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Additive Value of F^{18}-FGD-PET/CT in Pancreatic Mass Evaluation

Fathy, H[1]. Nasr, I[2]. Ali, I [3] and Tabashy, R[4].

[1]Nuclear Medicine Unit, National Cancer Institute, Cairo University. [2]Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University. [3]Radiology Department, Faculty of Medicine, Zagazig University. [4]Radiology department, National cancer Institute, Cairo University, Egypt.

ABSTRACT:

Background: Accurate diagnosis and staging of pancreatic cancer are essential for appropriate treatment. The ideal imaging test for pancreatic malignancy should both detect and stage pancreatic tumor. Currently, contrast-enhanced CT with three dimensional (3-D) reconstruction is the imaging modality used for the diagnosis and staging of pancreatic cancer. FDG PET–CT may provide additional diagnostic information and improve detection rates for suspicious pancreatic lesions. **The aim of the study** is to evaluate the diagnostic impact of FDG-PET/CT in patients with solid pancreatic masses, compared to the contrast enhanced CT (CECT) and Endoscopic Retrograde Cholangio-Pancreatography (ERCP).**Material and Methods**: Twenty seven patients with solid pancreatic masses underwent CECT of the neck, chest and pelvi-abdominal, ERCP and FDG-PET/CT examinations from January 2014 to May 2015. Both imaging methods were done within one month interval. PET–CT data sets were analyzed by two expert readers in a consensus reading. Biopsy from ERCP, surgery/fine needle aspiration with histological examination was also done for all patients. **Results:** Twenty four patients of the total 27 patients (88.9%) had pancreatic cancer and 3 patients (11.1%) had benign lesions. PET/CT detected head masses in (17/27) patients (63%) versus (12/27) for CECT (44.8%) and (9/27) for ERCP (33.3%).PET/CT had greater sensitivity than CECT (79.2% versus 62.5%) in diagnosis of pancreatic lesions. Corresponding specificities were similar between both imaging methods. Accuracy was 74.1% for PET/CT Vs 59.3% for

CECT. PET/CT had higher degree of accuracy for detection of distant metastases in LNs and liver compared with that of CECT. Three patients with vascular infiltration were diagnosed only with CECT. PET/CT upstaged 8 patients from stage IA, IB and IIB to stage III and stage IV.

Conclusion: PET/CT is valuable additional imaging method in characterization and staging patients with suspected malignant pancreatic masses. Incorporation of PET/CT improves the preoperative evaluation of patients with solid pancreatic lesions especially in detection of additional metastatic sites.

Key words: Pancreatic mass; F FDG-PET/CT; CECT; ERCP; Pancreatic cancer.

Corresponding Authors: *Nasr, I.* **E-mail:** *iminasr@gmail.com.*

INTRODUCTION:

Despite recent advances in clinical imaging and biomarker identification, differential diagnosis of pancreatic masses remains challenging [(1)]. Accurate diagnosis of pancreatic lesions and staging of pancreatic cancer are essential for appropriate treatments and for determining a more accurate prognosis [(2)]. The ideal imaging modality for pancreatic malignancy should both detect and stage pancreatic tumor so that the oncology team can make an informed preoperative decision on the proper treatment. Currently, thin-slice (1–3 mm), contrast-enhanced, dual phased multi-detector computed tomography (MDCT) with three-dimensional (3-D) reconstruction is the main imaging modality for the diagnosis and staging of pancreatic cancer [(3)].

18F-FDG PET/CT is a powerful imaging method for the staging of many cancers which may affect the oncologic management of pancreatic cancer patients [(4)].

A significant advantage of FDG-PET/CT is in identifying loco-regional or distant metastatic disease associated with increased metabolic activity in the form of FDG uptake, which may not be apparent based on CT morphologic features alone

[(5)]. Combined FDG PET–CT may improve detection rates, providing additional diagnostic information on suspicious solid lesions in the pancreas [(4)].

If FDG PET–CT would achieve a higher sensitivity and/or specificity in evaluating solid pancreas masses, invasive FNA with the inherent risk of tumor cell dissemination and also surgical

Interventions harboring relevant morbidity and mortality in patients with benign lesions might be avoided in doubtful cases and be replaced by this non-invasive procedure [6].

Aim of the study: To investigate the diagnostic impact of FDG-PET/CT in evaluation of patients who had solid pancreatic mass with or without elevation in the level of CA19-9, compared to the contrast enhanced CT (CECT), endoscopic retrograde Cholangio-Pancreatography (ERCP) and in correlation with histo-pathologic data.

MATERIALAND METHODS:

This prospective study was approved by the ethics committee of the board of Nuclear Medicine & Radiology at the National cancer Institute. The study includes 27 patients (19 male, 8 female with mean age 57 year) with pancreatic mass. They were diagnosed by pelvic-abdominal CT with or without elevations in pancreatic tumor markers. The patients were collected from Zagazig University hospitals and referred to National Cancer Institute at the period from January 2014 to November 2014. All patients underwent contrast enhanced CT, ERCP examination, whole-body FDG PET–CT and histopathologic examination. All PET/CT and CECT studies were done at the Nuclear Medicine Unit and Radiology department of the National Cancer Institute. Both CECT and PET/CT studies were performed within one month.

Contrast-enhanced CT scanning: CT scanning was performed using multi-detector CT scanner. Plain CT was followed by contrast-enhanced CT. Non-ionic iodinated contrast material (300 mgI/ml) at 2.0 ml per kilogram body weight was injected through an ante-cubical vein with a total injection time of 30 s in principle via automated injector. All contrast-enhanced CT images were interpreted by radiologists.

PET/CT scanning and image analysis:

The study was done using dedicated PET/CT scanner (GE, PET/CT discovery). This camera integrates a PET scanner with a dual-section helical CT scanner and

Allows the acquisition of co-registered CT and PET images in one session. All patients fasted for 4 - 6 hours before the injection of 370 MBq of 18 F-FDG. Scanning started 60 min after tracer injection (5–7 bed positions; acquisition time, 2-3 min/bed position). Blood glucose levels did not exceed 150 mg/dL. Intravenous contrast agent was administered in most patients. Initially, patients were examined in the supine position with arms elevated, and CT scanning was started at the level of skull base with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. The CT scans were acquired during shallow normal breathing and reached caudally to the mid thighs. PET over the same region was performed immediately after acquisition of the CT images. CT-data were used for attenuation correction, and images were reconstructed as 3-mm slices applying a standard iterative algorithm (ordered-subset-expectation maximization). Images were interpreted at a workstation equipped with fusion software that provides multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images in any percentage relation. Side-by-side image interpretation was accomplished by 2 experienced nuclear medicine physicians. Analysis was performed using a multimodality computer platform. For semi quantitative analysis, the nuclear medicine physician referred to the PET/CT fusion images and the CT images to set a spherical volume of interest (VOI) over the regions of interest and then recorded the peak standardized uptake value (SUV max) in the VOI. PET/CT images were analyzed by an experienced radiologist and an experienced nuclear medicine physician. **Endoscopic retrograde Cholangio-Pancreatography (ERCP)** was performed in all patients by a side viewing Endoscope. ERCP was performed by experienced physician at gastroenterology unit of surgery department. Histo-pathological analysis was done for all patients on the basis of the pathological record of the surgically respected specimens.

Statistical analysis: All data were analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) and Med Calc [(13)] for windows (Med Calc Software bvba, Ostend, Belgium). Continuous variables were checked for normality by using Shapiro-Wilk test. Mann Whitney U test was used to compare between two groups of normally distributed data. Percent of categorical variables were

Compared using the Pearson's Chi-square test or Fisher exact test when appropriate. Trend of change in percent of ordinal categorical variables was compared using Chi-square test for trend. Mc Nemar's test was used for comparison between paired data. Validity of ERCP, CECT and FDG-PET/CT was calculated using diagnostic performance depend on sample 2x2 contingency tables generation. The sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and accuracies with their respective 95% confidence intervals were calculated. Inter-rater agreement (Cohen's Kappa) was calculated, criteria to qualify for strength of agreement were as follows: K<0.2: poor; K 0.21 – 0.40: fair; K 0.41 – 0.60: moderate; K 0.61 – 0.80: good; K 0.81 – 1.00: very good. All tests were two sided with $p < 0.05$ was considered statistically significant and $p > 0.05$ was considered non-statistically significant.

RESULTS:

Twenty seven patients, 19 male and 8 female with an average age of 57.74 ± 11.48 years (range 28–79 years). All patients under went contrast enhanced CT, ERCP, FDG-PET/CT, for evaluation of the diagnostic impact of FDG-PET/CT in evaluation of patients who had solid pancreatic mass of unknown nature with or without elevation of CA19-9.The mean size of the solid pancreatic masses was3.8±1.7 cm. Seventeen patients (63%) had pancreatic head masses more than 2 cm with mean size 2.7±1.2 cm were diagnosed by PET/CT versus 12 patients (44.4%) for CECT and 9 patients (33.3%) for ERCP. Among the three methods, the statistically significant differences were noted only between ERCP and PET-CT ($p< 0.05$) ***(table1)***. According to the pathological findings, 24 (88.9%) patients had pancreatic ductal adenocarcinoma (PDAC).

Table (1): Comparison between PET/CT, CECT and ERCP for Diagnosis of Pancreatic Head Mass (>2 cm).

Pancreatic head mass	PET-CT (N=27) No. (%)	CECT (N=27) No. (%)	ERCP (N=27) No. (%)	p-value[1]	p-value[2]	p-value[3]
Present	17 (63%)	12 (44.4%)	9 (33.3%)			
Absent	10 (37%)	15 (55.6%)	18 (66.7%)	0.125‡	0.008	0.375‡

P-value1: PET-CT & CECT, p-value[2]: PET-CT & ERCP, p-value[3]: CECT & ERCP ‡Mc Nemar's test.

3 patients (11.1%) had benign lesions. Comparing the diagnostic performance of PET/CT to CECT in detection of PDAC in relation to pathological data. ***Table 2;*** shows better performance for PET-CT versus CECT (77.8% versus 63%). However no statistically significant difference between the three methods could be detected (P> 0.05). The Accuracy of both imaging modalities in relation to pathological data in diagnosis of PDAC we did not find a significant difference between both and histopathology with poor kappa value as described in ***(table 2)***.

Table (2): Comparison between CECT, PET/CT in relation to histopathology of Pancreatic Lesions.

	Pathology (N=27)	PET-CT (N=27)	CECT (N=27)	p-value[1]	p-value[2]	p-value[3]
Diagnosis	No. (%)	No. (%)	No. (%)			
Benign	3 (11.1%)	6 (22.2%)	10 (37%)	0.453‡	0.065‡	0.344‡
Malignant	24 (88.9%)	21 (77.8%)	17 (63%)			

P-value1: PET/CT Vs pathology, p-value2: CECT Vs pathology, p-value3: PET-CT Vs CECT

The agreement between PET/CT in relation to pathological findings is directed toward superiority of PET/CT over that of CECT (table 3). The sensitivity, specificity, NPV, PPV and accuracy of PET-CT and CECT versus pathological findings in detecting pancreatic cancer were79.2%, 33.3%, 90.5%, 16.7%, and 74.1% for (PET/CT) as compared to 62.5%, 33.3%, 88.2%, 10%, and 59.3% (CECT) respectively (table 4).In comparing diagnostic capabilities between PET-CT and CECT, PET/CT demonstrated significant better sensitivity and accuracy ***(Table 3)***. ***Figure 1, 2;*** showed additional revealed pancreatic lesion with peritoneal nodules and nodule deposits which are not seen in other modalities.

Table (3): Diagnostic performance of PET/CT and CECT in Relation to Histopathology in Diagnosis of Pancreatic Lesions.

Findings	True +ve No.(%)	False +ve No.(%)	True –ve No.(%)	False –ve No.(%)	SN% (95%CI)	SP% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Acc% (95%CI)
CECT	15 (55.6%)	2 (7.4%)	1 (3.7%)	9 (33.3%)	62.5% (45.5-79.5)	33.3% (0-86.7)	88.2% (72.9-100)	10% (0-28.6)	59.3% (40.7-77.8)
PET/CT	19 (70.4%)	2 (7.4%)	1 (3.7%)	5 (18.5%)	79.2% (62.2-96.1)	33.3% (0-86.7)	90.5% (77.9-100)	16.7% (0-46.5)	74.1% (57.6-90.6)

SN: Sensitivity. SP: Specificity. PPV: Positive Predictive Value. NPV: Negative Predictive Value. Acc: Accuracy. %CI: 95% Confidence Interval.

Table 4; explains the diagnostic performance of PET-CT versus CECT for diagnosis of pancreatic head mass (n= 16Vs 11), LNs deposits (n= 14 Vs 5), liver metastases (n=11 Vs 4) in addition to 3 cases with bone metastases detected by PET/CT only.

Table (4): Results of CECT versus PET/CT in Staging of PDAC

	CECT finding (N=24)		PET/CT finding (N=24)	
Findings	Positive No. (%)	Negative No. (%)	Positive No. (%)	Negative No. (%)
Head mass	11(45.8%)	13 (54.2%)	16 (66.7%)	8 (33.3%)
Omental deposits	1(4.2%)	23 (95.8%)	3 (12.5%)	21 (87.5%)
Vascular invasion	3 (12.5%)	21 (87.5%)	0 (0%)	24 (100%)
LNs deposits	5 (20.8%)	19 (78.2%)	14 (58.3%)	10 (41.7%)
Liver met.	4 (16.7%)	20 (83.3%)	11 (45.8%)	13 (54.2%)
Lung met.	2 (8.3%)	22 (91.7%)	3 (12.5%)	21 (87.5%)
Bone met.	0 (0%)	24 (100%)	3 (12.5%)	21 (87.5%)

The delectability of omental deposits and pulmonary deposits were comparable between both imaging methods. Three patients have vascular invasion (2 at superior mesenteric artery and one at portal vein), detected only by CECT ***(Table 5)***.

Table (5): PET/CT in staging of Pancreatic Lesions.

Findings	PET/CT finding (N=24)		Max. SUV	
	Positive No. (%)	Negative No. (%)	Mean±SD	(Range)
Head mass	16(66.7%)	8(33.3%)	6.6±3.2	(3-14)
Omental deposits	3(12.5%)	21(87.5%)	6.7±2.3	(5-9)
Vascular invasion	0 (0%)	24 (100%)	----	----
LNs deposits	14(58.3%)	10(41.7%)	5.1±2.6	(2-10.1)
Retro-Peritoneal. LN	6(25%)	18(75%)	---	---
Mesentric LN	2(9.3%)	22(91.7%)	---	---
Coeliac LN	4(16.7%)	20(83.3%)	---	---
Retrocaval LN	1(4.2%)	23(95.8%)	---	---
Para-aortic LN	8(33.3%)	16(66.7%)	---	---
Mediastinal LN	3(12.5%)	21(87.5%)	---	---
Supraclavicular. LN	3(12.5%)	21(87.5%)	---	---
Liver metastasis.	11(45.8%)	13(54.2%)	5.4±1.5	(3.3-7.9)
Lung metastasis.	3(12.5%)	21(87.5%)	2.7±0.4	(2.2-3)
Bone metastasis.	3(12.5%)	21(87.5%)	6.8±4.9	(2.9-12.4)

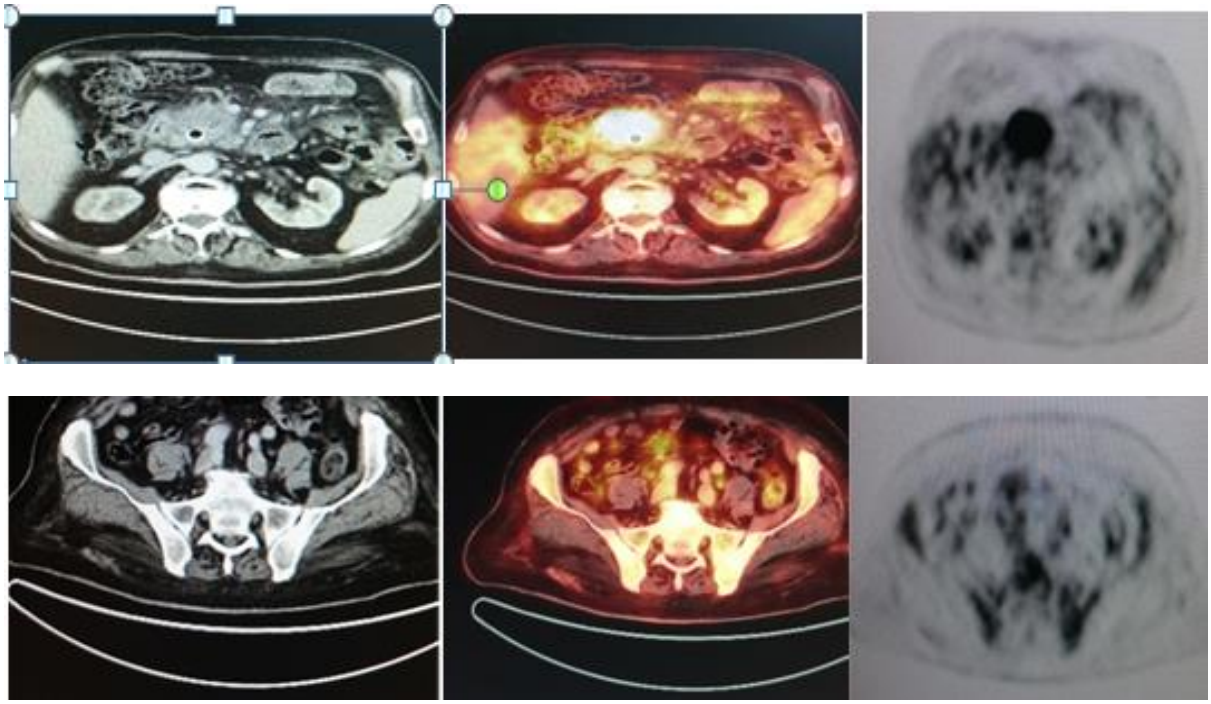

Figure (1): 50 years old male patient presented by pancreatic head mass, reported in CT underwent ERCP, PET /CT revealed pancreatic lesion and peritoneal nodule.

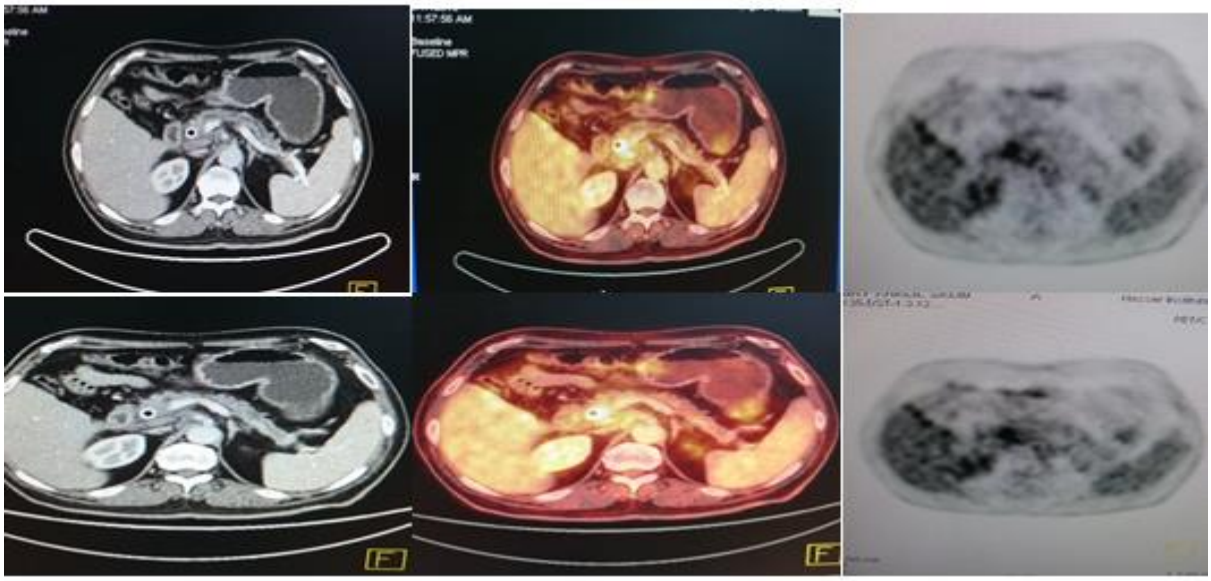

Figure (2): 47 years old male patient presented by pancreatic head mass underwent ERCP, PET/CT revealed active head mass associated with nodal deposits.

Table 6; shows overall and Differential SN, SP, PPV, NPV and accuracy of CECT in relation to PET/CT. The overall data showed moderate SN, SP and accuracy of CECT with high PPV and low NPV compared to PET/CT .Of 24 patients, 16 patients (66.7%) had malignant pancreatic head mass were diagnosed by PET/CT with mean size 3.8 and mean SUV value 6.6. Omental deposits were diagnosed in 3 patients by PET/CT. Fourteen patients have LNs deposits with mean size 1.9 cm and SUV value 5.1, their distribution is explained in ***Table 6***.

Table (6): Diagnostic performance of CECT compared to PET/CT

Findings	True +ve No.(%)	False +ve No.(%)	True –ve No.(%)	False –ve No.(%)	SN% (95%CI)	SP% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Acc% (95%CI)
Head Mass	11 (40.7%)	1 (3.8%)	9 (33.3%)	6 (22.2%)	64.7% (44.6-84.9)	90% (71.4-100)	91.7% (76-100)	60% (35.2-84.8)	74.1% (57.5-90.6)
Lymph Nodes	4 (14.8%)	2 (7.4%)	10 (37.1%)	11 (40.7%)	26.7% (5.2-48.1)	83.3% (62.2-100)	66.7% (28.9-100)	47.6% (26.3-69)	51.8% (33-70.7)
Peritoneal &Omental deposits	0 (0%)	1 (3.7%)	23 (85.2%)	3 (11.1%)	12.5% (0-54.1)	94% (84.7-100)	25% (0-85)	87% (74.4-99.7)	85% (71.9-98)
Vascular invasion	3 (11.1%)	0 (0%)	24 (88.9%)	0 (0%)	12.5% (0-54.1)	98% (92.5-100)	50% (0-100)	87.5% (75.3-99.8)	88.6% (77-100)
Liver Deposits	4 (14.8%)	0 (0%)	15 (55.6%)	8 (29.6%)	34.6% (11.6-57.7)	96.9% (88.3-100)	90% (63.7-100)	64.6% (45.4-83.7)	69.2% (52.4-86)
Pulmonary deposits	2 (7.4%)	0 (0%)	24 (88.9%)	1 (3.7%)	62.5% (20.9-100)	98% (92.5-100)	83.3% (41.2-100)	94.2% (85.3-100)	94.1% (85.5-100)
Bone Deposits	0 (0%)	0 (0%)	24 (88.9%)	3 (11.1%)	12.5% (0-54.1)	98% (92.5-100)	50% (0-100)	87.5% (75.3-99.8)	88.6% (77-100)

SN: Sensitivity, SP: Specificity, PPV: Positive Predictive Value, NPV: Negative Predictive Value, Acc: Accuracy. %CI: 95% Confidence Interval.

In the light of PET/CT versus CECT staging, the numbers of patients with unrespectable PDAC were increased; they include patients with liver deposit (7 Vs 4), pulmonary deposits (3 Vs 2), an additional 3 patients with the bone deposits, 3 patients with mediastinal and supraclavicular LNs deposits.

PET/CT did not detect any case of vascular invasion that diagnosed by CECT ***(Table 4)***.

Comparing CECT to PET/CT for TNM staging, T staging with PET/CT showed more accurate diagnosis of tumor size (*P* _ 0.001) and upstaged N disease from N-negative to N-positive in seven patients.

Difference between CECT and PET/CT in N staging was statistically insignificant (*P* _ 0.065) ***(Table 6)***. FDG-PET/CT imaging is also more useful for M staging. Metastases diagnosed on CECT versus PET/CT were 6 and 13 respectively (*P* _ 0.016) ***(Table 5)***.

According to American Joint Cancer Committee staging (AJCC), there is significant difference between CECT based TNM staging and PET/CT based AJCC TNM stage grouping (*P* _ 0.048). PET/CT upstaged 8 patients from stage IA, IB and IIB to stage III (one patient) and stage IV (7 patients) ***(Table 7)***.

Table (7): Comparison between CECT based TNM staging and PET/CT based on AJCC TNM stage grouping.

AJCC TNM staging	CECT (N=24)		PET/CT (N=24)		p-value
	No.	(%)	No.	(%)	
Stage IA	11	(45.8%)	7	(29.2%)	0.048‡
Stage IB	4	(16.7%)	1	(4.2%)	
Stage IIA	0	(0%)	0	(0%)	
Stage IIB	3	(12.5%)	2	(8.3%)	
Stage III	0	(0%)	1	(4.2%)	
Stage IV	6	(25%)	13	(54.2%)	

DISCUSSION:

Pancreatic cancer ranks as the fourth leading cause of cancer death in most countries. The 5-year survival rate is less than 5% [(7)]. Accurate differentiation of benign from malignant disease and correct assessment of disease stage is thus vital to determine optimal treatment approaches [(8)]. Furthermore, due to a non-specific clinical presentation of the cancer, it is often diagnosed at an advanced stage and is rarely amenable for curative treatment [(9)]. Approximately 65% of pancreatic cancers occur in the head (HD) of the pancreas, whereas 15% occur in the body and tail (BT); the remaining lesions diffusely involve the gland [(10)]. ***Rosewicz and Wiedenmann*** [(11)] proved that the pancreatic head is the most common location of pancreatic cancer (70%).

our results showed that PET/CT had higher sensitivity than CECT and ERCP in detection of pancreatic head mass. The present study showed that PET/CT had higher detection rate as compared to CECT and ERCP in evaluation of patients with suspected pancreatic neoplasms.

Our study is concordant with that of ***Farma et al.,*** [12] who stated that the sensitivity of PET/CT is higher than CECT in diagnosing pancreatic cancer (61% Vs 57%). Our observation is also in line with other studies published by ***Buchs et al., & tang et al.,*** [13,14] found high sensitivity values of PET/CT in detection of malignant pancreatic lesions. In addition, ***Zhang*** [15] revealed that FDG PET/CT is more accurate than other imaging methods in diagnosing pancreatic cancer and in differentiating malignant from benign pancreatic neoplasm.

Lytras [16] showed better accuracy of PET/CT compared with CECT in diagnosis of PDAC (91% vs. 78%), which is consistent with our results despite the lower value of our results (63% Vs 44.4%). On the contrary ***Casneuf et al., and Kauhanen et al.,*** [17, 18] proved that the overall sensitivity and specificity of 18F-FDG–PET/CT in the diagnosis of pancreatic cancer is equivalent to that of CECT (89% vs88%) }. We found that PET/CT showed better accuracy for detecting metastatic LNs than CECT, with statistically significant difference between both imaging methods ($P < 0.05$). They were concordant in 14 patients (4 true positive and 10 true negative) and discordant in 13 patients. PET/CT excluded 2 false positive and 11 false negative patients displayed in the CECT images. Our study is in agreement with that done by ***Jian et al*** [19] explained better sensitivity of PET/CT versus CECT in diagnosing lymph node metastasis (63.2% &78.9% respectively). Lymph node staging remains difficult at CT, with a dismal 37% sensitivity and a more acceptable specificity (79%) [20].

In the present study all cases with vascular invasion were diagnosed only by CECT. The sensitivities of PET and CECT in detecting adjacent artery invasions were 22.2% and 100%, respectively [21]. ***Strobel et al.,*** [22] also reported that unenhanced PET/CT failed to allow for the detection of arterial infiltration in all patients compared to enhanced PET/CT that allowed for correctly diagnosing arterial infiltration in all patients who were examined.

Our data proved that PET/CT is more sensitive than CECT in detection of distant metastases especially liver and bone metastases. Both methods are equally well in identifying lung deposits. ***Bang et al.*** [23] proved that 18F-FDG-PET/CT altered the respectability status and management in 22 % of patients. 18F-FDG-PET/CT is superior to CECT in the staging of pancreatic cancer in detection of distant Metastatic disease with sensitivity and specificity of 18F-FDG-PET/CT was 81 and 100 % compared to 56 and 95 % respectively for CECT (4). ***Saif et al.,*** [24] demonstrated that PET/CT improved selec-tion of patients for surgery by depicting primary pancreatic tumors not clearly evident at CT or MR imaging and prevent unnecessary pancreatic resection in as many as 25% of patients by depict¬ing unsuspected metastases. There were some limitations of our study is small number of patients evaluated with pancreatic mass and many patients' presents with metastatic disease at time of imaging.

CONCLUSION:

PET/CT is valuable method in characterization of pancreatic masses in patients where conventional imaging fails to detect it. PET/CT also improve diagnosis and staging in patients with suspected pancreatic cancer. It is significantly improves selection of patients eligible for potentially curative surgery that leads to an improvement in patient's outcome.

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