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Impact of ^{18}F-FDG-PET/CT in detection of the primary site and change management in patients with metastases of unknown primary.

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ABSTRACT:

Aim of work: To evaluate the significance of PET/CT in detection of the primary of metastases of unknown origin and its role in changing management. **Patients and methods:** A prospective analysis of 123 patients, with pathologically proved or clinico-radio logically suspected metastatic lesions of unidentified primary. All patients had previous examination and investigational check-up tests including labs, radiologic studies and histopathology before undergoing ^{18}FDG PET/CT study, with a follow-up period of 12 months. **Results:** This study included 66 males and 57 females with mean age 53.98±12.9 (range=23-85) years. Main sites of presenting metastases were bone (29%) and lymph nodes (22%) followed by liver (17%) and brain (11%). Histopathology revealed poorly differentiated carcinoma in 42% of patients; however, 27% of patients came with no pathology. PET/CT identified the primary site in 71 patients with commonest site in 16 patients in lung followed by pancreas and breast (9 patients each). False positive was evident in 6 patients, and it excluded malignancy in 19 patients. False negative results were found in 27 studies, 24 of which remained unknown till the end of follow-up period. Sensitivity, specificity, PPV, NPV and accuracy were 72%, 76%, and 79%, 41% and 73% respectively. PET/CT identified additional sites of metastases in 64 patients. PET/CT altered the management in 90 patients by avoiding unnecessary chemotherapy in negative patients or providing treatment targeting known primary tumor, including surgery with curative intent in 9% of patients.

During the follow-up period of the 71 patients, 12 patients achieved complete response, 12 patients showed partial response and 25 patients had stable disease.

Conclusion: ^{18}F-FDG PET/CT is additive imaging modality that help in early detection of the primary malignant site in patients with MUO and so enabling selection of suitable management protocols that might improve patients' outcome.

Key Words: MUO, 18FDG PET/CT.

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INTRODUCTION:

Cancer of unknown primary origin (CUP) includes a cluster of heterogeneous tumours that have exceptional clinical features: it is defined as early apparent metastatic disease with no recognizable primary site at the time of presentation **(1).** The incidence of CUP ranges around 2% of all new cancer diagnoses **(2).**

The work up list of CUP include; a biopsy proven malignancy, a detailed physical examination, many laboratory, radiological and endoscopy. However, these investigations may be costly time-consuming and may eventually fail to detect the site of the primary malignant tumor in the majority of patients **(3).** In this context, positron-emission tomography (PET) combined with computed tomography (PET/CT), using the radiotracer ^{18}F fluoro- 2-deoxyglucose (FDG) is an alternative, non-invasive imaging modality with accurate diagnostic performance. It considered good tool for diagnosis of patients with CUP **(4).** The basis for use of FDG as radiotracer for PET imaging in CUP depends on the fact that most of the malignant cancer phenotypes show an increased glucose metabolism rate **(5).**

Failure to identify the primary tumor hampers optimization of management planning, which in turn may adversely influence patient prognosis **(6).**

Patients with CUP are classified into subgroups and specific risk classifications according to the organs involved (disease stage) and histology in order to improve patient management **(7).**

Patients with the differentiated and chemo sensitive tumours (about 15-20%) have more favourable prognosis and longest survival rates. Unfortunately the majority of patients with CUP do not belong to any specific category.

They have the bad prognosis and displaying a substantial resistance to therapy being associated with diagnosis of: metastatic hepatic adenocarcinoma, malignant ascites, multiple cerebral deposits, many lung/pleural metastases, or systemic bone disease [8].

Aim of the work:

To evaluate the role of ^{18}FD-PET/CT in detection of the primary site and to assess its impact in directing the change management in patients with metastases of unknown origin or those with clinico-radiological suspicious of having metastases.

PATIENTS AND METHODS:

This prospective study included 123 patients (66 male&57 female, with mean age 53.98) from the National Cancer Institute (NCI) and Zagazig university hospitals between January 2011 and October 2015. All patients presented with either pathologically proven metastases or with clinic-radiological suspicious of having metastases.

In addition to the prior investigations that delivered with the patient on presentation, all patients were subjected to full clinical examination and routine investigational workup including (CT and / or MRI, tumor markers measurement and histopathological examinations of obtained specimens from metastatic sites or from the suspected primary sites). Upper & lower GIT endoscopies were also done for some patients with suspected GIT tumours.

Inclusion criteria: Patients with age more than 18 years presented with either pathologically proved metastases of unknown primary or with clinico-radiological suspicious of having metastases.

Exclusion criteria: Age below 18 years, patients with pathologically proved primary tumor, patients with life span less than 6 months, patients with severe illness, pregnant and lactating women.

PET/CT imaging protocol:

***Patient preparation*:** Patients fasted for 4 - 6 h before PET scanning to optimize the blood sugar level to 160mg/dl. F-18 FDG dose was 0.14 mCi/kg and injected via intravenous route. During the uptake phase of 18F-FDG patients were rested in a quite warm room. All PET-CT studies were done at the nuclear medicine unit of national cancer institute.

PET-CT images were interpreted at a workstation equipped with fusion software that offers multi-planar reformatted images and enables display of the PET images, CT images, and fused PET/CT images.

Image Interpretation: All Whole-body PET/CT images were qualitatively & quantitively interpreted by 2 nuclear medicine physicians.

Qualitative (Visual) assessment: Any focal 18F-FDG uptake more than the hepatic reference was interpreted as abnormal lesion.

Quantitative assessment: The maximum standardized uptake values (max SUV) were calculated and registered for each lesion in each patient. For further quantitative analysis, another sizable ROI was drawn over the normal liver, where its max SUV was considered reference activity to calculate max SUV Lesion/ liver ratio.

Data Analysis: All findings from whole-body ^{18}F-FDG PET/CT images were revised and any lesions of increased 18F-FDG uptake suggestive of a primary malignant lesion were identified. A suspected primary lesion was defined as a focal lesion with high FDG uptake on PET images with SUV max value more than the reference hepatic activity.

Follow up: Follow up were done for all true positive patients for 6-12 months after the end of the decided therapy plan (either chemotherapy and / or radiotherapy) according to the diagnosis of each patient. At the end of this follow up period, assessment of therapy response was done depending on Modified CT RECIST Criteria to assess response to therapy and divides patients accordingly in to complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) depending on size of the target lesion and presence or absence of new lesions.

It assesses response to therapy depending on: (activity of lesions & appearance or disappearance of new FDG avid lesions) and accordingly divide their response in to Complete Metabolic Response (CMR), Partial Metabolic Response(PMR), Stable Metabolic Disease (SMD)& Progressive Metabolic Disease (PMD).

True Positive PET/CT results: The site of the primary malignancy was classified as **true positive (TP)** only when it showed metabolically active FDG uptake with SUV max higher than the reference hepatic activity and confirmed histologically during the follow up.

False Positive PET/CT results: When the FDG avid lesion was proved benign by histological examination, or if the patient didn't show any signs of malignancy during the clinico/radiological follow-up period.

True Negative PET/CT results: if neither FDG-PET images nor histological findings clinical follow-up or other imaging determined the site of the primary or metastatic sites.

False Negative PET/CT results: If PET/CT imaging fails to detect the site of the primary or metastatic sites, but confirmed either histologically or by other follow up imaging studies.

Statistical Analysis: Data was analysed by SPSS win statistical package version 21 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. For quantitative data, comparison between two groups was done using either student t-test or Mann-Whitney test (non-parametric t-test) as appropriate. A p-value < 0.05 was considered significant.

RESULTS:

This study was carried out on 123 patients with either pathologically proved metastases of unknown primary or with clinico-radiological suspicious of metastases with unknown primary. From the 123 patients, 66 (54%) were males and 57 (46%) were females, their age ranged from 23 to 85 with mean of 53.98 ± 12.9 years. As regarding CT and/or MRI findings, 36 patients (29.3%) of the studied patients presented with bone lesions (the commonest site affected), 27 (22%) presented with LN lesions, 21 (17.1%) presented with liver lesions, 5 (4.1%) presented with lung lesions, 10 (8.1%) presented with malignant effusion, 13 (10.5%) presented with brain lesions and 11 patients (8.9%) had soft tissue masses, subcutaneous nodules or elevated tumor markers as shown in ***Table (1)***.

PET/CT detected metastatic lesions in 77/123 patients (62.6%); the most common site was LNs (61 patients), followed by bone (35 patients), lungs (18 patients), liver (10 patients), brain (5 patients) and others in 28 patients (including suprarenal glands in 10 patients, peritoneum in 7 patients, skin and subcutaneous tissue in 6 patients, 5 patients as intra muscular metastases, spinal cord & soft tissue lesions). The variation in mean value of SUV max according to site of metastatic lesion was also displayed in ***Table (1)***.

The remaining 46/123 patients (37.4%) were Non-FDG avid tumours and PET/CT wasn't able to identify the primary tumor.

Table (1): Sites of metastases detected by CT and/or MRI and Baseline PET/CT.

Site	CT and/or MRI (Total Patients No= 123)		Baseline PET/CT (Total Patients No= 77)	
	Patients No.	Percent (%)	Patients No.	Mean SUV ±SD
Bone	**36**	**29.3%**	**35**	**11.6±9.4**
LN	**27**	**22.0%**	**61**	**8.1±5.1**
Liver	**21**	**17.1%**	**10**	**9.5±5.7**
Lung	**5**	**4.1%**	**18**	**6.2±5.2**
Malignant effusion	**10**	**8.1%**	**10**	**------**
Brain	**13**	**10.5%**	**5**	**10.4±4**
Others	**11**	**8.9%**	**28**	**10.3±7.1**

We found FDG avid lesions, suggestive of primary malignant tumours in 77/123 patients (62.6%), malignant primary sites were proved pathologically in 71 patients. The commonest sites of malignant primary tumours were displayed in in descending order according to the frequency of the involved sites. The lung is more frequent primary site in 16 patients , followed by pancreas and breast (each 9 patients) , while the kidney, and ovary, colon and prostate (each 5 patients) ***(Table 2) . (Figure 1, 2)*** showed value of PET/CT in detection of primary site.

Table (2): Sites of Pathologically proved Primary Tumours detected by PET/CT:

Site	Patients No (Total=71)	Percent (%)	Minimum SUV	Maximum SUV	Mean±SD
Lung	16	22.5%	2.6	18.2	10.1 ± 4.7
Pancreas	9	12.8%	3.7	8.4	6.4 ± 1.7
Breast	9	12.8%	1.6	8.6	5.6 ± 2.3
Ovary	5	7%	4.8	9.4	6.7 ± 1.8
Colon	5	7%	5.7	17	10.4 ± 4.6
Prostate	5	7%	3.2	29.7	17.4 ± 9.8
Lymphoma	4	5.7%	2	10	6.8 ± 5.5
Thyroid	3	4.2%	14.6	97.2	45.8 ± 44.8
Liver	3	4.2%	4.9	11.6	7.9 ± 3.4
Uterus	2	2.8%	7.5	21.3	14.4 ± 9.7
Kidney	2	2.8%	19.2	26	22.6 ± 4.8
Nasopharynx	2	2.8%	10	16.7	-------
Mesothelioma	1	1.4%	5.6	11.2	-------
Seminal vesicle	1	1.4%	16	22.4	-------
Ependymoma	1	1.4%	3	6.5	--------
Thymoma	1	1.4%	13	18.9	--------
Vallecula	1	1.4%	16.3	23.6	-------
Urinary bladder	1	1.4%	11	19.2	-------

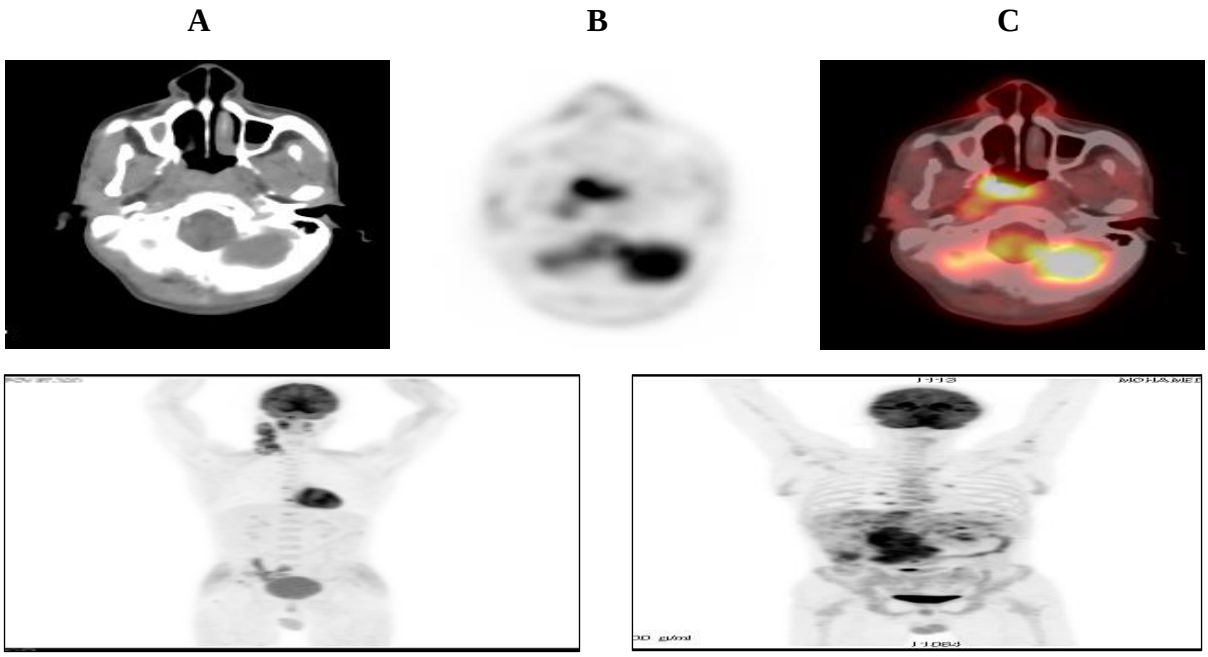

Fig. 1: Fifty two years old male patient presented with right cervical mass, ***(A, B &C)*** PET/CT axial fused images revealed FDG avid mild thickening at right side of the nasopharynx extending to the right parapharyngeal space that proved pathologically to be the primary site. ***(D)***: PET coronal (MIP) image revealed multiple FDG avid right cervical lymph nodes involving the whole right cervical chain down to right supraclavicular lymph node. (E***):*** Follow up PET/CT shows newly developed metastatic nodal, lung, hepatic and osseous deposits.

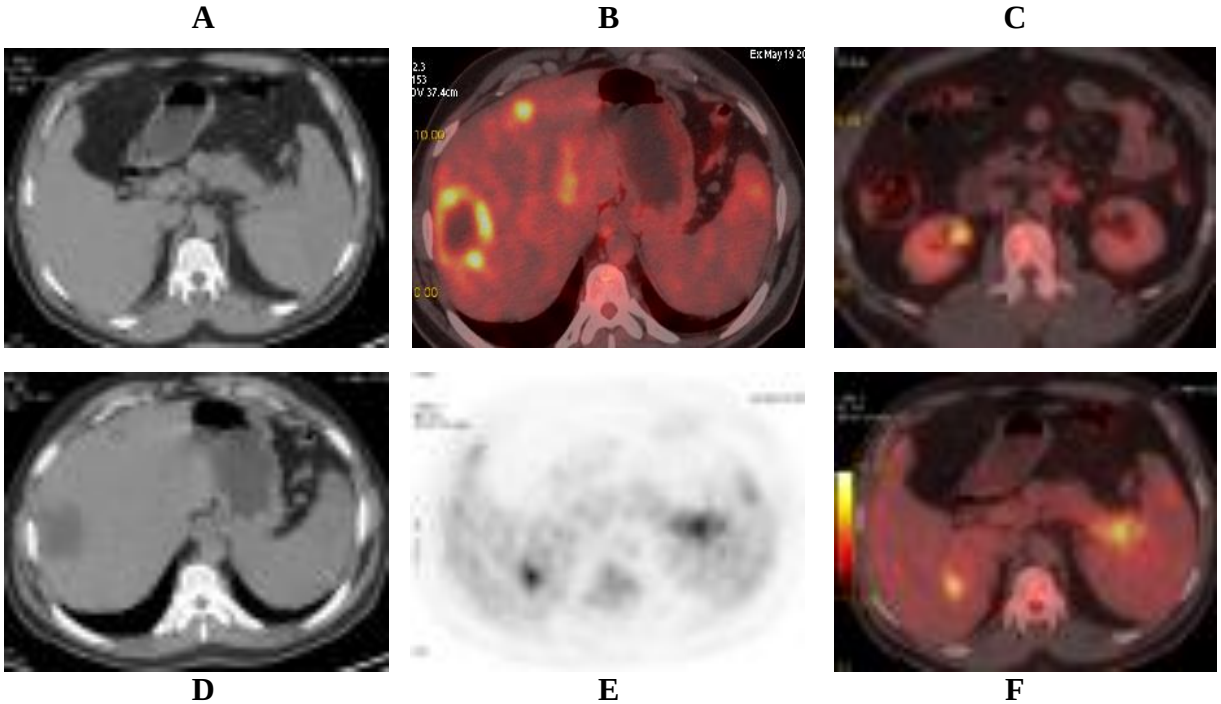

Fig. 2: Fifty one years old male, presented with hepatic focal lesion and elevated CEA. ***(A &B)***: PET, CT & axial fused images show multiple HFLs & splenic focal lesion. ***(C)***: PET, CT & axial fused images show metabolically active FDG avid left para aortic lymph node. **(D, E &F):** PET, CT& axial fused images show metabolically active FDG avid lesion at tail of pancreas that was confirmed by histopathology as the site of primary.

Histopathological subtypes: In 33 out of 123 patients (26.8%) with clinico-radiological suspicion of metastases was encountered without histopathologic evidence, while the remaining 90 (74.2%) patient's pathology was done. It showed 52 patients (42.3%) had poorly to undifferentiated carcinoma, 34 patients (27.6%) had well to moderately differentiated adenocarcinoma and 2 patients (1.6%) had squamous cell carcinoma. Other histopathologies were found in 2 patients (1.6%) and they included small cell carcinoma and round cell tumor.

Sensitivity, Specifity, PPV, NPV and Accuracy: PET-CT findings were concordant with histopathological data in 90 patients (71 patients (57.7%) were positive for malignancy and 19 patients (15.4%) didn't have malignant tumours).

All patients with negative FDG uptake (n=19) were proved to be free from any neoplastic lesions revealed for medical treatment being attributed to (osteoporosis in 1 patient, hyperparathyroidism in 3 patients, chronic nonspecific lymphadenitis in 3 patients, liver cysts in 4 patients, haemangioma in 3 patients, renal cysts with solid component in 2 patients, non-functioning ovarian cyst in 3 patients).

Discordance between PET-CT findings and histopathological results were found in 33 patients, as false positive results were seen in 6 patients (4.9%) and 27 patients (22%) showed false negative results. The false positive results include 3 patients with lung lesions (proved to be sarcoidosis, tuberculosis and inflammatory lung changes, on patient each). The remaining false positive lesions were hyperplastic colon polyp, thyroiditis and prostatitis. Among 27 patients with false negative results, malignant tumours were later detected and pathologically confirmed in 3 patients during the follow up period (1 breast cancer, 1 multiple myeloma & 1 cancer of vallecula). However, in the remaining 24 patients, primary tumor was still not known and they received empirical chemotherapy ***(Table 3).***

In our study, the false negative results of FGD-PET/CT (24 patients) were found to be due to undetectable lesions (small sized lesions less than 1cm) in 8 patients , low FGD avid tumours less than the hepatic reference SUV max value that represented in 4 patient with mucinous tumours (3 colonic & 1 ovarian lesions), broncho alveolar carcinoma in 3 patients, Hepatocellular carcinoma in 2 patients , 2 patient with well differentiated prostate cancer , 1 patient with renal cell carcinoma, as well as 4 patient with recent history of chemo and/ or radiotherapy.

In the search for an occult primary, the sensitivity, specificity, PPV, NPV and total accuracy of PET-CT were 72%, 76%, 78.9%, 41.3% and 73.1% respectively ***(Table 3)***.

Table (3): Sensitivity, Specifity, PPV, NPV and Accuracy in 123 patient's unknown primary site.

	Patient's No. (Total No=123)	Percent (%)
True Positive	71	57.7
True Negative	19	15.4
False Positive	6	4.9
False Negative	27	22
Sensitivity	--------	72
Specificity	--------	76
Positive Predictive Value	--------	78.9
Negative Predictive Value	--------	41.3
Accuracy	--------	73.1

Change of management:

PET/CT changed further management in 90 patients counting for 73.1% of the studied 123 patients including true positive and true negative patients. In all true positive patients (n=71), chemotherapy protocol was changed and received specific therapy for lung, pancreas, breast, ovarian, lymphoma, renal, uterine, Nasopharynx, liver, bladder, thyroid and prostate cancers. Also, detection of other metastatic lesions that was previously unrecognized prompted inclusion of relevant areas for radiotherapy in 40 patients who had brain, bone and nodal metastases. Furthermore, 8.9% underwent surgery with a curative intent.

Follow up of patients:

Regarding post therapy follow up for a period of 6 months of 71 true positive patients, 49 patients (69%) were responded to given therapy in the form of: 25 patients (35.2%) showed stationary course of the disease and 12 patients had partial remission whereas 12 patients were completely cured (4 patients had breast cancer, 2 patients with thyroid cancer, 2 patients with lymphoma and one patient with each of meningioma, Ependymoma, colon and vallecula cancer.

The remaining 22 patients, 9 patients had disease progression, while 7 patients lost follow up and 6 patients died ***(Table 4)***.

Table (4): Results of therapy response in true positive patients.

Response to therapy	Number (N=71)	Percent (%)
Complete remission (CR)	12	16.9%
Partial remission (PR)	12	16.9%
Stationary disease (SD)	25	35.2%
Progressive disease (PD)	9	12.7%
Lost follow up	7	9.8%
Died	6	8.45%

DISCUSSION:

Cancer of unknown primary (CUP) was described as metastatic tumor without sure primary site. The failure to recognize the primary site should be based on clinical evaluation, complete physical examination, routine laboratory and imaging tests as well as careful review of histological specimens [(8)].

In the present work, the lung is the most common primary site is the lung followed by pancreas and breast cancers. Then came ovarian, colon and prostate cancers.

Also, ***Le Chevalier et al.,*** in a study of 302 patients with metastases of unknown primary, reported that hidden pancreas & lung carcinomas are the most frequent sites of primary tumours. They were found in 26.5% & 17.2% respectively [(9)].

Pentheroudakis et al, in a retrospective study of 120 patients found that lung cancer is the most common site of primary malignant tumor in patients with metastases of unknown primary representing 19 out of 54 (35.1%) true positive patients [(10)].

In our study, FDG-PET identified the primary site in 71/123 patients (57.7%) presenting with either pathologically proven or clinically suspected malignancy. PET suggested primary sites in 6 patients (4.9%) but were proven to be false positive as none of them was malignant by histopathology. In the remaining 37.4% patients where FDG-PET did not identify a primary tumor site, 19 of them were proved to be free of malignancy, including (osteoporosis, hyperparathyroidism, chronic nonspecific lymphadenitis, liver cysts, haemangioma, renal cysts and non-functioning ovarian cyst). False negative PET-CT results were exhibited in 27 patients (27%), 3 of them eventually became clinically evident during follow up and were detected by conventional radiology and/or endoscopy and in the other 24 patients primary tumor still wasn't known.

We found that the sensitivity, specificity and accuracy of PET/ CT in detection of unknown primary were 72%, 76% and 73.1% respectively, indicating that it was an effective diagnostic tool that provide the advantage of metabolic information over conventional imaging methods.

Also ***Han et al,*** results were comparable except for a higher reported sensitivity in their study **(11).**

Our results showed an agreement with a meta-analysis by ***Kwee et al,*** including 11 studies during the period from 2005 to 2007, reported that the detection rate of PET/CT was 22-73% in patients with CUP; Sensitivity of FDG-PET/CT in primary tumor detection ranged from 55% to 100% and specificity is ranged from 73% to 100%. These variable diagnostic yields might be due to different patient inclusion criteria and the extent of the diagnostic workup in different studies **(4)**.

Our findings include 6 patients with false positive results. The diagnosis of these patients was tuberculosis, sarcoidosis, hyperplastic colonic polyp, inflammatory lung changes, thyroiditis &prostatitis.

Similarly, ***Man et al,*** FDG PET/CT suggested a primary tumor in 50 out of 149 patients (33.6%) ,37 patients of them proved to be true positive while the remaining 13/50 proved to be false positive involving 6 patients had FDG avid lung lesions (involving one case of active tuberculosis, two cases of stable tuberculosis, one of fungus infection, and one of granuloma, while the last case of them couldn't be confirmed pathologically but during follow up determined to be false positive) ,3 patients had head and neck lesions (involving one case of thyroiditis, one case of nasopharyngeal inflammation& one case of submandibular inflammation),3 patients had FDG avid gastrointestinal tract lesions (involving one of atypical hyperplasia with sinus ventriculi, one colonic polyp, and one rectal granuloma), and one case of FDG avid liver lesion that proved to be benign hepatic tumour **(12).**

In our study, Among 27 patients with false negative results, malignant tumours were later detected and pathologically confirmed in 3 patients during the follow up period (1 breast cancer, 1 multiple myeloma & 1 cancer of vallecula cases). However, in the remaining 24 patients, primary tumor was still not known and they received empirical chemotherapy.

The major causes of the false negative results in our work were attributed to small sized lesions (less than 1cm) and none or low FDG avid tumours as well as recent history of chemo and/or radiotherapy.

Also, ***Chang et al.,*** showed that false negative results can be explained by many reasons such as a small tumor size (if size smaller than 1 cm due to the 1-cm resolution of PET systems frequently used), low activity tumours as (bronchoalveolar carcinoma, carcinoid tumor& mucinous tumours), hyperglycaemia as well as post chemo and radiotherapy [(13)].In addition to the capability of PET/CT to identify site of an unknown primary tumor, also FDG PET/CT has the ability to detect or rule out additional metastatic sites, which may have important effects in patient management. This may mainly be of interest in patients with CUP who present with lymph node metastatic disease only, because M stage which has essential therapeutic and prognostic values is still to be unknown in these patients.

In a study for ***Karapolat et al.***, of 20 patients presented with metastases of unknown primary, PET/CT detected distant metastases in seven patients (35%) of study group and altered their treatment management [(14)].

Similarly, ***Taylor et al.,*** concluded that PET/CT has an added prospective benefit in discovery of unsuspected metastatic sites; this data may lead to a change of management, chiefly the avoidance of further unsuitable aggressive management [(15)].

In our study PET/CT changed further management in 90/123 patients (73.1%) including true positive and true negative patients.

In all true positive patients (n=71), chemotherapy protocol was changed and received specific therapy for the primary tumor.

Also, detection of new metastatic lesions that were previously unrecognized, lead to inclusion of relevant areas for radiotherapy in 40 patients who had brain, bone and nodal metastases. Furthermore, 8.9% underwent surgery with a curative intent.

At the same line, ***Elboga et al.,*** detected primary tumor in 37/112 patients with CUP and further metastases in 36 patients. The therapy plan was changed in 33 (29.4%) of 112 patients based on F-18 FDG PET/CT findings. Of these 33 patients, chemotherapy protocol was altered in 22 patients, while surgical treatment was cancelled and chemotherapy was initiated in 11 patients due to upstaging according to 18F- FDG PET/CT results [(16)].

Thus, PET/CT is valuable in CUP. It reduces the number of unnecessary investigations and so shortens the diagnostic pathway as well as it may lead to a favourable change in patient management.

CONCLUSIONS:

^{18}F-FDG PET/CT is an effective metabolic modality as additive imaging for early detection of the primary tumour site in MUO patients and facilitate selection of proper management strategies that might improve patients' prognosis.

REFERENCES:

1. *Briasoulis E and Pavlidis N.* Cancer of unknown primary origin. The Oncologist. P 142. Vol. 2 No.3: June; 1997.

2. *Plot L, Dovrish Z, Hadari R, et al.* Cancer of unknown primary site origin, advances in diagnosis and therapy. Harefuah. 147: p294-298; 2008.

3. *Saidha NK, Ganguly M, Siduh H, et al,.* The Role of 18 FDG PET-CT in evaluation of Unknown primary Tumors. Indian Journal Surgical Oncology. Vol. 4 No .3: p 236-241; Sep 2013.

4. *Kwee T, Basu S, Cheng G, et al,.* FDG PET/CT in carcinoma of unknown primary .European Journal of Nuclear Medicine . Vol. 37 No .3: p 635-644; Mar 2010.

5. *Park J, Yim J, Kang W, et al,.* Detection of primary sites in unknown primary tumors using FDG –PET or FDG –PET/CT. BMC ; 2011.

6. *Kwee TC and Kwee RM.* Combined FDG PET/CT for the detection of unknown primary tumours: systematic review and meta-analysis. European Radiology. Vol. 19 No. 3: p731-744; Mar 2009.

7. *Pavlidis N, Briasoulis E, Hainsworth J, et al,.* Diagnosis and therapeutic management of cancer of an unknown primary. European Journal of cancer. vol .39 No.14: p 1990-2005; Sep 2003.

8. *Stella G, Senetta R, Cassenti A.* Cancers of unknown primary origin: current perspectives and future therapeutic strategies. Journal of Transitional Medicine. Vol. 10: p10-12; Jan 2012.

9. *Le Chevalier T, Cvitkovic E, Caille P, et al,.* Early metastatic cancer of unknown primary origin at presentation. Vol. 148 No.9: p 2035-9; 1988.

10. *Pentheroudakis G, Greco FA, Pavlidid NB.* Molecular assignment of tissue of origin in cancer of unknown primary may not predict response to therapy or outcome: A systematic literature review Cancer Treat Rev. Vol. 35: p 221-227; 2009.

11. ***Han A, Xue J, Hu M, et al,.*** Clinical value of 18 FDG –PET –Ctin detecting primary tumor for patients with carcinoma of unknown primary. Cancer Epidemiology. Vol. 36 No.5: p 470-5; Oct 2012.

12. ***Man HU, Wei Z, pin liang Z, et al,.*** Clinical applications of 18 F – flurodeoxyglucse positron emission tomography /computed tomography in carcinoma of unknown primary .China Med Journal. Vol. 124 No.7: p 1010 -1014; 2011.

13. ***Chang J, Lee H, Goo J, et al,.*** False positive and False Negative FDG-PET Scan in Various Thoracic Disease. Korean Journal Radiol. Vol. 7 No.1: p 57-69; 2006.

14. ***Karapolat I and Kumanlioglu K.*** Impact of FDG –PET/CT for Detection of unknown primary Tumours in patients with cervical lymph node Metastases. Mol Imaging Radionucl Ther. Vol. 21 No.2: p 63-8; 2012.

15. ***Taylor M, Bromham N, Arnold S.*** Carcinoma of unknown primary; key radiological issues from the recent National Institute for Health and Clinical Excellence guidelines .Br J Radiol. Vol. 85 (1014): p 661-671; 2012.

16. ***Elbooga U, Kervancioglu S , Sahin E, et al,.*** Utility of F18 flurodeoxyglucse positron emission tomography /computed tomography in carcinoma of unknown primary. Int. J. Clin. Exp. Pathol. Vol. 7 No. 12: p 8941-6; 2014.