Original Article, PET/CT.

The value of ^{18}F-FDG-PET/CT in diagnosis of pancreatic cancer as compared to Contrast Enhanced-CT.

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ABSTRACT:

Background: In terms of mortality and malignancy, pancreatic cancer (PC) is one of the major causes of cancer-related deaths with 10% 5-year survival rate. Accurate diagnosis either initially or after therapy may potentially impact therapy and hence survival of patients. ***Aim of the work:*** To find out the value of FDG-PET/CT in initial staging of pancreatic cancer and compare it with contrast enhanced-CT (CE-CT). ***Patients and Methods:*** A retrospective study of thirty adult patients; 23 male and 7 female with pathologically proven pancreatic cancer mostly adenocarcinoma type (90%). The mean age ±SD is.56.3±1.15 years. Patient's data were retrieved from nuclear medicine and radiation oncology department *(NMROK*), faculty of medicine, Cairo university hospital between January 2018 and May 2021. To determine the value FDG-PET/CT in initial staging of PC as compared to contrast enhanced-CT (CE-CT), the findings of the CE-CT and the FDG-PET/CT were compared. ***Results:*** The statistical analysis of 30 patients with pathologically confirmed pancreatic cancer (PC) in this retrospective study found a statistically significant difference between FDG-PET/CT and CE-CT in detecting the primary tumor, lymph node metastasis, and distant metastasis, with P-values of 0.0001, 0.0007, and 0.0037, respectively. Also, there is a statistically significant difference between F-FDG-PET/CT and CE-CT in terms of overall staging (P-value = 0.003799). FDG PET/CT was more sensitive, specific and accurate than contrast-enhanced CT (CE-CT) in staging of primary tumor as well as lymph nodal and distant metastasis.

Conclusion: ^{18}F-FDG-PET/CT may be potentially beneficial to detect the primary pancreatic cancer as well as regional nodal and remote metastatic lesions. ^{18}F-FDG-PET/CT may alter management of pancreatic cancer either by up-staging or down-staging.

Key words: Pancreatic cancer, ^{18}F-FDG PET/CT, initial staging, CE-CT.

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INTRODUCTION:

Pancreatic cancer is an aggressive malignancy with poor prognosis; this is usually attributed to the non-specific and late symptoms as well as early regional and distant metastatic spread [(1)]. It is also considered as one of the major causes of cancer death in the United States with relatively few effective treatments [(2)]. Radical surgery is the only way to treat curable cases of pancreatic cancer [(3)]. However, at the time of the first staging work-up, more than 50% of pancreatic cancer patients have distant metastatic lesions, and only 20% of patients have resectable disease [(4)].

Also, surgical resection carries a high risk of death and illness during the operation. Therefore, accurate initial work-up is essential to find the best treatment modalities for patients [(5)]. Positron emission tomography/computed tomography with 2-deoxy-2-fluorine-18-fluoro-D-glucose (^{18}F-FDG PET/CT) may provide a non-invasive and safe alternative in initial staging pancreatic cancer than conventional imaging staging modalities alone, which could dramatically affect patient care [(6)].

AIM OF THE WORK

To find-out the value of ^{18}F-FDG-PET/CT in initial staging of pancreatic cancer as compared to CE-CT.

PATIENTS AND METHODS

Patient Population:

- Thirty adult patients with pathologically proven pancreatic cancer were retrospectively analyzed, 23 men and 7 women, 90% had biopsy proven adenocarcinoma-type of pancreatic cancer. The patients were presenting in our center for initial staging. All the patients performed whole-body contrast-enhanced diagnostic CT and ^{18}F-FDG-PET/CT study.

- Patient's data were retrieved from nuclear medicine and radiation oncology department, faculty of medicine, Cairo University. Between January 2018 and May 2021.

FDG-PET/CT imaging:

Thirty experiments were done on a PET/CT scanner from Philips Healthcare in Cleveland, Ohio, which has a modular, LYSO-based PET part and a 64-channel CT part.

All individuals were told to fast for at least 6 hours before the study. It was determined that the blood glucose level was under 200 mg/dL. A maximal dose of 15 mCi of ^{18}FDG was supplied intravenously at a dose of 0.125 mCi/Kg. Patients were advised to refrain from strenuous activity, talking, chewing, and excessive swallowing to prevent tracer buildup in their muscles.

Patients were instructed to drink 500 mL of water and urinate frequently before to lying down on the PET/CT scanner table. PET/CT imaging typically begins with the mid-thigh to the base of the skull, with the arms extended above the head, 60±10 minutes after injection. Patients were instructed to breathe fast and shallowly during imaging.

After the CT scan was completed, a caudal-cranial PET scan was performed. Depending on the size of the patient's body, the duration of the scan typically included 12 bed positions with a 2-minute acquisition interval at each bed position.

The PET component is comprised of 23 radial by 44 axial matrices of lutetium-yttrium ox orthosilicate (LYSO) crystal components. The detector modules have an axial field of view of 18 cm and a ring diameter of 90 cm.

The system has a typical field of view hardware coincidence window of 4.5 ns, operates in 3D mode, and logs events from all possible configurations of detector rings in list-mode format (FOV). We used the scanner's in-built reconstruction methods to re-create the data as gated or dynamic pictures.

CT acquisition:

Using 35 mAs and 120 kVp, a preliminary scout view was acquired. Finally, a spiral CT

was performed with exposure parameters of sixty mAs (quality reference), 120 kVp, and a reconstructed slice thickness of five mm for low-dose CT.

Interpretation: Diagnostic CT and PET/CT outcomes were compared to evaluate FDG-PET/ CT's additional role over CECT.

The PET/CT data were analyzed by a team of nuclear medicine physicians. All other imaging modalities' findings were kept secret from the reviewers. Using qualitative (visual) and semi-quantitative analysis, we recorded all regions of increased FDG uptake and classified them as positive or negative for malignancy.

The focus's size, shape, intensity, and localization were the basis for the qualitative analysis. More FDG uptake than the liver, which appeared as a "hot zone" within the pancreas, was used to define primary lesions.

A semi-quantitative measure, we employed the highest possible Standardized Uptake Value (SUVmax). All instances were evaluated using a Standardized Uptake Value (SUV) cutoff of 2.5, which is based on body weight. The lesion's SUV was calculated by analyzing its activity level in the region of interest.

Regardless of their size, malignant tumors have a higher maximum SUV (SUV max) (above a sub centimeter minimum size threshold). That's why it's possible that even the tiniest pancreatic lesions can be detected and monitored with FDG PET/CT.

A consultant radiologist evaluated and interpreted the diagnostic whole body CECT images. According to the established standards for suspicion of malignancy, the results were categorized as either negative or positive for malignancy.

Data analysis: The diagnostic CECT results were compared to the PET/CT findings, patient by patient.

The same anatomical locations, such as the pancreatic, were compared between PET/CT and CECT.

Performance evaluation was made possible by comparing PET/CT and CE-CT to our gold standard. PET/CT and CE-CT findings were classified as either true positive (TP), in which the presence of malignancy corroborated the positive imaging study, true negative (TN), in which the opposite was true, false positive (FP), in which the positive imaging study lacked supporting evidence, or false negative (FN), in which supporting evidence did exist.

Statistical Analysis:

1. Minimum, maximum, mean, standard deviation or number (%) was used to express the results. Using the Chi square test, categorical data were compared.
2. CE-CT and PET/CT were compared for main tumor, lymph node, distant metastasis, and total staging using the Chi-square test. The R statistical programming language (version 4.0.3) was used for this investigation.
3. To be statistically significant, the p-value had to be less than 0.05 and to be extremely so, it had to be less than 0.01.
4. Standard diagnostic indices such as sensitivity, specificity, PPV, NPV, and diagnostic accuracy were computed utilizing the performance tables.

a. The percentage of diseased cases that were correctly diagnosed (TP) out of all diseased cases (TP+FN) is known as the diagnostic sensitivity.

b. The diagnostic specificity is the proportion of non-diseased cases that the test (TN) really excludes from the total non-diseased cases (TN+FP).

c. A +ve test's predictive value: Its percentage of instances that were accurately diagnosed (TP) is calculated from all positive cases (TP+FP).

d. A -ve test's predictive value: Its percentage inside all cases that are actually negative (TN+FN) is what is meant by the definition.

e. The test's effectiveness or diagnostic precision: Its percentage among all instances (TP+FP+FN+TN) that are both truly ill and truly unwell (TP+TN) is its definition.

RESULTS:

This retrospective study incorporated data from 30 individuals whose diagnoses of pancreatic cancer (PC) were confirmed by pathology. Patient records from the Nuclear Medicine Department at Kasr El-Ainy Hospital were analyzed (NMROCK). Tissue biopsy and/or clinical follow-up were used as control criteria for the nature of the detected lesions. Patients encountered in the study were 23 males (76.7%) and 7 females (23.3%). With mean age ± SD = 56.3±1.15. The pathology is mostly adenocarcinoma type ***(Table 1)***.

Table (1): Demographic Features of the Studied Patients.

Characteristics	Frequency	Percentage
Gender: **- Male** **- Female**	 23 7	 76.7% 23.3%
Age: *mean ± SD*	56.3±1.15	
Pathology: **- Adenocarcinoma** **- Undifferentiated carcinoma** **- Mucinous carcinoma**	 27 2 1	 90% 7% 3%

Statistically significant differences were found between ^{18}F-FDG-PET/CT and diagnostic CT for T (primary tumor), N (nodal), and M (distant metastases) staging (P 0.0001, 0.0007, and 0.0037, respectively) ***(Table 2)***.

Table (2): Comparison of ^{18}F-FDG-PET/CT Versus diagnostic CT regarding primary tumor; nodal and distant metastases of 30 patients**.**

		PET/CT		CT		p-value
		No.	%	No.	%	
T (primary tumor)	T0	3	10%	7	23%	0.0001*
	T1	2	7%	2	7%	
	T2	4	13%	3	10%	
	T3	11	37%	11	37%	
	T4	10	33%	7	23%	
N (nodal)	N0	15	50%	16	53%	0.0007*
	N1	11	37%	11	37%	
	N2	4	13%	3	10%	
M (distant metastases)	M0	9	30%	13	43%	0.0037*
	M1	21	70%	17	57%	

Regarding overall staging by ^{18}F-FDG-PET/CT and diagnostic CT, there was statistically significant difference with *P*-value 0.0037. Stage IV was the most frequent stage among both modalities but CT can't assess the overall stage in one patient ***(Table 3)*.**

Table (3): Results of the overall staging among PET/CT and diagnostic CT of 30 patients.

	Zero	IA	IB	IIA	IIB	III	IV	*p*-value
PET/CT	2 (7%)	1 (3%)	1 (3%)	3 (10%)	0	2 (7%)	21 (70%)	0.0037*
CT	3 (10%)	1 (3%)	0	2 (7%)	2 (7%)	4 (13%)	17 (57%)	

**Statistically significant p value <0.005*

As compared with diagnostic CT; ^{18}F-FDG-PET/CT changed accurately overall staging in 6/30 patients (20%) by upstaging five cases and down staging one patient. Accordingly, it changed the plan of management in 7 patients ***(Table 4)*** ***(Figure 1, 2)***.

Table (4): Patient cases where FDG-PET/CT findings altered management.

Patient	PET/CT staging	Site	Diagnostic CT staging	SUVmax	Comment
1	T4N2M1 -(IV)	LNS	T4N2M0-III	3	Revealed metastatic cervical LNS
2	T1N0M1 -(IV)	Liver	T1N0M0-IA	2.8	Detects liver lesion
3	T4N1M1 -(IV)	Liver	T4N1M0-III	3	Detects liver lesion
4	T4N2M1 -(IV)	LNS	T4N1M0-III	4.2	Revealed metastatic supraclavicular LN
5	T0N0M1 -(IV)	Liver	T0N0M0-zero	5	Detects liver lesion
6	T2N0M0 -(IB)		T0N0M1- IV-(liver)		PET/CT ruled out suspected liver metastasis by CT

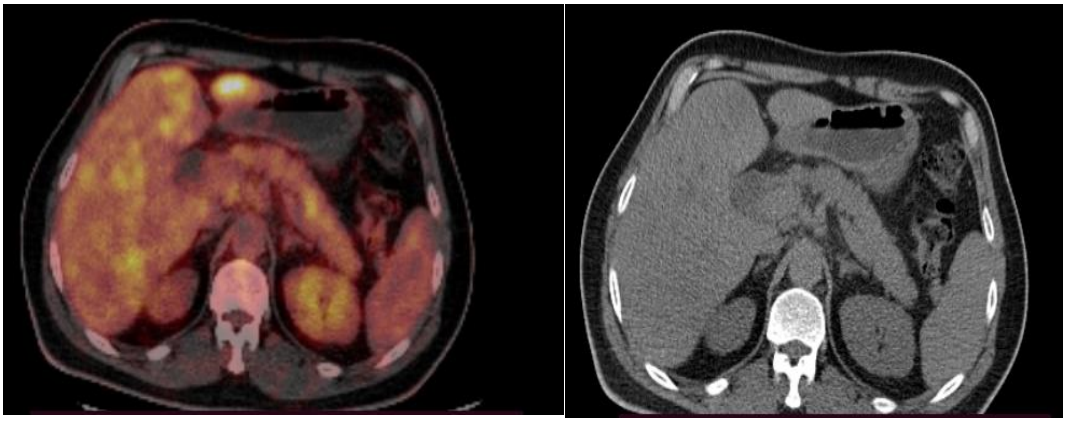

Figure (1): 57-year-old patient diagnosed with pancreatic adenocarcinoma. PET/CT showed hepatic focal lesion which is not seen in CT which resulted in upstaging of the patient from M0 to M1 saving the patient from unnecessary surgery.

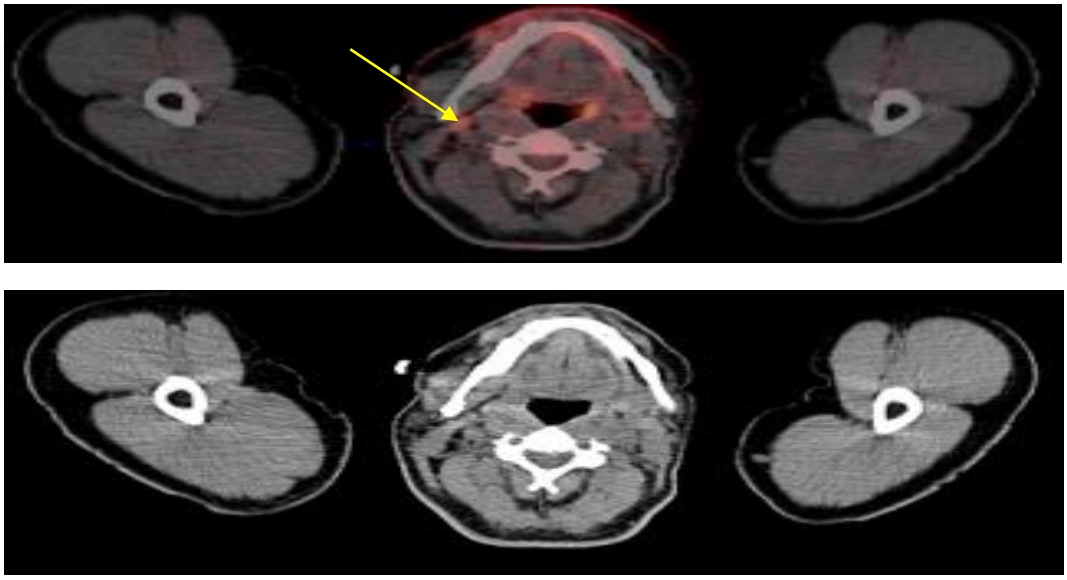

Figure (2): 60-year-old patient with pancreatic undifferentiated carcinoma. PET/CT showed right cervical lymph node that measured 1.2 cm with SUVmax 5. Biopsy revealed metastatic undifferentiated carcinoma.

Overall, primary lesion detectability was shown to be 96.2% sensitive, 75.0% specific, 96% positive predictive value (PPV), 75% negative predictive value (NPV) and 93% accurate with PET/CT and 76.9% sensitive, 75.0% specific, 95.2% positive predictive value (PPV), 33% negative predictive value (NPV) and 76.7% accurate with diagnostic CT ***(Table 5)***.

Table (5): Sensitivity, Specificity, PPV, NPV and accuracy of primary tumor detection.

	PET/CT	CT		PET/CT	CT
True Positive	25	20	**Sensitivity**	96.2%	76.9%
False Positive	1	1	**Specificity**	75%	75%
True Negative	3	3	**PPV**	96%	95.2%
False Negative	1	6	**NPV**	75%	33%
Total	30	30	**Accuracy**	93%	76.7%

Whereas diagnostic results for regional LNs metastases detection showed a Sensitivity, Specificity, PPV, NPV and accuracy are 65%, 100%, 100%, 58.8% and 76.7% for PET/CT and 36.8%, 72.7%, 70%, 40% and 50% for diagnostic CT, respectively ***(Table 6)***.

Table (6): Sensitivity, Specificity, PPV, NPV and accuracy of lymph node metastasis detection.

	PET/CT	CT		PET/CT	CT
True Positive	13	7	**Sensitivity**	65%	36.8%
False Positive	0	3	**Specificity**	100%	72.7%
True Negative	10	8	**PPV**	100%	70%
False Negative	7	12	**NPV**	58.8%	40%
Total	30	30	**Accuracy**	76.7%	50%

PET/CT was shown to have a sensitivity of 100%, specificity of 90%, PPV of 95.2%, NPV of 100%, and accuracy of 96.7% for the detection of distant metastases, while diagnostic CT had only 75% sensitivity, 80% specificity, 88.2% PPV, 61.5% NPV, and 76.7% accuracy ***(Table 7)***.

Table (7): Sensitivity, Specificity, PPV, NPV, and accuracy of distant metastasis detection**.**

	PET/CT	CT		PET/CT	CT
True Positive	20	15	**Sensitivity**	100%	75%
False Positive	1	2	**Specificity**	90%	80%
True Negative	9	8	**PPV**	95.2%	88.2%
False Negative	0	5	**NPV**	100%	61.5%
Total	30	30	**Accuracy**	96.7%	76.7%

As regarding the Sensitivity, Specificity, PPV, NPV and accuracy of overall staging, they are 96.2%, 75%, 96.2%, 75% and 93.3% for PET/CT and 76%, 50%, 90.5%, 25% and 72.4% for diagnostic CT respectively ***(Table 8)***.

Table (8): Sensitivity, Specificity, PPV, NPV and accuracy of overall staging**.**

	PET/CT	CT		PET/CT	CT
True Positive	25	19	**Sensitivity**	96.2%	76%
False Positive	1	2	**Specificity**	75%	50%
True Negative	3	2	**PPV**	96.2%	90.5%
False Negative	1	6	**NPV**	75%	25%
Total	30	29	**Accuracy**	93.3%	72.4%

DISCUSSION:

Pancreatic Cancer (PC) is currently considered the second most common cause of cancer-related deaths worldwide. It is usually less prevalent in Egypt's however; it is is diagnosed at a very young age [(7)]. It frequently manifests at an advanced stage, which adds to low five-year survival rates of 2% to 9%, placing it at the very bottom of all cancer sites in terms of patient prognoses [(8)].

Because of its aggressive, invasive character, pancreatic cancer has a poor prognosis (the depth of invasion is a prognostic predictor), and its early spread to both nearby (such as the lymph nodes) and far-off areas (such as the liver, peritoneum, or lungs). The lack of distinct symptoms and the delay in diagnosis further worsen the prognosis [(1)].

At the time of the first staging evaluation, only 20% of patients were considered to have moderate illness. However, distant metastatic lesions affect more than half of those with pancreatic cancer [(4)]. Therefore, the most important clinical factors for selecting the initial therapeutic strategy are an early diagnosis and an accurate staging [(9)].

Diagnostic contrast enhanced CT (CE-CT) is often the first-line imaging modality used to evaluate individuals suspected of having PC. Small lesions under 2 cm, iso-attenuating pancreatic cancer lesions, and post-treatment assessment are difficult to assess and can be missed on CT, nevertheless [(10)].

The liver and peritoneum are the most frequent sites of metastasis for pancreatic cancer; however, CE-CT may miss many of these lesions [(11)].

Compared to other conventional imaging methods, ^{18}FDG PET/CT is a promising non-invasive modality that may be more effective at diagnosing, staging, and evaluating pancreatic cancer patients after treatment Our goal with this retrospective study was to compare the utility of ^{18}F-FDG PET/ CT with that of diagnostic CT alone in the initial staging of individuals with proven PC.

The hallmark of our study analyzing 30 adult patients with biopsy proven PC was that the sensitivity, specificity and accuracy of FDG-PET/CT in initial staging of primary PC was 96.2%, 75% and 93% respectively compared to 76.9%, 75% and 76.7% respectively for CE-CT. These findings were in agreement with those from prior research by ***Shaban*** [(12)].

They retrospectively analyzed twenty patients with pancreatic cancer and they found that FDG-PET/CT is more sensitive, specific and accurate than CT in diagnosing pancreatic cancer with 100% sensitivity, 88.9% specificity and 95% accuracy compared to 77.8 sensitivity 54.5% specificity and 65% accuracy for CT.

Similarly, ***Asagai et al*** **(13)** and ***Kauhanen et al.*** **(14)** also found in their studies that the diagnostic accuracy of FDG PET/-CT in PC was more than 80% as compared to lower values according to diagnostic CT readings.

In our study, the primary pancreatic lesion was analyzed qualitatively (visual) and quantitatively. In the quantitative analysis of the primary pancreatic lesion we found that the SUVmax of the primary lesions in our sample varies from 3 to 26.8, with a median of 7.5. This was consistent with the findings of ***Myssayev et al.,*** **(15)**.

One case of false negative was found and one case of false positive in our study. It's possible that the mucinous nature of the tumor contributed to its underestimation (hypocellular tissue).

CT didn't show evidence of the primary disease in the pancreas in five cases which were recorded as T0. Three of them appeared as diffuse enlargement rather than mass lesion and the other two cases were small lesions, however, in these patients ^{18}F-FDG PET/CT showed the lesions with high metabolic activity.

Regarding lymph nodal staging (N stage), although PET/CT is more sensitive than CE-CT in detection of lymph nodal metastasis in our study, yet the sensitivity of PET/CT is not very high (65% compared to 36.8% for CT). Studies by ***Wang et al.*** **(16)** and ***Asagi et al.*** **(13)** also showed poor performance for assessing nodal metastasis, with sensitivity values of 30-53 and 17-30% with PET/CT and CECT, respectively. Since CT's usefulness in evaluating lymph nodes is contingent on factors including nodal size and enhancement, it may fail to pick up on very small lymph nodes.

Among the 30 patients recruited, ^{18}F-FDG PET/CT under-staged the nodal status in seven, although there were no false positives. Their N1 status, which was incorrectly identified as N0, was confirmed by subsequent research. These restrictions may be attributable to a lack of spatial resolution, which obscures details such as the number of cancer cells in the lymph nodes or microscopic metastases in normal-sized LNs, or to the masking effect of significant radioactive scatter from the main tumor on peripancreatic tiny LNs.

Regarding distant metastasis staging (M stage), our research demonstrated that PET/CT is more accurate than CE-CT in detection of distant metastasis and this matches with results of ***Shaban*** [(12)]. Our data showed that FDG-PET/CT was 100% percent sensitive, 90 percent specific, 95.2 percent positive predictive value (PPV), 100 negative predictive value (NPV) and 96.7 % accurate, while diagnostic CT was 75 % sensitive, 80 % specific, 88.2 % positive predictive value (PPV), 61.5 % negative predictive value (NPV) and 76.7 % accurate.

The interpretation of ^{18}F-FDG PET/CT identifies 20 patients (66.7%), with true positive distant metastases at initial presentation (M1), involving the liver (18 patients), distant lymph nodes (13 patients), the lungs (4 patients), the peritoneum (3 patients), and the bones (2 patients).

As a result, the treatment strategies for six (20%) of the 30 patients involved in the study were modified for the better; five were upstaged, and one was down-staged. By detecting undetected distant metastatic liver lesions in three cases and distant lymph nodes in two cases, the patients in these circumstances were spared unnecessary surgery, making this the most common reason for a change in treatment strategy. One patient's diagnosis was revised downward after PET/CT confirmed the absence of a liver lesion that had been suspected.

Similar research into the utility of PET/CT scanning for the management of operable pancreatic and peri-ampullary tumors was conducted by ***Burge et al.*** [(17)], who conducted a prospective trial including 56 patients. Multiple nodal groups, including the cervical, supraclavicular, mediastinal, and retroperitoneal, were also affected, as well as the liver, as seen on PET/CT. This research suggests that 9 of 56 patients (16%) made the right call by opting out of potentially dangerous surgery.

Also, ***Heinrich et al.*** [(18)], who conducted another investigation on the role of PET/CT in the management of advanced pancreatic cancer, found that in 13 of 43 cases of pancreatic adenocarcinoma, including 5 in which diagnostic CT was negative, PET/CT detected metastases. A spiral CT scan found one of three missing hepatic lesions, and laparoscopy uncovered the other two, each smaller than 5 mm. There were no false positives. This means that compared to CT alone, PET/CT diagnostics were 100% specific and (81% sensitive compared to 56%) in identifying distant metastases.

In a retrospective analysis, ***Farma et al.*** [19] discovered that FDG PET/CT revealed metastases in 14 of 82 patients with potentially credible PC, and in seven patients, metastases present in FDG PET/CT were not observed on morphological imaging (supraclavicular lymph node, , peritoneal carcinomatosis, peri-esophageal lymph node, liver, and supraclavicular lymph node).

Limitation of the study: We encountered few limitations in this retrospective study such as the relatively small sample size as we excluded patients with incomplete data like histopathology and that we only performed short term follow-up and didn't include the long-term follow-up of the patients and therefore the impact of change of management on patient' survival.

CONCLOUSION:

FDG PET/CT appears to be more sensitive than CE-CT in the initial diagnosis of pancreatic cancer, and is useful in detecting the primary tumor as well as regional nodal and distant metastases. Also, FDG PET/CT can alter management of pancreatic cancer by either upstaging or down staging.

Declaration of competing interest: Authors declares that there is no conflict of Interest.

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