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COMPARISON BETWEEN ENDOSCOPIC ULTRASONOGRAPHY AND ABDOMINAL CT AND MRI FOR DIAGNOSIS OF PANCREATIC CANCER

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ABSTRACT

Background and aim of the work: Pancreatic cancer is the fourth cause of cancer related death worldwide. Difficult early diagnosis of pancreatic cancer is the main cause of its poor prognosis. Previous studies indicated that CT and MRI equally perform at evaluating resectability of pancreatic cancer. Endoscopic ultrasound (EUS) is a reference method for diagnosing and staging different diseases and through which guided biopsies and fine needle aspirations can be obtained. The aim of this study is to compare EUS, CT and MRI in early diagnosis of pancreatic tumors.

Patients and methods: 48 patients with various pathological types of pancreatic masses were enrolled in this study. They were examined using the three diagnostic modalities and compared to the gold standard which is the cytologic / histopathologic diagnosis of an EUS guided biopsy.

Results: EUS detected 100% of pancreatic tumors even those smaller than 1 cm in diameter. EUS detected nodal metastasis in 65% of cases versus 37.5% in MRI and 7.5% in CT. EUS detected vascular invasion in 50% of cases versus 32.5% in MRI and 7.5% in CT. EUS and MRI detected hepatic metastasis in 20 % of cases versus 7.5% by CT. EUS has sensitivity of 100% and specificity of 75% which are the highest values among the three diagnostic modalities.

Conclusion: Endoscopic ultrasonography is a very sensitive method for detection of pancreatic cancer. EUS is the best diagnostic modality for staging of pancreatic tumors.

KEYWORDS : . EUS, pancreatic cancer, staging and resectability.

INTRODUCTION:

Pancreatic cancer comes the fourth in order as a common cause of malignancy related death all over the world with incidence rate approximating death rate indicating that patients who develop this disease die from it. Although great advances in early diagnosis and treatment of malignancies such as colorectal cancer, breast cancer and prostate cancer have already been established, early diagnosis of pancreatic cancer is still difficult and hence the five year survival rate is less than 5% and the death rate has not decreased over the last 20 years[1].Diagnosis of most cases of cancer pancreas at late stages is the main cause of poor prognosis[2]. Less than 20% of diagnosed patients have chance of successful radical resection and possible cure and even in patients with resectable disease, the survival rate is only 23%[3].

Causes of late diagnosis and hence poor prognosis of pancreatic adenocarcinoma include absence of early symptoms and invasive nature atearly stage. To improve prognosis, early diagnosis is critical [4].If a pancreatic mass is diagnosed as a neoplasm, it is necessary to determine whether it is benign or malignant. Malignant tumors are further classified according to the TNM staging system to determine resectability[5].

Previous studies showed that CT and MRI equally perform at evaluating resectability of pancreatic cancer [6]. In a more recent study, MRI had 96% accuracy versus 81% for helical CT in assessing resectability of pancreatic cancer [7]. Contrast enhanced MRI was found as accurate as contrast enhanced helical CT in the detection and staging of pancreatic cancer. MRI was more sensitive in detection of small liver metastases [8].

Endoscopic ultrasound (EUS) is a reference method for diagnosing and staging different diseases. EUS guided biopsies and fine needle aspirations are used to improve the diagnostic performance of this imaging modality and to obtain a definitive diagnosis. However, EUS guided tissue sampling requires experience and is associated with a low but not negligible risk of complications [9].

AIM OF THE WORK:

The aim of the present study is to compare the three diagnostic modalities EUS, CT and MRI as regard their ability to early detect pancreatic tumors and to differentiate benign from malignant lesions as well as their ability to determine extrapancreatic metastasis and resectability of these tumors.

PATIENTS AND METHODS:

This prospective cohort study included 48 patients admitted to El-Ebrashi's Unit of Gastroenterology and Hepatology, Internal Medicine Department, Kasr El Aini University Hospitals and Tropical Medicine Department, Zagazig University Hospitals during the period from June 2015 till December 2016.

Inclusion criteria:

- Patients suspected to have pancreatic cancer clinically and by conventional imaging techniques (ultrasound, CT and MRI) and referred for EUS.
- Operable pancreatic mass lesions seen by CT or MRI and referred for more confirmation by EUS.
- Inoperable pancreatic mass lesions seen by CT or MRI and referred for EUS-FNA for cytopathologic confirmation to start chemotherapy.
- Patients with obstructive jaundice of unknown etiology.
- Patients with raised tumor markers especially CA19-9 with no evident pancreatic masses in conventional imaging techniques.
- New onset DM in a thin elderly patient with a high suspicion of pancreatic malignancy clinically or by laboratory findings with no evident pancreatic masses in conventional imaging techniques.
- Patients having intractable severe upper abdominal pain with no evident pancreatic masses in conventional imaging techniques.

Exclusion criteria:

- Patients with bleeding tendency contraindicating FNA.
- Patients unfit for anesthesia and upper GIT endoscopy.
- Gastric outlet obstruction due to external compression or invasion by the pancreatic mass.
- All patients were subjected to the following:
- Full history taking (age, gender, residence, smoking, alcohol intake, presenting symptom(s) in the form of jaundice, abdominal pain, weight loss and change of colour of urine and/or stool, history of diabetes, operations and family history of a similar condition).
- Thorough clinical examination.
- Laboratory investigations in the form of CBC, LFT, KFT, PT, INR, FBS, serum amylase and lipase and serum CA 19-9.
- Computed Tomography (CT) scans were obtained for all patients using a high speed scanner (Siemens Somatom plus and X-vision Toshiba) after administration of oral and IV contrast. All images were interpreted on a picture archieving and communication system (PACS) workstation, curved and multiplanar reformations were obtained at a delicated post-processing workstation. Location of lesion(s), suspicion of malignancy and resectability were determined in all CT reports.
- Magnetic resonance imaging (MRI) was done for all patients using 1.5 T superconducting magnets (Magnetom Sonata) with a four-element torso phased array coil after injecting of gadolinium chelate.
- Endoscopic ultrasound (EUS) and EUS-FNA were performed for all patients by a single endoscopist using a Pentax linear array Echoendoscope type EG-3870UTK attached to a high end Hitachi Ultrasound AVIUS machine. Endosonographic scanning was always started at the 7.5 MHz frequency. This was switched to 12 MHz only when more details of a proximal lesion were needed. The duration of the examination lasted for 20-40 minutes. Patients were examined for the presence of previously undetected secondaries in the draining lymph nodes, liver, mesentery or peritoneum and for encasement/invasion of major extrapancreatic vessels (portal vein, superior mesenteric vein, superior mesenteric artery or celiac trunk).Endosonographic criteria adopted for diagnosis of involvement of the draining lymph nodes were circularity, homogeneity, relative hypoechointensity and proximity to the primary lesion. The malignant lymph nodes are usually large (longitudinal diameter is more than 2 cm), more rounded (transverse: longitudinal ratio is >1:2), homogenic and hypoechoic while the benign reactive LN are usually small (<2cm), oval (transverse: longitudinal ratio is < 1:2), non homogenic (preserved corticomedullary differentiation) and echogenic. 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. Presence of nodal involvement or vascular invasion defined unresectability and palliative bypass was the decision. The gold standard test was to obtain a biopsy which was aspirated by EUS-FNA. The specimen was sent for cytologic or histopathologic correlation and then the patient was sent for surgical consultation according to the tumor size, site and resectibility.

STATISTICALANALYSIS

Collected data were computerized and statistically analyzed through SPSS program version 24. Data were tested for normal distribution using Shapiro Walk test. Qualitative data were expressed as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact test were used to compare qualitative variables as indicated. Quantitative data were expressed as median and range for being non-parametric data (not normally distributed). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of different imaging tests were determined. P value <0.05 significant, p value <0.005 highly significant.

RESULTS:

Table (1): Demographic data, presenting symptoms, laboratory parameters and pathologic diagnoses of studied patients.

Demographic data		
Age (years): Mean ± SD Median (range)	56.9 ± 10.3 59 (37-77)	
Gender: No. (%)	Female	18 (37.5%)
	Male	30 (62.5%)
Residence: No. (%)	Rural	31 (64.6%)
	Urban	17 (35.4%)
Presenting symptoms: No. (%)		
Abdominal pain	48 (100%)	
Jaundice	35 (72.9%)	
Dark urine	28 (58.3%)	
Clay stool	20 (41.7%)	
Pruritus	21 (43.8%)	
Abdominal lump	4 (8.3%)	
Weight loss	26 (54.2%)	
Laboratory parameters: Median (range)		
HB(g/dl)	10 (8.5-12)	
WBCs(x103cells/ml)	6.9 (4.5-8)	
PLT(x103 cells/ml)	157.5 (110-450)	
T.Bil.(mg/dl)	4.5 (0.7-14)	
D.Bil. (mg/dl)	2.1 (0.2-9)	
T.Protien(g/dl)	8 (6.9-8)	
S.Albumin(g/dl)	4 (2.9-4)	
AST(IU/L)	41.5 (13-70)	
ALT (IU/L)	46.5 (22-99)	
ALP(IU/L)	197 (25-510)	
S.creatinine (mg /dl)	1.2 (0.7-1.8)	
BUN(mg/dl)	25 (23-78)	
PT(sec)	11 (10-13)	
INR	1.2 (0.8-1.4)	
Amylase(IU/L)	43 (12-130)	
Lipase(IU/L)	44 (9-125)	
S.CA19-9(IU/L)	135.5 (19-630)	
FBS(mg/dl)	197 (90-320)	
Pathological findings: No. (%)		
Ductal Adenocarcinoma	35 (72.9%)	
Neuroendocrine	4 (8.3%)	
Mucinous cystadenoma	3 (6.3%)	
Pancreatitis	3 (6.3%)	
Insulioma	1 (2.1%)	
Mucinous cystadenocarcinoma	1 (2.1%)	
Serous cystadenoma	1 (2.1%)	

Table (2): Criteria of pancreatic masses as detected by the three diagnostic modalities.

Finding		CT diagnosis		p	**MRI diagnosis**		P	**EUS diagnosis**		P
		Benign N=8	**Malignant N=40**		**Benign N=8**	**Malignant N=40**		**Benign N=8**	**Malignant N=40**	
Size (mm)	Negative	31 (64.6%)			21 (43.8%)			0 (0%)		
	1—10	0 (0%)			0 (0%)			3 (6.3%)		
	11—20	1 (2.1%)			3 (6.3%)			14 (29.2%)		
	21—30	9 (18.8%)			12 (25%)			16 (33.3%)		
	31—40	2 (4.2%)			9 (18.8%)			12 (25%)		
	41—50	3 (6.3%)			1 (2.1%)			1 (2.1%)		
	> 50	2 (4.2%)			2 (4.2%)			2 (4.2%)		
Site	Body	3(37.5%)	5(12.5 %)	0.22	3(37.5%)	6 (15%)	0.175	2 (25%)	7 (17.5 %)	0.068
	Head	1 (12.5%)	8(20%)		1(12.5%)	17(42.5%)		6 (75%)	33(82.5%)	

	Negative	4 (50 %)	27(67.5 %)		4 (50%)	17(42.5%)		0(0 %)	0(0%)	
Nature	Cystic	4 (50%)	0 (0%)	<0.001	3(37.5%)	3(7.5%)	0.03	4(50%)	3 (7.5 %)	<0.001
	Solid	0 (0%)	13(32.5%)		1(12.5%)	20 (50%)		4(4%)	37 (92.5 %)	
	Negative	4 (50%)	27(67.5%)		4 (50%)	17(42.5%)		0(0%)	0(0%)	
Size	Negative	4(50%)	27(67.5%)	0.006	4 (50%)	17(42.5%)	0.027	0(0%)	0(0%)	0.036
	1-10 mm	0(0 %)	0(0 %)		0(0%)	0(0%)		1(12.5%)	2(5%)	
	11-20 mm	1(12.5%)	0(0%)		0 (0%)	3 (7.5%)		1(12.5%)	13(32.5 %)	
	21-30 mm	1 (12.5%)	8(20%)		2 (25%)	10 (25%)		2(25%)	14(35%)	
	31-40 mm	0 (0%)	2(5%)		0 (0%)	9 (22.5%)		2(25%)	10(25%)	
	41-50 mm	0 (0%)	3(7.5%)		0 (0%)	1 (2.5%)		0(0%)	1(2.5%)	
	> 50 mm	2 (25%)	0 (0%)		2 (25%)	0 (0 %)		2 (25%)	0(0%)	
Density	Hyperdense	1 (12.5%)	0 (0 %)	0.034	0 (0%)	1 (2.5%)	0.332	4 (50%)	0(0%)	<0.001
	Hypodense	1 (12.5%)	6(15%)		1(12.5%)	14 (35%)		1(12.5%)	22(55%)	
	Isodense	1 (12.5%)	0 (0 %)		2 (25%)	2 (5%)		1(12.5%)	2(5%)	
	Heterogeneous	1(12.5%)	7 (17.5%)		1(12.5%)	6 (15%)		2(25%)	16(40%)	
	Negative	4 (50%)	27(67.5%)		4 (50%)	17(42.5%)		0 (0%)	0 (0%)	
Extra-pancreatic invasion	LN	1(12.5%)	3(7.5%)	0.64	2(25%)	15(37.5%)	0.694	3(37.5%)	26(65%)	0.147
	Vascular	0(0%)	3(7.5%)	0.424	0(0%)	13(32.5%)	0.885	0(0%)	20(50%)	0.295
	Liver	0(0%)	3(7.5%)	0.424	0(0%)	10(20%)	0.171	0(0%)	8(20%)	0.121
	resectability	3(37.5%)	11(27.5%)	0.619	2(25%)	12(30%)	0.954	6(75%)	22(55%)	0.295

Table (2) depicts that EUS could detect all pancreatic masses examined no matter their size, site, nature and density. CT could not detect 31 masses (64.6%) and MRI could not detect 21 masses (43.8%). All masses smaller than 1 cm in diameter were missed by CT and MRI.Most masses missed by CT and MRI were of small size (less than 2 cm in diameter), of solid nature and were hyperdense benign masses or hypodense/isodense malignant masses. This table depicts that EUS is superior to CT and MRI at detecting LN metastasis and vascular invasion and shows also that EUS is superior to CT but not to MRI at detecting liver metastasis. This table depicts that EUS is superior to CT and MRI at determining resectability.

Table (3): Clinical performance of the three diagnostic modalities.

Validity	CT		MRI		EUS	
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity	32.50%	18.57% to 49.13%	57.50%	40.89% to 72.96%	100.00%	91.19% to 100.00%
Specificity	50.00%	15.70% to 84.30%	50.00%	15.70% to 84.30%	75.00%	34.91% to 96.81%
Accuracy	41%	0.27 to 0.56	54%	0.39 to 0.68	88%	0.75 to 0.95
Positive predictive value	76.47%	50.10% to 93.19%	85.19%	66.27% to 95.81%	95.24%	83.84% to 99.42%
Negative predictive value	12.90%	3.63% to 29.83%	19.05%	5.45% to 41.91%	100.00%	54.07% to 100.00%

Table 3 compares the clinical performance of the three diagnostic modalities. It shows that EUS is the most sensitive and specific of them followed by MRI.

DISCUSSION:

Pancreatic cancer is a major health problem with an aggressive course and increasing frequency. Approximately 30,000 new cases in 2002 and 32,000 in 2004 were diagnosed in the USA. This malignancy is the leading cause of cancer related death among all gastrointestinal malignancies and the fourth leading cause of cancer related death in the USA with a very poor prognosis [10].

Most patients with pancreatic malignancy are diagnosed when the tumor is 3cm or more in diameter. Most pancreatic cancers have already had metastasized to other organs by the time of diagnosis and the median survival is only 18-28 month. The five year survival is about 10% and it has not much increased over the last 3 decades. The difficulty in early diagnosis of pancreatic malignancy remains a major obstacle in improving outcome in such patients.

However, recent developments in endoscopic ultrasound (EUS) and histopathology of EUS-guided fine-needle aspiration (FNA) or fine-needle biopsy (FNB) allow confirmed early diagnosis of pancreatic malignancy. EUS - FNA and FNB in conjunction with spiral CT or MRI providea reliable preoperative staging of pancreatic tumors [11].

The main role of EUS in a suspected pancreatic tumor is the accurate diagnosis and staging andthe determination of surgical resectability. EUS staging of a pancreatic malignancy is based on the classic TNM staging system where T reflects the depth of local infilteration, N reflects the presence of lymph node metastasis and M reflects vascular invasion. The FNA/FNB of a pancreatic mass and regional lymph nodes for cytology or histopathology is occasionally required to confirm the findings or to plan for a neoadjuvant or palliative therapy [12].

This prospective cohort study included 48 patients with pancreatic masses (8 benign masses and 40 malignant masses). Results revealed that pancreatic malignancy ismore common amongpatients older than 56 years and this is in agreement with Schima et al., [13] who found through results of multiple studies that the typical age was 60-65 years and the risk of developing pancreatic cancer increases with increase of age.Results showed that pancreatic malignancyis more common in males and this is in agreement with Dabizzi et al.,[14]who reported that pancreatic cancer has higher incidence among males. This finding can be explained by genetic and hormonal predisposition and the more common to exposure to cigarette smoking and alcohol intake.

The present study reported that abdominal pain was the commonest presenting symptom found in all 48 cases followed by jaundice in 35 cases and significant weight loss in 26 cases and this is in agreement with Huggett and Pereira,[15] and Albores-Saavedra et al., [12] who stated that common symptoms leading to suspicion of pancreatic cancer were obstructive jaundice, persistent epigastric pain and unintended significant weight loss. Universality of recent onset persistent abdominal pain - which is a subjective symptom - especially in high risk groups necessitates performing serious investigations of this symptom and promotes addition of EUS to the heading of the list of these investigations. Absence of obstructive jaundice - which is an objective symptom - in some cases supports the fact that its occurrence has no relation to tumor size and hence to tumor stage as it depends on the proximity of the tumor to the CBD. Generally, obstructive jaundice is not an early symptom of pancreatic cancer and even it may not occur until the tumor has reached a large size.

As regard our laboratory findings,there was mild anemia among patients with median hemoglobin value of 10 g/dL and range between 8.5 and 12 g/dL and this is in agreement with Mudan, [16]who found that decrease of baseline hemoglobin level was one of the most common laboratory changes affecting more than 60% of pancreatic cancer patients. Decrease of hemoglobin may occur either as a direct effect of malignancy or more commonly as a side effect of cancer treatment. FBS showed significant elevation among studied patients with a median value of 197 mg/dL and this is in agreement with Saruc and pour.,[17] who stated that about 70% of pancreatic cancer patients

had impaired glucose tolerance. This observation support the hypotheses that pancreatic cancer destroys β cells of islets of Langerhans causing diabetes and/or the metabolic derangements associated with diabetes promote the development of pancreatic cancer.

Our results showed that there was a significant elevation in CA 19-9 > 135 U/L and this is in agreement with Zhang et al.,[18] who stated that frequencies of elevated CA 19-9 (68%) were significantly higher ($P < 0.01$) than those for CEA (28%) among 40 patients with pancreatic cancer and concluded that CA19-9 can be considered a good marker for differentiating benign from malignant pancreatic lesions.

In the present study, histopathologic diagnosis of most pancreatic masses was ductal adenocarcinoma detected by EUS and FNA. Out of 48 masses, 35 (72.9%) proved to be ductal adenocarcinoma,4 (8.3%) proved to be neuroendocrine tumors, 3 (6.3%) proved to be mucinous cystadenocarcinoma, 3 (6.3%) proved to be pancreatitis, 1 (2.1%) proved to be insulinoma, 1 (2.1%)proved to be mucinous cystadenocarcinoma and 1 (2.1%) proved to be serous cystadenoma. These results are in agreement with De Angelis et al., [19] who found that ductal adenocarcinoma constitutes up to 90% of all primary malignant tumors arising from the pancreas.

In this study, the detection rate of pancreatic tumors by EUS was 100 %. Compared with CT and MRI, EUS had a better ability to detect masses smaller than 2 cm in diameter. In this study, 17 out of 48 masses were equal to or less than 2cm in diameter. All these 17 masses could be detected by EUS, only 3 of them could be detected by MRI and only 1 of them could be detected by CT. By the 3 diagnostic modalities, there was 2 masses of more than 5 cm in diameter. By EUS and MRI, there was 1 mass of 4-5 cm in diameter while by CT, there was 3 masses of 4-5 in diameter. This means that there is size overestimation in CT but not in MRI and EUS. These findings are in agreement with Greer and Brand, [20]who reported that the detection rate for pancreatic tumors by EUS is 90-100% with good detection for tumors less than 2 cm in diameter.

As well, this study compared between EUS, CT and M.R.I as regard detection of liver metastasis. CT detected 3 out of 17 cases compared to 8 out of 48 cases detected by EUS and 10 out of 27 casesdetected byMRI. These results show that MRI is superior to CT and EUS at detection of liver metastasis and are in agreement with Lee and Lee, [21] who reported similar results.

Moreover, this work compared between EUS, CT and MRI in detection of vascular invasion. 20 out of 48 cases for EUS versus 2 out of 17 cases for CT and 13 out of 27 cases for MRI show that EUS is superior to CT and MRI as regard detection of vascular encasement/ invasion. These results are in agreement with Nawaz et al.,[22]who stated that EUS is a new technique with great accuracy showing superiority to CT withspecificity 86% versus 78%, positive predictive value 67% versus 50% and accuracy 88% versus 81%taking in consideration that EUS is almost always is operator dependent.

Comparison between EUS, CT and MRIat detection of lymph node involvement revealed that 29 out of 48 cases, 4 out of 17 cases and 17 out of 27 cases respectively had lymph node enlargement. These results showthat EUS is superior to CT and MRI at detecting lymph node enlargement. These results are in disagreement with Hewitt et al.,[23] who stated that CT with contrast and MRI were more accurate than EUS at detection of lymph node involvement. Discrepancy in results can be explained by taking in consideration the operator's experience and the new era in technology field of devices which made life much easier.

In the present study, it was clear that EUS was the most sensitive and specific method for diagnosis of pancreatic masses when compared with cytology/histopathology of FNA/FNB as a gold standard followed by MRI. This finding is similar to that of Dewitt et al., [24] who analyzed eleven well designed studies (meta-analysis) comparing EUS and CT for preoperative staging of pancreatic cancer. Regarding the T stage accuracy, 4 of 5 studies concluded that EUS was superior to CT (63-85%) versus (25-73%). EUS was also superior to CT in 5 of 8 studies that assessed N staging accuracy (44-75%) versus (25-63%). As regard M stage accuracy (vascular invasion), EUS was superior to CT in 6 out of 8 studies (68-100%) versus (41-83%). Among the 4 studies that assessed resectability, 2 showed no difference between EUS and CT and 1 favored each modality.

Finally, this study clearly depicted that EUS is an accurate pre-operative tool in the evaluation of nodal staging, vascular encasement/ invasion and resectability in patients with pancreatic adenocarcinoma. This agrees with Nawaz et al, [22] who found that the sensitivity of EUS in detection of LN, vascular encasement/invasion and resectability is significantly higher than that of CT. Yusoff et al, [25] also found that it is highly specific at detection of non resectable malignant pancreatic tumors.

Conclusion:

EUS staging should be the standard of care with CT and MRI for the preoperative assessment of patients with pancreatic malignancies because combination of more than one modality improves the diagnostic yield of these modalities.

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