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F 18 FDG PET/CT in Evaluation of Loco-regional and Distant Recurrent Cervical Carcinoma.

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ABSTRACT:

Aim: To evaluate the diagnostic performance of F-18 FDG PET/CT for the detection of local and distant disease relapse in treated patients with cervical carcinoma. **Materials and Methods:** This retrospective study includes 43 patients with pathologically proven cervical carcinoma, 36 patients were pathologically proven as Squamous Cell Carcinoma (SQ.C.C.) and 7 were adenocarcinoma. They received initial treatment and with clinico-laboratory suspected recurrence. They referred to nuclear medicine unit, to perform F-18 FDG PET/CT study. Sites of the relapse (classified as positive or negative) were categorized into local and distant recurrence. The final diagnosis of disease status was made on subsequent follow up by conventional imaging (CT/MRI), F-18 FDG PET/CT, or histopathology whenever possible.

Results: 34 (79.1%) of the patients were proven to have loco-regional &/or distant recurrence based on histopathology & or follow up. F-18 FDG PET/CT changed management in 8 patients (18.6% of the group). On per patient based analysis for detection of loco-regional and distant recurrence, F-18 FDG PET/CT, outperformed Ce-CT alone as regards the sensitivity indices with NPV 88.89% for F-18 FDG PET/CT compared to 66.67% for Ce-CT alone.

As regards loco-regional recurrence, and on per lesion based analysis, statistically higher sensitivity and NPV were seen with F-18 FDG PET/CT of 100% exceeding those of Ce-CT alone(SN 71.11% & NPV 80.6%) with P-value 0.0001 & 0.002 respectively, with overall diagnostic accuracy reached 98.06% with F-18 FDG PET/CT compared to 83.5% with Ce-CT (P-value 0.017).

Distant metastases were also analyzed on per lesional basis where PET/CT revealed higher sensitivity and specificity indices compared to Ce-CT, with sensitivity, specificity, NPV and overall accuracy were 97.92%, 83.33%, 89.29%, & 95.4% respectively compared to 82.64%, 66.67%, 44.44%, 79.89%, for Ce-CT respectively with P-value <0.05.**Conclusion**: F-18 FDG PET/CT appears to be an efficient tool in detection of loco-regional and distant recurrence in cervical carcinoma patients.

Key Words: Cervical carcinoma, F-18 FDG PET/CT, recurrence.

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INTRODUCTION:

Cancer cervix constitutes the 3rd leading cause of death among the gynecological tumors [(1)]. Five-year recurrence rate has been reported by The International Federation of Gynecology and Obstetrics (FIGO) in 28% of patient with cancer cervix [(2)]. Though current advances in surgical and non-surgical lines of treatment, recurrence after initial management still a major problem [(3)].

Early and accurate detection of sites of recurrence has a great influence on tailoring appropriate therapy strategy and improving overall survival [(4)]. Beside physical examination and tumor markers, conventional imaging techniques including CT and MRI are the commonly used modalities. Diagnostic accuracy of such modalities sometimes hindered by inevitable post-therapy and post-radiation changes .Also their interpretation is based on gross structural changes or certain pattern of enhancement which may interfere with early recurrence detection [(5)].

In contrast, 18F-labeled 2-fluoro-2-deoxyglucose (18F-FDG) positron emission tomography (PET) provides a non-invasive whole body surveying technique that depends on lesional metabolic activity regardless its morphology [(6)]. 18F-FDG PET/CT has been investigated and revealed promising accuracy in many solid tumors including cervical carcinoma recurrent cervical cancer and has shown relatively high sensitivity and specificity [(7-12)].

Being supported by previously published encouraging data, we aimed, in the current study, at assessing the diagnostic performance of F-18 FDG PET/CT in Egyptian patients previously treated and with suspicion for recurrence during follow up. In addition, to explore the performance of F-18 FDG PET/CT compared to using Ce-CT alone in recurrent cervical carcinoma patients.

PATINTS AND METHODS:

This retrospective study enrolled 43 female patients with previously treated pathologically proven cervical carcinoma. Out of the 43 case, 36 (83.7%) patients were pathologically proven as SQ.C.C. and 7 (16.3%) were adenocarcinoma. They were suspected of developing recurrence and were referred to the nuclear medicine unit in National Cancer Institute (NCI) to perform F-18 FDG PET/CT study, from March 2014 to October 2018. Suspicion for recurrence was based on symptoms as vaginal bleeding, abnormality on physical examination, raised serum tumor marker (CEA) levels, and/or development of new lesion on follow up imaging.

FDG PET-CT scanning and image analysis:

18F-FDG PET/CT scans were performed using Discovery PET/CT scanner (GE Medical System, USA). All scans were performed 60 min after the intravenous administration of approximately 370 MBq of F-18 FDG in 3D mode from the vertex to mid-thigh, encompassing 7-9 bed positions (180 s per bed position). Low dose CT scanning was started at the level of skull vault to mid-thigh with the following parameters: 40 mAs; 130 kV; slice thickness, 2.5 mm; pitch, 1.5. This low dose CT was used for attenuation correction. After which the PET acquisition was obtained, followed immediately by diagnostic CT using the following parameters: 300 mAs, 120 kV, slice thickness 1.5 mm. Nonionic contrast media were used based on recent kidney function tests at a dose of 1–2 ml/kg (maximum 150 ml).

Both PET and CT scans were performed for patients under normal tidal breathing.

From the raw emission data collected, the image was reconstructed by iterative reconstruction with CT-derived attenuation correction using the ordered subsets expectation maximization algorithm.

The spatial resolution of the reconstructed PET image was 3.75 mm. F18 FDG PET/CT images were reviewed on the manufacturer's GE Advantage workstation 4.6.

The PET-CT images for each patient were examined, in axial, coronal, and sagittal planes, by two experienced nuclear medicine physicians (with 8 and 12 years' experience) simultaneously, and in case of not reaching a consensus, a third opinion of a senior consultant (of 30 years' experience) was obtained. A radiologist (with 10 years' experience) reviewed and interpreted Ce-CT data separately.

For PET quantitative analysis a 3D volume of interest was drawn over the region of abnormal FDG uptake that exceeds normal surrounding physiological background activity, as such areas were judged positive on F-18 FDG PET/CT images.

For Ce-CT considered positive depending on presence of new sizable lesions, pattern of contrast enhancement, reaching pathological size (as in case of nodal involvement; maximum 10 mm short axis diameter is considered the upper limit for normal nodes) or development of lytic or sclerotic boney changes.

The results of F-18 FDG PET/CT were verified by the available pathological data as well as the clinico-laboratory and follow up data retrieved from patient's medical records.

Statistical analysis:

Data was analyzed using SPSS win statistical package version 21 (SPSS Inc., Chicago, IL). Trend of change in percent of categorical variables was compared using Chi-square test for trend. The sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), and accuracies were calculated using standard statistical formulas. . Chi-square test was used to determine statistical significance of differences among PET/CT and Ce-CT interpretations all tests were two sided with $p < 0.05$ was considered statistically significant.

RESULTS:

Presence or absence of either loco-regional or distant disease recurrence was finally diagnosed , based on follow up by CT/MRI or PET/CT , clinico-laboratory follow up data for minimum duration of one year or by histopathology. Pathological confirmation was performed in only 18 patients out of the whole group. Recurrence was accordingly diagnosed in 34 patients (79.1%) of our group.

Regional and/or distant recurrence occurred in our group of patients with median duration 10 months (range of 5 to 24 months) from end of treatment.

No significant difference was noticed as regards the mean age for patients with either SQ.C.C or adenocarcinoma. Patients of our group were initially staged according to FIGO staging system for cervical carcinoma [(2)]. 11 (30.6%) patients out of the 36 SQ.C.C. Group were staged as IB, while 3 (42.9%) out of the 7 adenocarcinoma patients were of stage IIIB, however was not of statistical significance (p-value 0.08).

In our group 34 out of the 43 patients experienced tumoral recurrence; where 12 (35.2%) patients had loco- regional recurrence only, 11 (32.4%) had distant recurrence only and 11 (32.4%) had both loco-regional and distant recurrence. After F-18 FDG PET/CT imaging 8 (18.6%) out of the 43 patients had their treatment changed from curative to palliative intent ***(Table 1)***.

In order to evaluate the diagnostic performance of F-18 FDG PET/CT in detection of loco-regional and / or distant tumoral recurrence and its added value over using contrast enhanced CT alone, per patient analysis was performed. In per patient analysis, F-18 FDG PET/CT revealed higher diagnostic sensitivity indices than Ce-CT and was statistically significant as regards the NPV. F-18 FDG PET/CT revealed sensitivity and NPV of 97.06% & 88.89% compared to 88.24% and 66.67% for Ce-CT (P-values 0.12 & 0.01 respectively) ***(Table 2)***.

Table (1): Clinico-pathological data of patients with recurrent cervical carcinoma (No. =43).

Pathological subtypes	SQ.C.C (no.=36)	Adenocarcinoma (no.=7)	P-value
Age (mean)	55.8	42.7	0.15
FIGO staging			
IIA	5 (100%)	0 (0%)	
IIIA	7 (77.8%)	2 (22.2%)	
IB	11 (100%)	0 (0%)	0.08
IIB	10 (83.3%)	2 (16.7%)	
IIIB	3 (50%)	3 (50%)	
Recurrence			
Regional	8(66.7%)	4(33.3%)	
Distant	9(81.8%)	2(18.2%)	0.19
Loco-regional & Distant	10(90.9%)	1(9.1%)	
No recurrence	9(100%)	0(0%)	
PET-based change in management	7/36(19.4%)	1/7 (14.3%)	0.75

Table (2): Per patient based assessment of the diagnostic performance of F-18 FDG PET/CT versus Ce-CT in regional and/or distant recurrence (No. of patients =43).

Modality	PET/CT	Ce-CT	P-value
TP	33	30	
FP	1	1	
TN	8	8	
FN	1	4	
SN (95%CI)	97.06% (84.67% to 99.93%)	88.24% (72.55% to 96.70%)	0.12
SP (95%CI)	88.89% (51.75% to 99.72%)	88.89% (51.75% to 99.72%)	1
PPV (95%CI)	97.06% (83.86% to 99.53%)	96.77% (82.48% to 99.48%)	0.9
NPV (95%CI)	88.89% (53.36% to 98.24%)	66.67% (43.64% to 83.78%)	**0.01**
Accuracy (95%CI)	95.35% (84.19% to 99.43%)	88.37% (74.92% to 96.11%)	0.24

In our group based on F18 FDG PET/CT interpretation, 47 positive local and / or regional nodal lesions were detected in 24 patients. As regards Ce-CT 36 loco-regional lesions were interpreted as being positive in 18 patients. Based on histopathology (11 patients) as well as clinico-laboratory data &/or follow up (in 13 patients), truly positive local and regional lesions turned out to be 45 lesion proven in 23 patients where 12 patients had loco- regional recurrence only, 11 had both loco-regional and distant recurrence. F-18 FDG PET/CT was able to detect all of these true lesions with sensitivity and NPV of 100% exceeding those of Ce-CT alone(SN 71.11% & NPV 80.6%) with P-value 0.0001 & 0.002 respectively, which subsequently influence the overall diagnostic accuracy that reached 98.06% with F-18 FDG PET/CT compared to 83.5% with Ce-CT (P-value 0.017) ***(Table 3)***. There was true positive and negative agreement in detection of loco-regional recurrence between both modalities in 37 out of the 43 patients, No false agreement and disagreement was revealed in the remaining 5 patients.

Table (3): Per lesion based assessment of the diagnostic performance of F-18 FDG PET/CT versus Ce-CT in Loco-regional recurrence (No. of true lesions =45).

Modality	F-18 FDG PET/CT	Ce-CT	P-value
TP	45	32	
FP	2	4	
TN	56	54	
FN	0	13	
SN (95%CI)	100% (92.13% to 100.00%)	71.11% (55.69% to 83.63%)	**0.0001**
SP (95%CI)	96.55% (88.09% to 99.58%)	93.10% (83.27% to 98.09%)	**0.46**
PPV (95%CI)	95.74% (85.22% to 98.87%)	88.89% (75.32% to 95.45%)	**0.23**
NPV	100%	80.60% (72.32% to 86.85%)	**0.002**
Accuracy (95%CI)	98.06% (93.16% to 99.76%)	83.50% (74.89% to 90.08%)	**0.017**

With quantitative analysis the mean value for SUV max was higher (~ 14.1) in local recurrence for patient with SQ.C.C compared to 10.7 for those with adenocarcinoma, however was not of statistical significance (P-value 0.23).

Per lesion analysis was also done for assessment of diagnostic performance of F-18 FDG PET/CT in distant recurrence. Total number of truely positive lesions based on the standard of truth (SOT) , turned out to be 144 lesion in 22 patients where 11 had distant recurrence only and 11 had both loco-regional and distant recurrence. The gold standard reference (SOT) was pathology in 5 patients while clinico-laboratory, radiological and follow up were used to otherwise verify the distant metastases in the remaining patients 17 patients. PET/CT was able to identify 141 true positive lesion out of the 144 finally pathologically and/or clinico-laboratory proven lesions, and revealed higher sensitivity ,specificity , NPV & overall accuracy compared to Ce-CT all of statistical significance and were 97.92%, 83.33%, 89.29%,& 95.4% respectively compared to 82.64%, 66.67%, 44.44%, 79.89%, for Ce-CT respectively with P-value <0.05 ***(Figure 1)*** & ***(Table 4)***. There was true positive and negative agreement in detection of distant recurrence between both modalities in 136 lesion, 5 false agreement and disagreement was found in 33 lesions.

It is worth mentioning that false positive results by F-18 FDG PET/CT related to FDG avid mediastinal and inguinal lymph nodes turned out on follow up by CT to be of inflammatory etiology as they showed spontaneous regression without intervening therapy. While the false negative results were related to sub-centimetric metastatic lung nodules showed progression on follow up CT and were associated with elevated tumor markers.

Prevalence of sites of distant metastases and their average SUV max illustrated in ***Table (5***), where the most common site for distant metastases was nodal, commonly abdominal (para-aortic) nodes , followed by peritoneal (that were all of nodular/focal pattern) and the least common in our group were the brain and bone.

Table (4): Per lesion based assessment of the diagnostic performance of PET/CT versus Ce-CT in distant recurrence (No. of true lesions =144).

Modality	F-18 FDG PET/CT	Ce-CT	P-value
TP	141	119	
FP	5	10	
TN	25	20	
FN	3	25	
SN (95%CI)	97.92% (94.03% to 99.57%)	82.64% (75.45% to 88.44%)	**< 0.0001**
SP (95%CI)	83.33% (65.28% to 94.36%)	66.67% (47.19% to 82.71%)	**0.0011**
PPV (95%CI)	96.58% (92.68% to 98.43%)	92.25% (87.71% to 95.20%)	**0.1102**
NPV (95%CI)	89.29% (72.89% to 96.27%)	44.44% (34.07% to 55.33%)	**< 0.0001**
Accuracy(95%CI)	95.40% (91.14% to 97.99%)	79.89% (73.15% to 85.57%)	**0.0001**

Table (5): Prevalent sites of distant metastases in patients with recurrent cervical carcinoma.

Site	No. of patients	No. of lesions	Mean value of SUV max
Distant nodes	14	74	9.8
Peritoneal	7	39	10.9
Lung	6	16	8.4
Liver	4	10	8.7
Subcutaneous	2	3	10.7
Bone	1	1	4.6
Brain	1	1	9.7

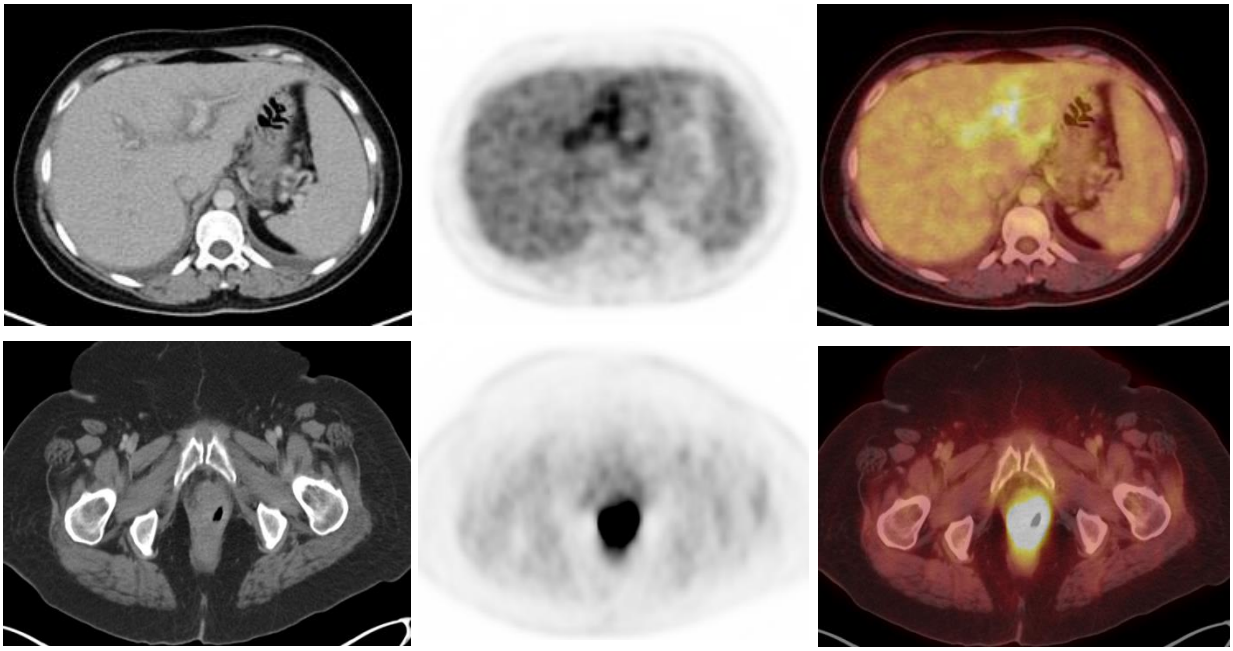

Figure (1): 58-y-female patient with pathologically proven SQ.C.C cervical carcinoma. She underwent total abdominal hysterectomy and bilateral oophorectomy and received post-operative chemo- and radio- therapies. After 5 months and on follow up, she developed vaginal bleeding. F-18 FDG PET/CT performed and revealed; FDG avid cervical stump irregular soft tissue lesion with SUV max 23.6 and FDG avid peri-portal infiltrates of SUV max 8.

DISCUSSION:

Cervical carcinoma is one of the most common gynecological carcinoma worldwide [(1)]. According to histopathology, there are many subtypes; the most common are Sq.C.C representing about 80 to 90% and adenocarcinoma that represents about 10 to 20 % [(13)]. This also was reflected in our study group where 83.7% of patients were pathologically proven as SQ.C.C and 16.3% were adenocarcinoma.

Survival rate in patients with cervical: carcinomas is linked to several factors including early detection of post-treatment recurrence and its proper management [(4)]. Conventional imaging techniques including CT and MRI are the frequently used modalities; however, the reliability on gross structural changes can interfere with the concept of early detection [(5)]. F-18 FDG PET/CT as a functional technique can overcome this obstacle with its ability to mirror-image even early tumoral burden [(6)]. Previous studies investigated the role of F-18 FDG PET/CT in detection of recurrent cervical carcinomas.

Ryu et al. analyzed a large group of cervical carcinoma patients suffered from post-treatment recurrence; they reported sensitivity of 90%, a specificity of 76%, and an accuracy of 74% [(14)].

Chung et al. also reported a sensitivity of 90.3%, a specificity of 81%, and an accuracy of 86.5% [(15)].

Also ***Kitajima et al.,*** analysis showed sensitivity of 92%, a specificity of 93%, and an accuracy of 92% for F-18 FDG PET/CT while for CT alone sensitivity, specificity & accuracy were 68.2%, 87.0%, and 77.8% respectively [(16)]. In the current study F-18 FDG PET/CT, outperformed Ce-CT alone as regards the sensitivity indices with NPV 88.89% for F-18 FDG PET/CT compared to 66.67% for Ce-CT alone.

It was noted that the majority of the previous studies assessed the event of recurrence globally lacking site based discrimination likely due to non-feasibility of pathological confirmation of every detected lesion, which considered the most reliable standard of truth, especially in case of distant metastases; however we tried in our current study to provide more detailed analyses according to site of recurrence. In our study per lesion analysis was done to assess performance of both investigated modalities in detection of loco-regional recurrence, statistically higher sensitivity and NPV were noticed with F-18 FDG PET/CT of 100% exceeding Ce-CT alone (SN 71.11% & NPV 80.6%) and subsequently higher diagnostic accuracy that reached 98.06% with F-18 FDG PET/CT compared to 83.5% with Ce-CT. Also higher FDG uptake as reflected in terms of SUV max was noted with Sq.c.c compared to adenocarcinoma that may indicate a state of more aggressive tumoral behavior and dedifferentiation meanwhile still not conclusive with the number of the current population.

For detection of distant sites of recurrence, F-18 FDG PET/CT showed high diagnostic indices where its sensitivity, specificity, NPV and accuracy were statistically outperforming Ce-CT and were 97.92%, 83.33%, 89.29%, & 95.4% respectively compared to 82.64%, 66.67%, 44.44%, and 79.89 % for Ce-CT respectively.

From this study and previously published studies [(14-16)]. F-18 FDG PET/CT showed superiority in diagnostic accuracy with its ability to provide whole body non-invasive screening which allows distinction between local and distant patterns of recurrence,

Thus its integration in assessment of patients with suspected recurrence may assist optimal therapy selection and prevent unnecessary additional treatment, as in our group where F-18 FDG PET/CT converted 8 (18.6%) patients from curative to palliative treatment.

In the same line ***Kitajima et al.,*** demonstrated that F-18 FDG PET/CT changed management in 42% of his group which represents 38 out of 90 patients ***(16)***. Also Chung et al and ***Park et al***., reported change in management in 23% & 22% of their study groups respectively [15,17]. With such reported results , F-18 FDG PET/CT was endorsed (whenever available) as a diagnostic modality by the NCCN Guidelines Version 4.2019 Cervical Cancer not only in initial staging , but also, follow-up/surveillance whole body PET/CT became recommended within 3–6 months of completion of therapy and with suspected recurrence or metastasis [18].

In our study distant nodal, mainly abdominal para-aortic, was the most common site of distant metastases. ***Kitajima et al.***, reported in their study sensitivity, specificity and accuracy for F-18 FDG PET/CT, in detection of regional and distant metastases, of 90.9%, 99.8%, and 99.1% respectively [16]. The diagnostic accuracy of morphological imaging as CT and MRI in detection of nodal involvement is hindered by dependency on pathological size, being the most accepted criterion that subsequently lowers their reported sensitivity to 27-50% [19, 20]. However, in F-18 FDG PET/CT metabolic based criterion enables detection and localization of even sub-centimetric metastatic nodes.

False positive and negative F-18 FDG PET/CT results in our study were the same as previous ones [14-16], where inflammatory related FDG activity may compromise the specificity of PET study with false positive results, also sub-centimetric lung nodules as well as tiny para-aortic and iliac nodes closely related to ureters are easily missed and falsely interpreted as negative results.

CONCLUSIONS:

In patients with suspected recurrent cervical carcinoma, F-18 FDG PET/CT appears to be an efficient tool in detection of local and distant recurrence with subsequent influence on tailoring further therapy strategy.

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