterology and Hepatology. These patients presented with obstructive jaundice, abdominal pain or loss of weight.

Patient's ages ranged from 35-65 years with mean of 56.3[±7.19] years. There were 25 male patients, their ages ranging from 36-64 years, with a mean of 57.6[±6.54] years. There were 15(37.5%) females, their ages ranging from 38-65 years with a mean of 54[±7.85] years. All patients participated in the study after fully explaining to them the implications of the procedure and a written consent was obtained from all patients.

Patients were subjected to: 1) **clinical evaluation** especially for symptoms and signs of biliary obstruction, 2) **laboratory tests** including total and direct bilirubin, AST, ALT, alkaline phosphatase, prothrombin time and concentration, serum albumin, fasting blood glucose, CBC, blood urea and creatinine and serum level of Ca19-9, 3) **abdominal ultrasonography** using Toshiba echosee ultrasonography machine to detect dilatation of common bile duct, common hepatic duct and intra-hepatic radicles and also to detect pancreatic masses, liver metastasis, ascites and enlarged lymph nodes, 4) **Percutaneous sonar guided fine needle** aspiration of pancreatic lesions. It was done for all patients under complete sonographic guidance using a biopsy attachment. The patient must be fasting for at least 8 hours. Platelet count must be more than 70,000 and prothrombin concentration should be more than 50%. 5) **Endosonography** examination was carried out utilizing the forward oblique viewing Olympus video machine GF-EU-M200 (keymed ltd, Essex, UK) having a 360 mechanical radial scanner with dual frequency switchable from 7.5 MHz to 12 MHz. It was performed in 32 out of the 40 patients. Endosonographic criteria for vascular involvement were: Loss of the hyperechoic vessel wall/tumor interface, direct visualization of the tumor in the vascular lumen and non-visualization of a major portal vessel in the presence of collateral vessels.

Surgical Interference

Surgical interference was done to 32 patients. It was not done to five patients diagnosed as having benign lesions and 3 patients with distant metastases or bad general conditions. In patients undergoing surgical interference, surgical findings were used as the gold standard for calculating the sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV) of the different diagnostic modalities as abdominal ultrasound, EUS, sonar guided biopsy and CA19-9. In benign patients not undergoing surgical interference, lesions were followed up for a period of ten months, with no change in size or appearance of new lesions in the pancreas or elsewhere as the liver, peritoneum or lymph nodes. Routine preoperative preparation was done. Bilateral subcostal incision was used for cases suspected to have operable pancreatic tumors, while midline incision was used for those cases suspected to have inoperable tumors. Pancreatic odoudenectomy (Whipple operation) was performed for operable pancreatic tumor, while cholecystojejonostomy was done for inoperable tumor causing biliary obstruction. The surgical findings were correlated to that of the diagnostic procedures as regard the diagnosis and tumor staging.

Statistical Analysis

Analysis was performed using Student t test, Spearman correlation coefficient test, Chi square test and logistic regression. Sensitivity, specificity, PPV, NPV and diagnostic accuracy were done for all of the diagnostic modalities as abdominal ultrasound, EUS, sonar guided biopsy and CA19-9.

3. Results

Forty patients with pancreatic masses were included in this prospective study. They were 25(62.5%) males, and 15(37.5%) females, with mean age of 56.3 (+7.19) years. Thirty three patients proved to have malignant pancreatic disease, while seven patients proved to have benign disease; pancreatitis. Of the 33 malignant patients 21 (63.6%) were males, their ages ranged from 47 to 64 years, with mean 57.24 (± 6.21)years, while 12 (36.4%)patients were females, their ages ranged from 47 to 64 years, with mean of 55.25 (±7.71)years. Ages of 7 patients with benign lesion ranged from 35-61

with mean 51.9 (+ 10.12), there was no statistical difference between their mean ages and mean age of patients with malignant pancreatic masses. The clinical data of our patients are presented in **(Table 1).**

Ultrasonography was done for all patients. It showed the pancreatic lesions in the form of a mass, diffuse pancreatitis, swollen head or complex cystic lesions. Of the 7 benign lesions 6 appeared as diffuse swelling, while of the 33 malignant lesions 22 appeared as focal defects, 8 were as a swollen head, 2 showed diffuse swollen pancreases and one was a cyst.

Table 1: Clinical picture of all the patients

	MALIGNANT	BENIGN	TOTAL
Jaundice	19	3	22
Abdominal pain	19	6	25
Weight loss	22	2	24
Jaundice + Weight loss + pain	3	-	3
Jaundice + weight loss	11	1	12
Jaundice + Abdominal pain	6	2	8
Abdominal pain + weight loss	13	1	14

Endosonography was done for only 32 patients, of whom 2 were eventually benign, which appeared as swollen head. The remaining 30 lesions proved to be malignant. They appeared in the form of either mass in the head in 21(70%) patients or in the body in 5 of 30 patients (17%). Swollen head was noted in 2(5%), cystic mass in the head in 1 and pancreatitis in another one patient. In the patient who had pancreatitis appearance surgery showed a small papillary mass with associated pancreatitis in the rest of the pancreas.

Surgical exploration was done in 32 patients, two patients proved to have pancreatitis while 30 patients proved to have malignant pancreatic masses. The other three patients with pancreatic malignancy were not operated upon due to metastases or poor general condition. Intraoperative staging revealed the presence of 14 operable masses with radical excision (Whipple operation). Sixteen patients were inoperable, choledoco-jejunostomy was done in eight patients for fear of progressive jaundice, while eight patients were left without more surgical procedure and were sent for chemotherapy as the tumor was away from the pancreatic head and not causing biliary obstruction.

Table 2: Final diagnosis of our patients

	Final diagnosis
Pancreatitis	7
Adenocarcinoma	27
Cystadenoma	2
Lymphoma	1
Myxoma	1
Neuroendocrine tumor	2
Total	40

Staging using endosonography was done using **TNM staging system** according to the American Joint Committee of cancer **(AJCC).** Staging was done in 30 patients, of whom 14(47%) were operable and 16(53%) were inoperable.28 patients had both endosonography and surgery.

No statistical difference between endosonography T staging and surgical T staging. **(Table 3)**

Table 3: Difference in T staging between EUS and surgery

stage	**T1**	**T2**	**T3**	**T4**
Surgery	1	6	11	10
EUS	0	8	15	5

Chi-square = 4.310; DF = 3; $P = 0.229$ (NS)

There was no difference in N staging between endosonography and surgery. **(Table 4)**

Table 4: Difference in N staging between EUS and surgery

	No	N1
endosonography	18	10
surgery	13	15

Chi-square =1.156; DF = 1; $P = 0.282$ (NS)

Stages T4 or M1 are advanced stages and are inoperable. Some tumors with stage N1 were also inoperable. Endosonography is not oriented for M staging but only for T and N staging. Endosonography underdiagnosed T stage in six patients. Also six patients proved to have distant metastasis, two of whom were diagnosed by ultrasonography, one metastasizing to the liver, the other to the Paraaortic lymph nodes. In one case metastasis to the lung was detected by CT chest, the remaining three patients were diagnosed during operation to have liver metastases. Endosonography also understaged N in five cases.

The tumor marker CA 19-9 was determined in all 40 patients. The serum levels in benign lesions were all normal ranging from

19-30 Iu/ml with mean of 24.57 (±4.32), normal value was up to 37 Iu/ml. CA19-9 levels in 33 malignant patients ranged from zero to 5000 with mean of 755.92 (±1397.25) and was significantly raised (P<0.0001) compared with levels in benign lesions.

Among malignant patients there were 11(33.3%) patients with normal CA19-9 levels (≤37) and 22 patients (67%) with levels more than 37 Iu/ml.

CA19-9 was not elevated in any patient presenting with pancreatitis (although it may be elevated especially in association with obstructive jaundice, however some of our patients had ERCP with stenting before measuring CA19-9 level).

CA19-9 had a sensitivity of 67%, a specificity of 100%, a positive predictive value 100% and a negative predictive value of 39 % for detection of malignant lesions

CA19-9 was only elevated in adenocarcinoma and cystadenoma, while it was negative in other tumors; lymphoma, neuroendocrine and myxoma. In detecting adenocarcinoma CA19-9 had a sensitivity of 74%, a specificity of 100%, a positive predictive value 100% and a negative predictive value of 50%.

In patients having CA19-9 levels below 300 U/L 12 were operable and eight inoperable, while in 13 patients having CA19-9 above 300 U/L, only two were operable and 11 patients were inoperable **(Table 5)**.This difference was statistically significant. This means that CA19-9 was significantly higher in inoperable patients with more extensive malignant lesions.

Table5: CA19-9 level below or above 300 in relation to operability

	CA 19.9 >300	CA 19.9 <300
operable	2	12
Non operable	11	8

Chi-square (df=1) 6.42 p= .0113
Fisher exact *p*= .0133

Needle biopsy was done for all 40 patients studied. In the seven patients who proved later to be benign, fine needle did not show any malignancy. In patients with malignancy, the needle biopsy was positive in 20(61%) and negative in 13(33%). Fine needle aspiration was positive in 20 out of 33 (61%) lesions whether having the appearance of masses or swollen head. It was positive in 11 of 16 (69%) of large masses, and was positive in nine of 15 (60%) small masses, this difference was not statistically significant X2 = 0.025 P = 0.9480. (Table 6)

Table6 Difference in FNA between small and large lesions by US

	Large lesions	Small lesions
FNA positive	13	9
FNA negative	5	6

In 25 patients having head lesions, biopsy from head lesions was positive in 16 (64%) but negative in 9(36%).Biopsy from the body of the pancreas or diffuse pancreatic lesion, was positive in 4/8(50%) but negative in other 4(50%) X2=0.84 P=0.7720. This means that there was no difference whether the biopsy was taken from the head or the body.

Biopsy was taken from five patients with malignancy by needle size 18, from 11 patient by size 20 and from17 patients with needle size 22. Five of five (100%) biopsies taken with needle size 18 were positive, while in 6(55%) of 11 by needle size 20 and 9(53%) of 17 by needle size 22 were positive. X2= 3.31 P= 0.069 Fisher exact=0.1058.

FNA had a sensitivity of 61%, specificity of 100%, positive predictive value 100 % and negative predictive value of 35%.

CA19-9 showed sensitivity of 67%, specificity of 100%, positive predictive value 100% and negative predictive value of 39%. Ultrasonography showed sensitivity of 70%, specificity of 86%, positive predictive value 96 % and negative predictive value of 38%. It showed 10 false negative cases and one false positive case. When adding CA19-9 to ultrasound, the Sensitivity was 94%, Specificity 86, positive predictive value 97%, and negative predictive value75%. When adding FNA to US sensitivity was 85%, specificity was 86%, positive predictive value 97% and negative predictive value of 55%. Ultrasound when combined with CA19-9 and FNA the sensitivity became 94%, specificity 86%, positive predictive value 97% and negative predictive value of 75 %, with only two false negative cases.

Endoscopic ultrasonography showed sensitivity of 90%, specificity of 100%, positive predictive value 100% and negative predictive value of 40%.Three cases appeared to have pancreatitis but were found to be malignant. Adding CA19-9 to EUS showed sensitivity of 94%, specificity of 100%, positive predictive value 100% and negative predictive value of 50%. Adding FNA to EUS showed sensitivity of

97%, specificity of 86%, positive predictive value 96% and negative predictive value of 67%, which was equal to the combination of EUS and FNA and CA19-9. Endoscopic ultrasonography and US showed sensitivity of 94%, specificity of 86%, positive predictive value 96% and negative predictive value of 50%, with two false negative cases only (Table 7).

Table 7: Sensitivity and specificity of different tools used in our thesis

	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
US	**70%**	**86%**	**96%**	**38%**	73%
EUS	**90%**	**100%**	**100%**	**40%**	91%
CA19-9	**67%**	**100%**	**100%**	**39%**	70%
US-FNA	**61 %**	**100%**	**100%**	**35%**	82%
US + US-FNA	**85%**	**86%**	**97%**	**55%**	82%
EUS+US-FNA	**97 %**	**100%**	**100%**	**67%**	97%
EUS+CA19-9 + US-FNA	**97%**	**100%**	**100%**	**67%**	97%
US+CA19-9+ US-FNA	**94%**	**86%**	**97%**	**75%**	93%

4.Discussion

Pancreatic cancer is a very aggressive tumor with an extremely poor prognosis. In our study we evaluated the role of CA19-9 and ultrasound guided fine needle aspiration in the workup evaluation of patients with cancer pancreas. Our study included 40 patients with suspected malignancy of the pancreas of whom 33 proved to be truly malignant [65.6% were males and 34.5% were females]. This is in concordance with **Gudjonsson*et al.*, 1987** who mentioned that the incidence male : females was 1.3:1. In our study adenocarcinoma was present in 82% of cases and this is comparable to **Warshaw*et al.*, 1991** who stated that adenocarcinoma accounts for 85-95% of pancreatic tumors. The most common site of pancreatic masses was in the head region (72%), while body masses occurred in 18%. **Del Castillo and Jimenez, 2002** mentioned similar results, showing that 60-70% of tumors are localized to the head of the gland.

At present the common modalities used for imaging are CT, abdominal ultrasound, EUS and ERCP. Abdominal ultrasonography is used for initial evaluation of patients with symptoms suggestive of pancreatic disease and often provides the first opportunity to diagnose pancreatic abnormalities. Findings on ultrasound are useful to determine the need and priority of subsequent imaging techniques such as CT and EUS that may be require to assess extent and stage of pancreatic tumors (**Maringhini*et al.*, 1998**). CT is an appropriate imaging test because it detects tumors in the pancreas and can be used to stage for resectability and to detect liver metastasis. The sensitivity of conventional CT for the diagnosis of tumors less than 3 cm is 53%, but the sensitivity of spiral CT or resectable tumors is higher ranging from 85-95% (**Blumke*et al.*, 1995; Eugene *et al.*, 1999**). In our study the diagnostic accuracy of ultrasound in the detecting of pancreatic lesions was 73%. It had a sensitivity of 70%, specificity of 86%, a PPV of 90% and a NPV of 38%. The reported sensitivity and specificity of ultrasound in diagnosing pancreatic cancer ranges from 75-89% and 90-99% respectively; however these numbers are dependent on the expertise of the ultrasonographer, the extent of the tumor and the presence or absence of bile duct obstruction (**Del Castillo and Jimenez, 2002**). **Del Maschio*et al.*, 1991** showed an overall accuracy for diagnosing cancer pancreas by ultrasound of 72% and positive and negative predictive values of 95%. The accuracy and positive predictive values are in concordance with our study.

Endosonography has emerged as one of the best methods in diagnosing and staging cancer pancreas. Studies comparing EUS with spiral CT for cancer pancreas showed that EUS is equal to spiral CT (**Legmann*et al.*, 1998, Midwinter *et al.*, 1999**) or even superior to spiral CT (**Mertz*et al.*, 2000, Tienery et al 2001**). The sensitivity of endosonography in our study was 90%, specificity was 100%, PPV was 100% and NPV was 40%. Our results are comparable to that of **Muller *et al.*, 1994** who stated that EUS has a sensitivity of 94%, specificity of 100%, and accuracy of 96%. **Agarwal*et al.*, 2004** also reported that EUS has a sensitivity of 100% a PPV of 93% and a diagnostic accuracy of 94%. Contrary to our results, they found the specificity to be 50%. In

our study EUS understaged 5 cases with pancreatic masses (15%). **Rosch*et al.*, 2001** evaluated 75% with pancreatic adenocarcinoma and stated that EUS staging of T stage was 20-305 of cases which was similar to our results.

Endoscopic ultrasonography is more valuable than conventional ultrasound in diagnosis of pancreatic lesions. It is more superior in diagnosis and definitive staging of malignancy of the pancreas, particularly when the mass is small. However, EUS is still not found in all medical and is more troublesome to the patients.

Fine needle aspiration (FNA) has made significant contribution to the preoperative and intraoperative diagnosis of cancer pancreas. By ultrasonography guidance, FNA seems to be reliable enough in reaching a diagnosis (**Mallery*et al.*, 1998**). In our study FNA had an overall accuracy of 82%, a sensitivity of 61%, and specificity of 100%, PPV of 100% and NPV of 35%. **Di Stasi *et al.*, 1998** recorded that the sensitivity of FNA was 94%, while the diagnostic accuracy was 91%.

Ultrasound guided biopsies using 18 gauge needle with automated spring-loaded sampling devices under complete sonographic guidance has a reported sensitivity of 92-94% (**O'toole*et al.*, 2001**). This was the method used in our study. FNA was positive in 64% of head lesions, while it was positive in 50% of body masses; however the difference was statistically insignificant, possibly due to the small number of patients included in our study. All biopsies from the seven benign patients were negative, emphasizing the specificity of FNA for malignancy detection (100%). This was also shown by **Brandt *et al.*, 1993** who showed that biopsy positive or malignancy has a specificity of 100%.

Conventional sonographic or EUS guided biopsy for tissue diagnosis has major clinical impact and cost savings for patients with malignant pancreatic disease in many aspects: 1) operative time waiting for a frozen section biopsy is decreased, 2) tissue diagnosis combined with EUS staging determines whether the patient is a candidate for curative resection, adjuvant therapy or palliative surgery, 3) diagnosis of lymphoma would warrant chemotherapy instead of surgical resection, 4) non-operative palliative therapy requires tissue diagnosis before initiation.

On the other hand, FNA is not without disadvantages and complications: 1) acute pancreatitis, 2) peritonitis and pancreatic fistula, 3) abdominal wall or cutaneous implantation or cancer seedlings (**Divani, 1996**). Moreover, ultrasound guided FNA is operator dependent and needs a lot of experience.

In our study, the diagnostic accuracy of combined EUS and conventional ultrasound guided FNA was 97%, while the sensitivity, specificity, PPV, and NPV were 97%, 86%, 96% and 67% respectively. These results are comparable to or even better than the results reported by authors studying the value of Endosonographic guided FNA (EUS-FNA) as **Chang *et al.*, 1996** who reported an accuracy of 85%, sensitivity of 83%, specificity of 90%, PPV 100% and NPV 80%. **Agarwal*et al.*, 2004**, as well as, **Gress*et al.*, 2001** reported sensitivity and specificity values similar to our results. IN Egypt EUS-FNA costs L.E. 1300, while combined EUS and sonar guided FNA costs L.E. 390, thus saving expenses with the same or better accuracy.

In our study, CA19-9 was elevated in 22 malignant patients. It was only elevated in adenocarcinoma and cystadenoma, while it was negative in other tumors. It had a sensitivity of 67%, a specificity of 100%, a PPV of 100% and a NPV of 100% for detection of malignant lesions. Regarding the detection of adenocarcinoma, CA19-9 even had a higher sensitivity of 74%, a specificity of 100%, a PPV of 100% and a NPV of 50%. When the level of CA19-9 was above 300U/L it was significantly related to inoperability and advanced stage of malignancy. Adding CA19-9 to ultrasound increased the sensitivity to 94%. When ultrasound was combined with CA19-9 and FNA, Its accuracy increased to 93%. Combining EUS to CA19-9 improved the sensitivity to 94%, and accuracy to 93%. Addition of FNA to the above-mentioned two investigations improved the sensitivity and the diagnostic accuracy to 97%.

In conclusion, ultrasound guided FNA with EUS shows a high diagnostic accuracy and should be recommended to any patient with focal lesions of the pancreas to permit staging, as well as, histopathological diagnosis as guidance for therapy. CA19-9 is also recommended to assess operability of extensive malignant lesions of the pancreas.

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