Original Article

^{18}F FDG PET/CT EVALUATION OF PATIENTS WITH CERVICAL CARCINOMA

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ABSTRACT

Objectives: *^{18}F FDG PET/CT is becoming widely available as a powerful imaging modality, combining the ability to detect active metabolic processes and their morphologic features in a single exam. The role of ^{18}F FDG PET was studied in a variety of cancers, including cervical carcinoma, however, not PET/CT was not used in the majority of the published studies. Therefore, the airs of this work is to show role of PET/CT in the management of patients with cervical carcinoma.*

Methods: *This is a retrospective study of 30 women with cervical carcinoma, age is reneged from 28-87 years old (average: 49.6 ± 15.7). whole-body PET/CT was done in Stanford university hospital during the period from Jan 1st, 2003 to Aug 31st, 2006. Reinterpretation of the imaging studies for accuracy and data analysis from medical records were performed. Sensitivity and specificity were calculated with pathology results (76% of the patients) or clinical follow-up (24% of the cases). Confidence interval (CI) estimations were performed using the Wilson score method.*

Results: *All patients had the study requested for disease re-staging. A total of 42 scans were performed: 18 pts had 1 scan and 12 pts had 2 scans. The administered doses of ^{18}F FDG ranged 10.5 - 20.0 mCi (average: 15.3 ± 2.31). PET/CT was 92.8% sensitive (95% CI: 66.4-99.9) and 92.8% specific (95% CI: 76.3-99.1) for detection of the primary lesion and 95.6% (95% CI: 77.3-99.9) sensitive and 94.7% specific (95% CI: 73.5-99.9) for metastases detection. The SUV_{max} ranged 5.3-28.2 for the primary lesions (average: 12.5±6.96) and 2.8-22.9 for the metastases (average: 7.72±4.46). This difference was statistically significant (P value: 0.0058).*

Conclusion: *This study confirms the good results of ^{18}F FDG PET/CT for identification of residual/recurrent cervical cancer, as well as for distant metastases localization. FDG PET/CT should be an integral part in evaluation of patients with high risk cervical cancer, prior to selection of the most appropriate therapy.*

INTRODUCTION

Cervical cancer is the second most frequently diagnosed gynecologic malignancy in women worldwide [1]. The International Federation of Gynecology and Obstetrics (FIGO) reported a 5- year recurrence rate and a 5- year overall mortality rate of cervical cancer as 28% and 27.8% respectively [2]. Accurate and expedited evaluation of recurrent lesion may allow the optimal treatment to be applied in each patient with recurrent cervical cancer.

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As early detection and diagnosis of recurrent cervical cancer may result in favorable impact on patients' survival [3, 4], sensitive and accurate diagnostic tools that can detect recurrent lesions before emergence of self- conscious symptoms would be desirable. Serum tumor markers as squamous cell carcinoma antigen (SCC-Ag) and carcinoembryonic antigen (CEA) have been identified as sensitive indicators of cancer cervix recurrence [5-7], however conflicts between elevated tumor markers and the diagnosis of recurrence was reported [8]. Various imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) have traditionally been used. The detection of recurrence and lymph node metastases with both CT and MRI remains difficult as they rely on the morphological size of disease. The reported sensitivity of CT to detect local recurrence and retro-peritoneal or para-aortic Lymph node metastases was modest with some studies showing values of 34-44% [9, 10]. The clinical application of FDG-PET for recurrent cervical cancer has been investigated and shown high sensitivity and accuracy [11-14], even in the presence of unexplained elevation of serum tumor markers without evidence of recurrent disease on conventional work up of CT or MRI [15]. [16]. Recently, PET/CT integrating morphologic data of CT with functional data of PET has widely been used successfully in many solid tumors as in lung, breast and colorectal cancer [17]. In addition PET/CT is useful to evaluate locoregional and distant spread in cervical cancer [18, 19]. The published data on PET role in recurrent cancer cervix are based on dedicated PET acquisitions, with only few published reports [20-22] relaying on data from integrated PET/CT studies.

The objective of this study is to evaluate the usefulness of integrated PET/CT as a post-therapy surveillance of cervical cancer and its added role in the management of patients with cervical carcinoma.

MATERIAL AND METHODS

The study included 30 women with cancer cervix collected on a retrospective basis during the period from January 1st 2003 till August 31st 2006 to nuclear medicine division in Stanford University, California. The referred patients underwent PET/CT whole body studies as part of their surveillance work-up. A minimum of 6 months follow-up after the post-treatment PET/CT scan was required to be included in this study. The international Federation of Gynecology and Obstetrics (FIGO) classification was used for clinical re-staging. Eligibility requirements for the current study included; patients with histologically confirmed carcinoma of the uterine cervix, who were subjected to primary treatment with curative intention and they reached complete remission after initial treatment. Complete remission was defined as absence of detectable disease on physical and gynecological examination, cytological/histological evaluation and imaging studies. Patients were ineligible for the study if they were having associated other malignancy than cancer cervix, had an initial diagnosis of advanced cancer cervix unsuited for treatment with curative intent. The referred patients underwent PET/CT whole body scans based on various clinical indications that included 1) presence of symptoms suspecting recurrence, 2) had new lesions on surveillance conventional imaging studies, 3) had abnormal findings on physical and gynecological examinations on routine follow up, 4) wanted surveillance PET/CT scan for fear of recurrence without evidence of disease.

^{18}F FDG-PET/CT scanning procedure:

The PET/CT scanning was performed with a GE Discovery LS

PET/CT scanner. The patients were fasting for a minimum of 6 hours prior to intravenous FDG injection. The injected dose of FDG (^{18}F-fluoro2-deoxy-glucose) ranged from 10.5 – 20.0 mCi (average: 15.3 ± 2.31 mCi). Immediately before scan start, they were asked to void. We did not use bladder catheters or diuretics for bladder emptying. The examination was performed with the patient positioned supine with the arms placed over the head.

CT scans were performed immediately prior to the PET scan with the multi-detector eight slice spiral CT scanner. The CT scan was performed with a rotation time of 0.5 s, speed 15.0 mm/rotation, helical thickness 5 mm, pitch 1.5:1, kV and mA relative to the body mass of the patient.

The PET scan followed immediately with an acquisition time of 3-5 min per bed position. Whole-body PET scanning (2D, 1 slice overlap) consisted of imaging from the proximal thigh to the base of the skull using 5–7 axial fields of view with coverage of 14 cm.

Image interpretation

The CT data were used for attenuation correction of the PET data. Both image sets were reconstructed in trans-axial, coronal and sagittal images with a slice thickness of 5 mm. Two nuclear medicine physicians with consensus reviewed the PET and the fused PET/CT images on the GE ENTEGRA PET workstation (GE Medical Systems) and all the studies were retrieved through Picture archiving and communication system (PACs). Visual interpretation was carried initially based on comparing abnormal lesion FDG uptake to the physiological uptake in liver. Lesions were considered positive if they have uptake more than liver accumulation but less than brain cortical activity and highly positive if it is comparable to brain cortex accumulation. Maximum standardized uptake values (SUV_{max}) were measured for each lesion with FDG accumulation based on the CT-determined anatomical locations of the FDG accumulations. Lesions with FDG accumulation that had SUV_{max} over 2.5 were determined as positive.

Statistical analysis

Diagnostic accuracy was evaluated by comparing the PET results with final diagnoses, confirmed by histological evaluation, clinical follow-up or imaging studies. Statistical analysis of PET findings depends on confirmation of recurrent cancer cervix disease after reviewing and reanalysis of patients' medical records depending on either tissue biopsy or the demonstration of progressive disease by serial imaging studies.

The sensitivity, specificity and accuracy of PET/CT were computed for local pelvic disease and distant sites. Confidence interval (CI) estimations were performed using the Wilson score method.. A P value of less than 0.05 was considered statistically significant.

RESULTS

The age for the included patients in this study ranges from 28-87 years with an average of 49.6 ± 15.7 years. The standard method used for analysis of PET/CT data were histopathology results in 23 patients (76%) , whereas clinical assessment with imaging follow up was used in 7 patients (24% of the cases). The included patients had PET/CT studies requested for cancer cervix restaging. A total of 42 scans were performed: 18 pts had 1 PET/CT scan and 12 patients had 2 scans. In these 12 patients the intervals between the 1st and 2nd scans were variable with a mean time of interval 8.7 ± 12.4 months.

Histological and FIGO classification

The clinical FIGO staging and the histology of the 30 patients who had been included are shown in table 1.

Table (1): The distribution of patients according to initial clinical stage and histopathological diagnosis.

FIGO	Histological diagnosis		Others	Total
	Squamous Cell carcinoma	Adenocarcinoma		
1B2	2	0	0	2 (6.6%)
2A	2	1	1	4 (13.3%)
2B	7	2	1	10 (33.3%)
3A	1	0	0	1 (3.3%)
3B	8	2	1	11 (36.9%)
4A	2	0	0	2 (6.6%)
Total	**22 (73.3%)**	**5 (16.7%)**	**3 (10%)**	**30**

Cancer cervix histopathology in this cohort showed that the most common is squamous cell carcinoma (73.3%), followed by Adenocarcinoma (16.7%), and other pathologies like papillary squamous carcinoma, adenosquamous carcinoma and other rare types.

Local recurrence, local recurrence with metastases

The histopathological examination for the local recurrence at the primary sites showed that 13/14 scans were truly disclosed positive by PET/CT (figure 1), with only one as false negative. The pathology or follow up for the local masses at primary site was negative in 28 scans. The PET/CT was truly negative in 26 with false positive PET findings in 2 scans only as seen in table 2.

The calculated sensitivity for PET/CT was 92.8% (95% CI: 66.4-99.9) and the specificity 92.8% specific (95% CI: 76.3-99.1) for detection of the local recurrence at the primary site.

Table 3 illustrates the PET/CT findings compared to histopathological results of metastatic disease in the included cohort. Twenty-two PET/CT scans had true positive findings (figure 2) and only one PET/CT scan had false negative iliac lymph node which did not show significant FDG uptake suspicious of malignancy. The negative PET/CT scans that did not show pathological FDG uptake to detect metastases compared with the pathological findings are detailed in table 3.

Table (2): Distribution between PET/CT and pathological or follow up findings for the local recurrence at primary sites.

PET/CT	Histology/Follow-up		
	Positive	Negative	Total
Positive	13	2	15
Negative	1	26	27
Total	**14**	**28**	**42**

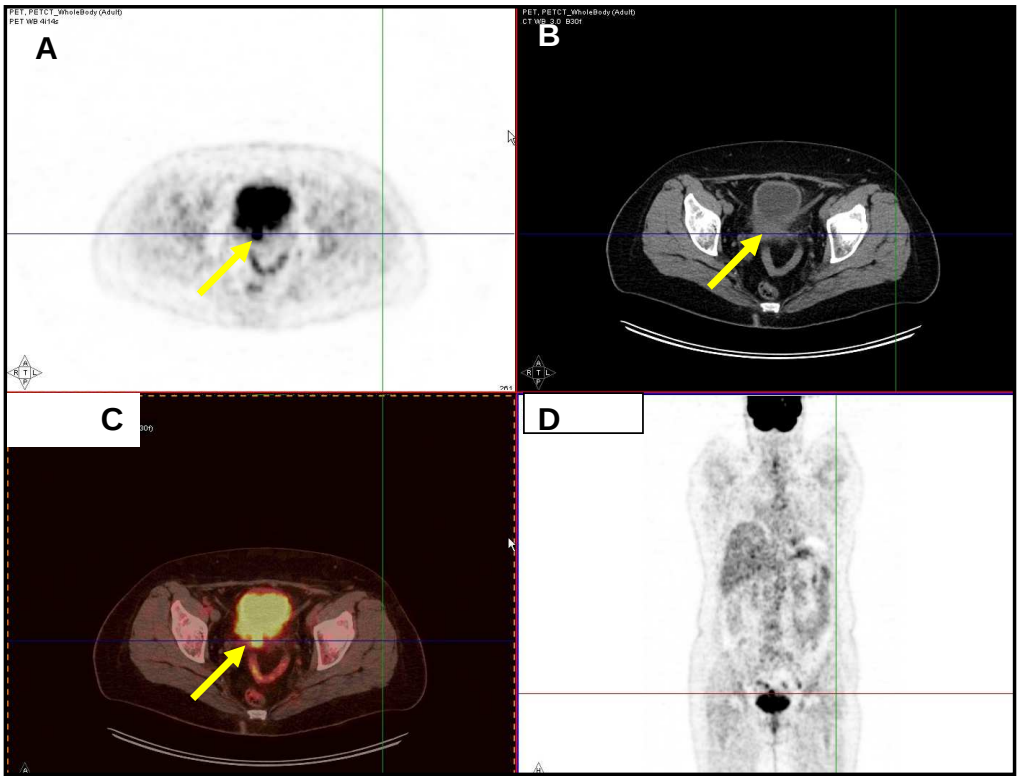


Figure (1): 62 years old lady with cancer cervix stage 2B showing retrovesical focal high FDG uptake (A), In the CT image (B), soft tissue recurrence at the primary site (yellow arrow) which is confirmed in the fusion PET/CT (C) and the coronal (D) images.

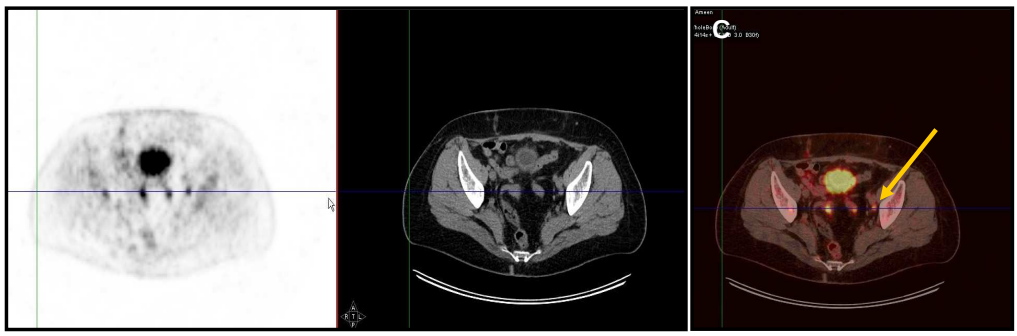


Figure 2: (A)The FDG-PET image showed three focal areas of uptake in the pelvis. (B) CT image and fusion images (C), the left arrow is pointing to the pathological FDG uptake in the left iliac lymph node while the right arrows showed that the other two FDG focal areas are due to physiological intestinal uptake.

Table (3): Results of PET/CT compared to Pathological findings for the distant metastatic sites.

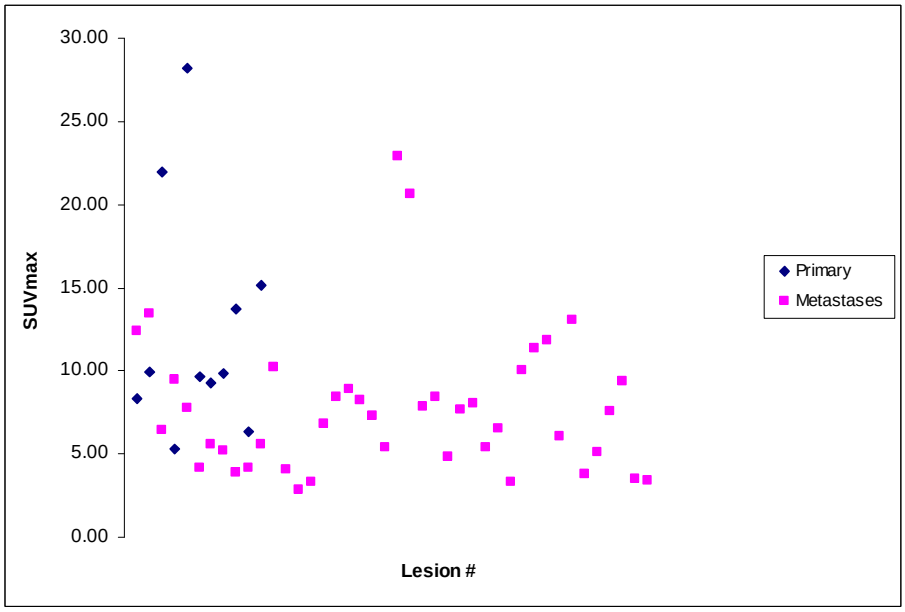
PET/CT	Histology/Follow-up		
	Positive	**Negative**	**Total**
Positive	22	1	23
Negative	1	18	19
Total	**23**	**19**	**42**

Accordingly, for distant metastases detection the sensitivity of PET/CT was 95.6% (95% CI: 77.3-99.9), while the specificity was 94.7% (95% CI: 73.5-99.9). Figure 2 showed the tendency of PET/CT to have higher sensitivity and specificity for detection of distant metastases compared with visualizing local recurrence sites.

The focal Positive FDG-PET was seen in 125 sites. The number of recurrent focal lesions at primary site that showed positive FDG-PET in the 15 positive PET/CT scans was 18 areas as 3 scans showed two focal areas at the primary site. The numbers of focal FDG-PET at distant sites in the 23 positive PET/CT scans for metastases are shown in table 4. The majority of distant metastases seen by FDG-PET were nodal and namely iliac and para-aortic sites. Other sites of distant metastases were seen in retroperitoneal, pleural, liver and one patient with splenic metastases

Table (4): Details of recurrent, nodal and metastatic lesions detected by PET/CT

	Numbers	**+Ve PET lesions**
Scans with local recurrence	15	18
Scans with distant Metastases	23	107
Nodal and Distant Metastases		107
	Iliac	24
	Para-aortic	31
	Retro-peritoneal	8
	Other nodal sites	6
	Pelvic	18
	Liver	11
	Pleural	4
	Other sites	4



**** P value = 0.0058***

Figure (3): The distribution of SUV_{max} values at local recurrence sites and distant metastatic sites.

Standardized Uptake Value (SUV_{max})

The maximum Standardized Uptake value (SUV_{max}) was calculated in all areas that showed visually pathological FDG uptake in the PET/CT study. The local recurrence at primary sites exhibited high SUV_{max} Values that ranged from 5.3 to as high as 28.2, while the SUV_{max} values at the metastatic sites were of lower values and ranged from 2.8 to 22.9 as illustrated in figurverage value of SUV_{max} at local recurrence sites was 12.5±6.96, which is significantly higher ($P = 0.0058$) than average SUV_{max} at metastatic sites (7.72±4.46) (figure 3).

DISCUSSION

The objective of the current study is to evaluate the clinical usefulness of PET/CT scan in women previously treated for cervical cancer. Earlier detection of recurrent disease has the potential to improve effectiveness of treatment and survival. This work found that PET/CT is a useful imaging tool for restaging of cancer cervix. It has a high diagnostic yield for detection of recurrent disease at primary sites and in revealing distant metastases.

Local recurrence at Primary site

In the current work we analyzed the 42 PET/CT scans done on the 30 patients included. The PET/CT detected 13 cases with local recurrence at the primary site and was false negative in only one scan with a sensitivity of 92.8%. There was true absent FDG uptake in 26/28 scans and only 2 scans showed false positive uptake whom proved later to be free from local recurrent disease at the primary site with a specificity of 92.8% (table 2). In this respect, many investigators have shown the usefulness of FDG-PET scan as a sensitive tool for detecting recurrent cervical cancer [13, 14, 23, 24]. For diagnosing recurrence, the sensitivity of FDG-PET varies from 75% to 100% and the specificity from 57% to 100% [12-14, 25-28]. When used in post-treatment surveillance (i.e. without clinical suspicious of recurrence) the sensitivity ranges from 80 -90% and the specificity from 76% to 100% [8, 24, 26, 28]. The sensitivity of PET in 41 patients was 100% while the specificity was 90 % [29]. Similarly, Unger et al., [14] on 21 patients with recurrent cancer cervix, reported a sensitivity of 100% and a lower specificity of 85.7%. Chang et al. [15] on 27 patients showed a sensitivity of 94% and a limited specificity of 78%. Havrilesky et al. [13] showed that the pooled sensitivity and specificity of FDG-PET for diagnosing recurrence when clinical suspicion was present were 96% and 81%, respectively. One of the reasons for the limited specificity of PET in the pelvic region is the lack of anatomical verification in a region where there is many causes for physiological uptake [19].

Compared with CT alone, FDG-PET has been shown to have significantly improved sensitivity in diagnosing recurrence [23, 30]. Yen et al. [31] reported the sensitivity of FDG-PET to detect recurrent cancer cervix lesions to be 89.2%, compared with 39.2% for CT or MRI ($P < 0.0001$). In a series of 26 patients with recurrent cervical cancer, Lin et al. [32] showed improved sensitivity of FDG-PET compared with CT and MRI for detecting local recurrence (100% vs. 71.4%).

There are limited data on the role of integrated PET/CT in detection of recurrence in cancer cervix, Chung et al. [22] on 52 patients reported a sensitivity of 90.3%, specificity of 81% and accuracy of 86.5%. Loft et al. [18] using PET/CT reported a 96% specificity in detecting local recurrence after radical surgery for cancer cervix, yet the sensitivity was 75% only. Their explanation for such limited sensitivity was related to the surgical resection of all pelvic suspicious areas and lymph nodes with increased risk of false negative PET due to the presence of micro-metastases by histopathology.

PET/CT for detection of distant metastases.

Table 3 illustrates the PET/CT findings compared to histopathological or follow up results of distant metastatic disease. The detection sensitivity of PET/CT was 95.6% and the specificity was 94.7%. In the 42 PET/CT scans included, only one false positive and one false negative PET/CT scans were found.

The superiority of FDG-PET in detecting nodal and metastatic disease in restaging of cancer cervix was seen in several studies. Ryu et al. [24] reported a 100% sensitivity of FDG-PET for detecting nodal metastases, liver, spine, and chest wall recurrences, but only 75% for detecting retrovesical lymph nodes. This is related to the high physiological FDG content in urinary bladder. Interestingly, in their work, the reported sensitivity was only 85% for lung recurrences and 75% for para-aortic recurrences. Lin et al. [34] on his work on 50 patients reported a sensitivity and specificity of 85.7% and 94.4% respectively. Yeh et al. [35] on 42 patients has a sensitivity for detecting nodal metastases of 83.3% and specificity of 96.7%. In these 2 studies FDG-PET was used in the setting of negative conventional CT and that explains the lower sensitivity. In this respect, when negative CT was used as an inclusion criterion, further lower sensitivities of 50% [10] and 75% [36] were reported for FDG-PET in detecting nodal disease. This demonstrates the value of tumor volume and the size-dependent limitation of tumor detection by FDG-PET.

The past few, Choi et al. found that PET/CT had a higher sensitivity (77%) than MRI (39%) concerning lymph node detection [40]. Sironi et al. studied 47 patients with stage 1 disease with PET/CT and found a sensitivity of 73% for detection of lymph node metastases [41]. A larger study, including 60 patients stage 1A2–2A, found a low value of PET, but this was performed without combined CT[42]. Loft et al. [18] on their work on 119 patients by PET/CT had a sensitivity of 100% and a specificity of 99% for para-aortic nodal disease in all patients and sensitivity and specificity of 100% and 94% for distant metastases. It has been demonstrated that combined PET/CT has a higher accuracy than separate PET and CT scans read side-by-side [43].

SUV_{max} values

Previous studies have shown that FDG uptake in cancer cells in various malignancies, evaluated as SUV_{max} reflects tumor aggressiveness [44-47]. In addition, SUV_{max} may be of clinical aid for outcome prediction in several different cancers [31, 47]. At present, however, data on potential usefulness of SUV_{max} in cervical cancer are scarce. In this work, the SUV_{max} ranged from 5.3-28.2 for the primary lesions (average: 12.5±6.96) and 2.8-22.9 for the metastases (average: 7.72±4.46). This difference was statistically significant (*P* value: 0.0058) (figure 3). The higher values at recurrent sites compared to distant metastatic sites are most likely related to tumor size. Good correlation was demonstrated between tumor volume and SUV_{max} values [47, 48]. Kumar et al. [48] showed that the SUV_{max} increases as tumor size increases and vice versa. Kidd et al. [49] demonstrated that primary tumor size with high SUV_{max} at initial diagnosis is predictive of lymph node involvement. This prognostic implication was highlighted in the study of Xue et al. [50] who showed that low pretreatment $SUV_{max} < 10.2$ in primary cervical cancer (stage I-IV) is associated with a better prognosis (71% 5-year disease free survival versus 52% in those with $SUV_{max} > 10.2$). However, in our study we did not identify a cutoff SUV_{max} due to the different patient selection and the retrospective nature of the work.

CONCLUSION

This study confirms the good results of ^{18}F FDG-PET in detection of recurrent disease and distant metastases in patients previously treated for cancer cervix. The PET/CT fusion of FDG-PET with a cross sectional CT has allowed better localization of an abnormal FDG uptake with accurate identification of residual/recurrent cervical cancer, as well as for distant metastases localization. We advocate that inclusion of FDG PET/CT in treatment planning for patients with high risk cancer cervix will lead to a better treatment strategy.

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