Original Article

Role of F-18 fluorodeoxyglucose positron emission tomography/computed tomography in the detection of recurrence in patients with cervical cancer

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ABSTRACT

Introduction: Treatment of cervical cancer is usually surgery in the early stages and radiotherapy or chemoradiotherapy in more advanced stages of the disease. Recurrence may occur in multiple sites following primary treatment. Although recurrent metastatic disease is not curable, surgical treatment may be of great help if locoregional recurrence is detected early. Fluorine-18 Fluorodeoxyglucose positron emission tomography - computed tomography (F-18 FDG PET/CT) forms an important part of investigations in the diagnosis of clinically suspicious recurrent cervical cancer. **Objective:** To assess the role of F-18 FDG PET/CT in diagnosing recurrence in patients with clinical suspicion of recurrent cervical cancer. **Materials and Methods:** We retrospectively evaluated 53 histopathologically proved patients of cervical cancer. All the patients had been treated with either surgery/radiation therapy with or without chemotherapy. The standard PET/CT acquisition protocol, with delayed post void static pelvic images, wherever required, was followed in all patients. Significant uptake of FDG in the lymph nodes was considered to be a recurrence suggestive of metastasis. Para-aortic lymph nodal involvement was considered to be distant metastasis. Any significant uptake in the lung nodule on FDG PET was evaluated either by histological confirmation, by taking fine needle aspiration cytology (FNAC), or by a follow-up chest CT done after three months. **Results:** Of the 53 patients with clinically equivocal recurrence, FDG PET/CT suggested recurrence in 41 patients (local recurrence in 14 patients and distant recurrence/metastasis with or without local recurrence in 27 patients). It had a sensitivity of 97.5%, a specificity of 63.6%, positive predictive value of 90.9%, and negative predictive value of 87.5%. **Conclusion:** PET/CT appears to have an important role in detecting recurrence following primary treatment of cervical cancer. The high positive and negative predictive values of PET/CT may be helpful in planning management of recurrent cervical cancer.

Keywords: Cancer of the cervix, chemoradiotherapy, fluorine-18 fluorodeoxyglucose, positron emission tomography - computed tomography, recurrence

INTRODUCTION

Cervical cancer is the third most common cancer and leading cause of cancer deaths in women worldwide.[1,2] Incidence rates vary from about 10/100,000 women in many western nations to 40/100,000 in developing countries.[1-4] Of the estimated approximately half million reported cervical cancer cases in the world every year, at least 80% occur in developing countries.[3] It is the second most common cancer among women in India.[4,5]

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Primary treatment of cervical cancer consists of surgery, radiotherapy, chemotherapy or a combination of the modalities, depending on the disease stage. The cure for cervical cancer mostly depends on the tumor staging at the time of presentation. Although lymphovascular invasion does not alter the International Federation of Gynecology and Obstetrics (FIGO) staging, it is associated with the risk of recurrence. Following primary surgery or radiotherapy, approximately 10-20% of the patients with stage IB-IIA, with no evidence of lymph node involvement at presentation, come back with recurrence.[6,7] On the contrary, almost 70% of the patients with nodal metastases and/or more locally advanced tumors develop recurrence.[6,7] Recurrence of cervical cancer

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in a majority of the cases occurs within two years of diagnosis, and the prognosis is poor.[6]

Recurrent disease is usually treated with palliative therapy,[8-11] while some of the patients with localized recurrence may be treated with appropriate aggressive therapy.[9,10] Unnecessary morbidity may be induced if curative therapy is practiced in the presence of distant metastasis. The clinical suspicion of recurrent disease most often arises from symptoms such as pain, bleeding per vagina, lymphedema or radiological findings. Distinguishing recurrence by means of morphological imaging such as computed tomography (CT)/magnetic resonance imaging (MRI) is not without its own limitations.[12,13] The identification of lymph node metastasis facilitates tailored treatment strategies, reducing the morbidity of unnecessary treatment and has a higher curative and survival rate.[14] Local recurrent disease is often difficult to detect on pelvic examination due to thickening of the soft tissue structures following radiation and/or surgery. The detection of recurrent disease in the pelvis using MRI/CT is also problematic in this setting, as growth of the cancer may also be due to infiltration of tissues causing only subtle changes in architecture.[14,15] Moreover, a biopsy of radiologically equivocal lesions is difficult, making the diagnosis of recurrent disease a clinically challenging task and leading to delayed treatment of the patient.

In contrast to CT or MRI, F-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET) can non-invasively assess the metabolic activity in tumors. FDG PET has been widely used for detection of early recurrence and is reported to be more accurate than a CT or MRI in detecting recurrent lymph node metastases in several human cancers.[15-17] FDG PET has also been shown to have an acceptable diagnostic performance in preoperative staging, response evaluation to the treatment,[17,18] evaluation of suspected recurrence,[14,15,18,19] detecting the effect on patient management,[20] and predicting the prognosis of recurrent cervical cancer.[20,21] However, limited literature exists from tropical countries like India, reporting the role of FDG PET in the detection of recurrent cervical cancer. In this study we have tried to evaluate the usefulness of PET/CT imaging in the detection of clinically equivocal recurrent cervical cancer.

MATERIALS AND METHODS

Data of 53 previously treated patients with histologically proven cervical cancer, who underwent FDG PET/Computed Tomography (CT) with a suspicion of recurrence, either clinically (n = 23) or with conventional imaging (n = 30), were reviewed. All the patients had been treated with either surgery/radiation therapy, with or without chemotherapy, according to the FIGO stage. The conventional workup (CWU) comprising of a physical examination, laboratory findings, and radiological imaging was done in all the patients. Morphological imaging in the form of CT/MRI had been done as per the treating physician's recommendation. Patients were subjected to further regular follow-up and the duration of the follow-up ranged from six months to 26 months (mean, 16 months). The detection rate of FDG PET for recurrences was analyzed retrospectively. A negative tissue biopsy within three months or no clinical evidence of recurrence within six months after the PET scan was considered to be clinical proof of no disease recurrence.

Positron emission tomography/computed tomography imaging

All the studies were acquired on a hybrid PET/CT scanner (Discovery STE-16, GE healthcare, Milwaukee, USA). Patients were prepared with minimum six hours fasting, before F-18 FDG injection. Plasma glucose levels were checked and were ensured to be <150 mg/dl. A dose of 370-444 MBq of F-18 FDG was injected intravenously and imaging was done 45-60 minutes later. Immediately prior to the procedure, all the patients were hydrated with 1000-1500 ml of water, but were asked to void the urine. Delayed post void static pelvic images were taken wherever found necessary. For delayed imaging, intravenous furosemide 40 mg was also administered to reduce tracer activity in the bladder. Static FDG-PET/CT imaging in 3-D mode, covering the upper torso from forehead to mid thighs (two-minute emission scan/position) was done. The CT scan was obtained in the same bed position, with the patient in shallow respiration. Tube voltage was 120 kV, while the current was determined individually using an automated modulation system.

Data obtained from CT acquisition was used for low-noise attenuation correction of PET emission data and for fusion of attenuation-corrected PET images, with corresponding CT images. After completion of PET acquisition, the attenuation-corrected reconstructed PET images, CT images, and fused images of matching pairs of PET and CT images were reviewed in the axial, coronal, and sagittal planes. The data was also viewed in maximum intensity projections, in a three-dimentional cine mode. After image reconstruction, a volumetric region of intrest (ROI) was drawn over the lesion. The maximum standardized uptake value (SUV max) corrected for lean body mass was calculated. Any focal uptake of FDG, which was not considered to be physiological on PET images, was measured on the basis of the standardized uptake value. FDG PET and CWU results were compared with the true lesion status obtained by histopathology or clinical follow-up and were classified as true positive, true negative, false positive or false negative.

Significant uptake of FDG in the lymph node was considered to be recurrence suggestive of metastasis. Para-aortic lymph nodal involvement or abnormal FDG uptake in any organ was considered to be distant metastasis. Any significant uptake in the lung nodule on FDG PET was evaluated either by histological confirmation, by performing FNAC or by a follow-up chest CT done after three months. If there was no change in size on the follow-up CT scan, the patients were further followed up at intervals of three months by the treating physician.

RESULTS

A total of 53 eligible patients were evaluated (age range = 32-70 years, mean age = 53 years, median age = 51 years at the time of presentation). Most of the patients presented with cervical cancer of FIGO stage ≥ IB. The patient characteristics are given in Table 1. The median time for FDG PET was 20 months from the primary presentation of cervical cancer and 4.2 months from the first suspicion of recurrence. The median follow-up after FDG PET was 12 months for the total patient population and 16 months for patients with a negative FDG PET result.

Of the 53 patients with clinically equivocal recurrence, FDG PET/CT detected recurrence in 41 patients (local recurrence in 14 patients and distant recurrence/metastasis with or without local recurrence in 27 patients). Of these, four were false positive and 37 were true negative. Nine patients had a normal scan of which one was false negative. In the remaining three patients PET/CT was suggestive of a second primary elsewhere in the body. Overall, PET/CT had a sensitivity of 97.5%, a specificity of 63.6%, positive predictive value of 90.9%, and negative predictive value of 87.5%. Figure 1 depicts images from three patients diagnosed to have locoregional/distant metastatic recurrent disease.

Table 1: Patient characteristics

Total patients	(*n*)=53
Histopathology	
Squamous cell carcinoma	36
Adenocarcinoma	14
Poorly differentiated carcinoma	03
Mode of primary treatment	
Chemoradiation	25
Surgery and chemoradiation	12
Radiotherapy	08
Surgery and radiotherapy	05
Surgery	03
Indications for FDG PET/CT of suspected recurrence	
Bleeding and pain	18
Equivocal lesions on CT or MRI	35

CT: Computed tomography, MRI: Magnetic resonance imaging, FDG: Fluorodeoxyglucose, PET: Positron emission tomography

Fourteen patients with local recurrence were continuously followed up clinically and with a PET/CT repeated at six months. One patient, diagnosed to have local recurrence, had a normal scan at six months suggesting a falsely positive PET/CT finding in the initial scan. There were three more false positive results, one with an FDG-positive lung nodule showing regression on a follow-up scan, while the other two – a non-FDG avid lung nodule with mediastinal lymphadenopathy and another with supraclavicular and abdominal retroperitoneal lymphadenopathy – subjected to FNAC from the mediastinal and supraclavicular lymph nodes, respectively, were found to have inflammatory cells on a histopathological examination. Figure 2 shows a patient with false-positive results. Of the three patients diagnosed to have second malignancy, two had a lung primary, while another one had colonic malignancy. Figure 3 shows the second primary in the lung in one such patient. These patients were subsequently treated accordingly. One patient with a normal PET/CT scan had a flare-up of the disease after four months, and thus, was found to be falsely negative. Another patient with normal FDG PET/CT died and the cause of death could not be ascertained, as an autopsy was not performed. This patient had been excluded from the total number of the patients for final statistical analysis. PET/CT findings influenced management in 58% (30/52) of the patients, by detecting distant metastases in 27 and secondary malignancy in three patients.

DISCUSSION

Recurrence or persistence of disease after treatment is noted in approximately one-third (35%) of the patients with invasive

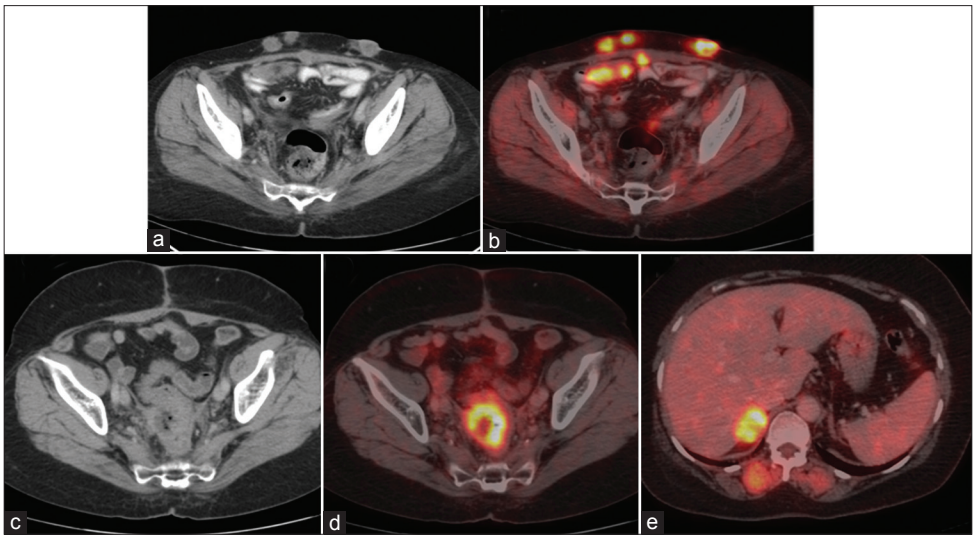

Figure 1: F-18 FDG PET/CT transaxial images (a) CT and (b) fused PET and CT of a patient with cervix cancer on follow-up showing abdominal wall metastasis. Transaxial CT image (c) and fused PET and CT image (d) of another patient reveal metastasis in the rectosigmoidal region; fused PET and CT image (e) of a third patient showing right adrenal metastasis

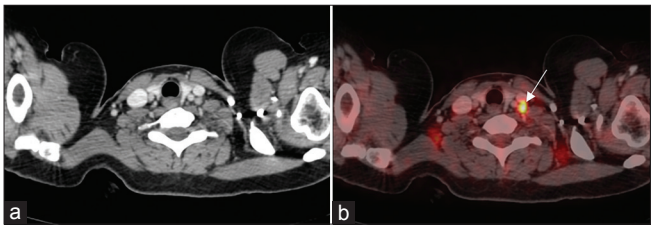

Figure 2: F-18 FDG PET/CT images (a) transaxial CT and (b) transaxial fused PET/CT of a patient with cervix cancer showing FDG avidity in left supraclavicular node (arrow). This uptake was found to be false positive for metastatic involvement

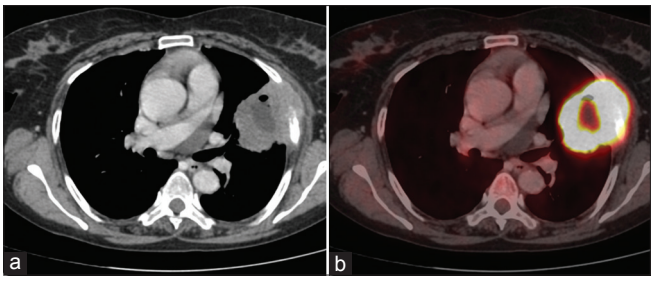

Figure 3: F-18 FDG PET/CT images (a) transaxial CT and (b) transaxial fused PET/CT of a patient with cervix cancer on follow-up showed an FDG avid mass lesion in the left lung, which was interpreted and confirmed to be a second primary

cervical cancer.[22] CT and/or MRI are the most commonly performed investigations to evaluate the suspected recurrence of the disease, but the detection rate by these morphological imaging modalities is quite low,[23] as the anatomical picture usually changes after the patient has been subjected to curative/palliative treatment.

Positron Emission Tomography/Computed Tomography seems to provide a better answer to the equivocal morphological imaging findings, as it helps to detect the local, distant, and lymph nodal metastasis more accurately than morphological imaging alone. Sugawara *et al.*,[24] has reported that lesions as small as <1 cm, in the vaginal cuff, pelvic sidewall, and retrovesical areas, which are usually obscured by post-radiation fibrosis, are specifically better detected by FDG PET. The higher feasibility of metabolic imaging over morphological imaging in detecting recurrences of cervical cancer is possible by the fact that FDG PET/CT scans provide functional information of the lesions along with the anatomical imaging, and detection of recurrent lesions is possible independent of the size. FDG PET is reported to be better interpretable, especially with distortion of the regional anatomy due to surgery or radiation treatment, in other malignancies such as head and neck cancers.[25]

Approximately 70% of the recurrences of cervical cancer are either due to distant metastases or a combination of local and distant metastases.[23] In our patients with cervical cancer, 58% were seen to have distant metastases, with three having secondary malignancies. This led to a change in the management from locoregional to systemic chemotherapy, making the whole body PET/CT highly beneficial, and it had a major impact on the treatment of these patients.

Most recurrences in cervical cancer are known to occur within two years after therapy;[22] the peak period of recurrence detected by FDG PET in our study was 18 months, comparable to the literature data. The superiority of the PET over CT and MRI, in detecting pelvic and para-aortic lymph node metastasis is well reported.[26-30] The sensitivity of PET for the detection of para-aortic metastasis had ranged from 57-75% in patients who had undergone lymphadenectomy.[28] In studies where the surgical staging of the lymph nodes was not done, PET positive para-aortic nodes were seen to be significant prognostic indicators of disease-free and overall survival in these set of cervical cancer patients.

A high sensitivity of 90% and a specificity of 100% for FDG PET has been reported in the diagnosis of recurrence of cervical cancer by Sun *et al.*,[31] in a group of 20 patients. Ryu *et al.*,[17] in a larger set of 249 patients reported the sensitivity, specificity, and positive and negative predictive values of FDG PET to be 90.3, 76.1, 35, and 98.2% in detecting recurrences of cervical cancer. Our study had sensitivity, specificity, positive, and negative predictive values of 97.5, 63.6, 90.9, and 87.5%, respectively, which were quite comparable, taking into account the limited number of patients taken in the study, but they showed a high positive predictive value. The high sensitivity could be due to the use of Lasix with fluid intake, to dilute the radioactive urine, followed by static pelvic images, and two hours of delayed dual time imaging in suspicious cases was used wherever deemed necessary.

The two-year progression-free survival had been reported to be 64% in CT-negative and PET-negative patients; 18% in CT-negative and PET-positive patients; which subsequently dropped to 14% in CT-positive and PET-positive patients.[32] In spite of the efficacy of the PET/CT, the limitation of the PET in terms of difficulty in resolution of lesions <5 mm and brain metastasis, due to high glucose uptake in the brain, made early detection and resolution difficult. Diffuse peritoneal carcinomatosis detection may be difficult in some, due to physiological bowel uptake.[21]

As per the latest National Comprehensive Cancer Network (NCCN) guidelines, whole body PET/CT may be considered as part of a surveillance workup in patients who are at high risk for loco-regional (central or para-aortic) failure. The PET/CT may be useful in detecting isolated recurrence or persistent disease in asymptomatic patients, which is amenable for potentially curative salvage therapy. However, the most important step for detection of early recurrences still remains to be the clinical suspicion of recurrence, leading the clinician to further investigate with functional/morphological imaging. The high negative predictive value in this study suggests that it must be given consideration in patients suspected of recurrence depending on its availability and cost-effectiveness during the course of a follow-up.

CONCLUSION

Positron Emission Tomography/Computed Tomography appear to play an important role in detecting recurrence following primary treatment of cervical cancer. If performed early during the clinical suspicion, PET/CT may help in treating the patient with curative intent.

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