Published in final edited form as:

Eur J Nucl Med Mol Imaging. 2009 December ; 36(12): 1952–1959. doi:10.1007/s00259-009-1206-x.

Efficacy of ^{18}F -FDG PET/CT in the evaluation of patients with recurrent cervical carcinoma

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Abstract

Purpose—Only a limited number of studies have evaluated the efficacy of ^{18}F -FDG PET/CT for recurrent cervical carcinoma, which this study seeks to expand upon.

Methods—This is a retrospective study of 30 women with cervical carcinoma who had a surveillance PET/CT after initial therapy. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were calculated using a 2×2 contingency table with pathology

results (76%) or clinical follow-up (24%) as the gold standard. The Wilson score method was used to perform 95% confidence interval estimations.

Results—The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT for the detection of local recurrence at the primary site were 93, 93, 93, 86, and 96%, respectively. The same values for the detection of distant metastases were 96, 95, 95, 96, and 95%, respectively. Seventy-one percent of the scans performed in symptomatic patients showed true-positive findings. In comparison, 44% of scans performed in asymptomatic patients showed true-positive findings. But, all patients subsequently had a change in their management based on the PET/CT findings such that the effect was notable. The maximum standardized uptake value ranged from 5 to 28 (average: 13 ± 7) in the primary site and 3 to 23 (average: 8 ± 4) in metastases which were significantly different ($p=0.04$).

Conclusion—This study demonstrates favorable efficacy of ^{18}F -FDG PET/CT for identification of residual/recurrent cervical cancer, as well as for localization of distant metastases.

Keywords

PET/CT; ^{18}F -FDG; Cervical cancer; Restaging; Efficacy

Introduction

Cancer of the uterine cervix is the third most frequently diagnosed and third leading cause of death from gynecological malignancy in women after cancers of the ovary and uterine corpus [1]. The International Federation of Gynecology and Obstetrics (FIGO) reports both the 5-year recurrence rate and 5-year overall mortality rate of cervical cancer at 28% [2]. As such, rapid and accurate evaluation to define the extent of both the initial and recurrent disease is important [3, 4]. Accordingly, various serum biomarkers and noninvasive imaging modalities have been employed. The primary serum tumor markers for cervical cancer include squamous cell carcinoma antigen (SCC-Ag) and carcinoembryonic antigen (CEA) [5].

The noninvasive imaging tests for cervical cancer include computed tomography (CT) and magnetic resonance imaging (MRI). While useful, their primary limitations (especially for detection of recurrence and lymph node metastases) are in their reliance on morphological size to diagnose pathology and the limited body area that is imaged. The reported sensitivity of CT to detect local recurrence and lymph node metastases was modest, with several studies showing values of 34–44% [6, 7].

In contrast, ^{18}F -labeled 2-fluoro-2-deoxyglucose (^{18}F -FDG) positron emission tomography (PET) allows for noninvasive metabolic characterization of lesions. ^{18}F -FDG PET for recurrent cervical cancer has been investigated and shown relatively high sensitivity and specificity [8–11], especially in the presence of an unexplained elevation in serum tumor markers without evidence of recurrent disease on CT or MRI [12]. The anatomical landmarks of PET, however, are limited due to low soft tissue background activity and inherent resolution deficiency of isotopic imaging [13].

Combined positron emission tomography and computed tomography (PET/CT) is promising and has already been successfully applied to many solid tumors such as lung, breast, lymphoma, and colorectal carcinoma [14]. Multiple studies have shown the utility of PET/CT in the staging of cervical cancer, especially in the evaluation of locoregional and distant spread of disease [15–20]. For recurrent cervical cancer, however, only a few published reports from integrated PET/CT imaging are available [21–23]. As such, the objective of this study is to further evaluate the efficacy of integrated ^{18}F -FDG PET/CT in the post-therapy surveillance of cervical cancer.

Material and methods

Patients

This is a retrospective study of 30 women with cervical cancer referred for ^{18}F -FDG PET/CT from 1 January 2003 until 31 August 2006. The patients underwent standard whole-body (skull base to mid-thigh) PET/CT scans for surveillance purposes. The International Federation of Gynecology and Obstetrics (FIGO) classification was used for clinical restaging (Table 1). 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 who reached complete remission after initial treatment. Treatment is guided by the initial stage and may involve surgical resection, external beam radiation, brachytherapy, and chemotherapy. Among these 30 patients, 53% had surgery, 90% external beam radiation, 30% brachytherapy, and 47% chemotherapy. 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 had other malignancies, had an initial diagnosis of advanced cancer cervix not suitable for treatment with curative intent, or did not achieve complete remission. The various clinical indications for their surveillance PET/CT imaging included: (1) presence of symptoms, (2) abnormal findings on physical and gynecological examinations, (3) concerning lesions on conventional imaging studies, or (4) were referred for a surveillance PET/CT scan without concerning symptoms, physical exam, or radiologic findings.

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

The PET/CT scanning was performed with a GE Discovery LS PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA). The patients fasted a minimum of 6 h prior to intravenous injection of 400–555 MBq ^{18}F -FDG. Immediately before scan start, they were asked to void. Bladder catheters or diuretics were not used. The examination was performed with the patient positioned supine and with the arms placed over the head.

CT scans were performed immediately prior to the PET scan with a multidetector four-slice spiral CT scanner. The CT scan was performed with a 0.5-s rotation time, 15 mm/ rotation speed, 5-mm helical thickness, and a 1.5:1 pitch, at 140 kVp and 90 mAs.

The PET scan followed immediately with an acquisition time of 3–5 min per bed position. Whole-body PET scanning (2-D, 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 transaxial, coronal, and sagittal images with a slice thickness of 5 mm. Two nuclear medicine physicians reviewed the PET and the fused PET/CT images on a GE Xeleris workstation (GE Medical Systems, Milwaukee, WI, USA) to arrive at a consensus read. Visual interpretation was based on comparing uptake in an abnormal lesion to the background uptake and correlating with abnormalities on CT. Maximum standardized uptake values (SUV_{max}) were also measured for each lesion. However, a specific threshold value of SUV was not used to classify lesions as either normal or abnormal.

Statistical analysis

Diagnostic accuracy was evaluated by comparing the PET results with final diagnoses (as confirmed by histological evaluation), clinical follow-up, or imaging studies. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of PET/CT were calculated separately for local pelvic disease or distant metastases. 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 patients ranged in age from 28 to 87 years with an average of 50 ± 16 years. A total of 42 surveillance scans were performed with 18 patients receiving one PET/CT and 12 patients having two scans. In the latter 12 patients, the interval between the first and second scans was 8.7 ± 12.4 months. The gold standard used for analysis of the PET/CT data were histological results in 23 patients (76%) and clinical follow-up in 7 patients (24%). Of note, the histological verification was done on a per-patient basis (i.e., not every lesion was biopsied) and so may correspond to either the primary or metastatic lesion. The mean clinical follow-up time for these patients was 3.9 ± 1.7 years from the first scan and 2.7 ± 1.3 years from the second scan.

Histological and FIGO classification

The clinical FIGO staging and the histology of the 30 patients who had been included are shown in Table 2. The most common histological findings were squamous cell carcinoma (73.3%) and adenocarcinoma (16.7%), followed by much less common types including papillary squamous carcinoma and adenosquamous carcinoma.

PET/CT results by patient

Of the total 30 patients referred for surveillance imaging after definitive treatment, ^{18}F -FDG PET/CT detected an abnormality in 22 of 23 patients with recurrent disease. The scan was negative in five of seven patients without recurrence. The one false-negative scan was in a patient with a solitary hypermetabolic (SUV 5.3) pelvic lymph node which was felt to be

reactive, but was in fact disease recurrence. The two false-positive scans included one patient with increased ^{18}F -FDG uptake in the primary site which was subsequently biopsy proven (twice) to be granulation tissue, and another patient with hypermetabolic cervical and axillary lymph nodes which were subsequently biopsy proven to be reactive lymphadenopathy. Positive PET/CT findings in 22 patients included 5 patients with local recurrence only, 4 patients with distant metastases only, and 13 patients with both local recurrence and distant metastases (Table 3). Figure 1 shows a typical example of widespread metastases from cervical cancer detected by PET/CT.

PET/CT results by site

Abnormal ^{18}F -FDG uptake was identified at 125 sites. Those patients with only local recurrence had fewer lesions in total than those with only distant metastases, who had fewer than those with both local and distant metastases. The number of abnormal foci in these groups was 8, 38, and 79, respectively. The eight lesions in the group with local recurrence only represent the primary tumor with multifocality in three patients. The majority of distant metastases were nodal and primarily involved the iliac and para-aortic lymph node regions. Other sites of distant metastases included the retroperitoneum, pleura, liver, and a splenic lesion in one patient (Table 4).

PET/CT results by scan

Of the 42 total surveillance scans, 2 (5%) were performed because of concerning symptoms, 13 (32%) were performed because of concerning signs or physical exam findings, 9 (22%) were performed because of concerning conventional imaging findings, and 18 (44%) were performed without any specific concerning findings. Combining the three groups in which concerning signs, symptoms, or findings prompted the PET/CT, 17 scans (71% of that group or 41% of the total scans) showed true-positive findings. Of the group referred for a PET/CT without concerning symptoms, physical exam, or radiologic findings, eight scans (44% of that group or 20% of the total scans) showed unexpected but true-positive findings which subsequently led to a change in patient management.

Comparison of the PET/CT findings (classified as either positive or negative overall) to the histological results at the primary site showed that 13 of 14 scans were true-positives and 26 of 28 scans were true-negatives (Table 5). Figure 2 shows an example of a false-positive finding at the primary site. This translates to a calculated sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 93 (95% CI: 76–99), 93 (95% CI: 84–96), 93 (95% CI: 81–97), 86 (95% CI: 71–92), and 96% (95% CI: 87–99), respectively, for detection of the local recurrence at the primary site.

Evaluation of the PET/CT findings in distant sites showed that 22 of 23 scans were true-positives and 18 of 19 scans were true-negatives (Table 5). This translates to a sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 96 (95% CI: 86–99), 95 (95% CI: 83–99), 95 (95% CI: 84–99), 96 (95% CI: 86–99), and 95% (95% CI: 83–99), respectively, for detection of distant metastases.

Standardized uptake value

The SUV_{max} was measured in all areas that showed visually pathologic ^{18}F -FDG uptake. The SUV_{max} ranged from 5 to 28 (average: 13 ± 7) in the primary site and 3 to 23 (average: 8 ± 4) in metastases. While the ranges are similar, the average SUV_{max} at the primary site is significantly higher ($p=0.04$) than in metastases (Fig. 3). For the primary site itself, the SUV_{max} for those patients without metastases also ranged from 5 to 28 (average: 13 ± 10) while for those patients with metastases ranged from 6 to 22 (average: 12 ± 5). These differences were not significantly different ($p=0.85$).

Discussion

Cancer of the uterine cervix (cervical cancer) is among the top three leading diagnoses among gynecological malignancies both worldwide and in the USA. It has both a relatively high 5-year mortality and recurrence rate (28%). As such, enhanced staging, therapy, and evaluation of recurrence are essential to improve the prognosis for these patients.

CT and MRI have been used for staging and restaging of cervical cancer. However, multiple studies have now shown the improved efficacy afforded with functional imaging such as PET, and especially PET/CT, for the staging of cervical cancer [15–20, 24]. Based on such reports, the Centers for Medicare Services (CMS) have approved PET/CT for the initial staging of cervical cancer when conventional imaging is negative for extrapelvic metastasis.

Only a limited number of reports are available which evaluate the efficacy of PET/CT imaging for recurrent cervical cancer [25–28]. However, these too are promising and show sensitivity and specificity values above 80% [21–23, 29]. As such, the newest guideline put forth by the CMS now covers cervical cancer for subsequent treatment planning (i.e., restaging or response to therapy). The National Comprehensive Cancer Network (NCCN) also endorses PET/CT for both the staging and restaging of cervical cancer [30].

The results of this study confirm the results of prior studies and show that PET/CT has favorable efficacy for the evaluation of recurrence after initial treatment with curative intent. This applies to both local recurrence and metastatic disease (Table 5). For the former, our results show a sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 93 (95% CI: 76–99), 93 (95% CI: 84–96), 93 (95% CI: 81–97), 86 (95% CI: 71–92), and 96% (95% CI: 87–99), respectively. The same values for the detection of distant metastases are 96 (95% CI: 86–99), 95 (95% CI: 83–99), 95 (95% CI: 84–99), 96 (95% CI: 86–99), and 95% (95% CI: 83–99), respectively. This compares favorably with sensitivity and specificity values calculated in other reports (Fig. 4). In the latter, the sensitivity ranges from 92 to 93%, the specificity from 81 to 100%, and the accuracy from 87 to 96% for the detection of combined local and metastatic recurrence of cervical cancer [21–23].

With relation to the various indications for doing the surveillance scan, combining the three groups in which concerning signs, symptoms, or findings prompted the PET/CT, the majority of scans (71%) showed true-positive findings. In comparison, 44% of the scans that were performed without concerning symptoms, physical exam, or radiologic findings

showed unexpected but true-positive findings. Nonetheless, all these patients subsequently had a change in their management plan based on the PET/CT findings such that the effect was notable.

Analysis of our data on a per-lesion basis (Table 3) showed that the majority of patients who did have recurrence had both local and distant metastatic disease (13), while approximately equal numbers of patients had either local disease (5) or distant disease alone (4). However, those who had distant disease had, on average, many more lesions than those who had local recurrence only (38 lesions compared to 8 lesions, respectively). Those 13 patients with both local and distant metastatic disease also had more lesions in the pelvis than those with only local recurrence (79 lesions compared to 8 lesions, respectively). These findings make sense as those who tend to recur may be expected to have more aggressive histology (and thus a higher stage disease) and would therefore be more likely to develop metastatic disease.

The distribution of distant metastatic disease (Table 4) is also in accord with what one would expect from spread of a primary malignancy originating in the pelvis. The majority of the metastases were to local lymph nodes in the retroperitoneum, iliac chain, and pelvis, in that order. Less common metastases were to more cranial sites including the liver, superior retroperitoneal nodes, neck and chest nodes, and the lung pleura.

With relation to the above discussion, evaluation of the maximum ^{18}F -FDG uptake (SUV_{max}) within the primary and distant sites of disease was somewhat surprising in that the primary recurrence had a significantly higher SUV_{max} (mean: 13 ± 7) across the scans than did the metastases (mean: 8 ± 4) (Fig. 3). The opposite is often true given the more aggressive tumor biology in those cancers that have metastasized. While this finding may partially be due to artifacts (i.e., secondary to a partial volume effect from the relatively smaller metastasis, or intense uptake in the adjacent bladder leading to falsely elevated SUV values in the primary recurrences), it is more likely a true finding related to the histology of these cancers. However, comparison of the SUV_{max} within the primary tumor of those patients who did not have metastases (mean: 13 ± 10) did not significantly differ from those patients with metastases (mean: 12 ± 5). As such, in this small series of patients with cervical carcinoma, it appears that SUV_{max} of the local lesion was not predictive of distant metastatic disease (though this would need to be verified in larger patient cohorts).

The primary limitations of this study are in its retrospective nature, with its inherent biases, primarily in patient selection. To that end, care was taken to ensure that all patients had initially achieved complete remission yet were being reevaluated by PET/CT for a variety of indications ranging from concerning findings on conventional imaging or physical exam to patients who were still thought to be without evidence of disease. Another limitation of the retrospective study design relates to the fact that, as mentioned previously, the histological verification was done on a per-patient rather than per-lesion basis. While this is the standard of care, certain equivocal lesions may have been miscategorized leading to an error in the sensitivity and specificity values. Additionally, these scans were performed without the use of a bladder catheter or diuretics to decrease physiologic ^{18}F -FDG accumulation in the bladder. This may affect both the sensitivity and specificity as the intense ^{18}F -FDG uptake

in close proximity to the site of primary malignancy can mask focal lesion in the cervix, or may lead to falsely believing that abnormal uptake exists.

Overall, these findings further show that PET/CT is very useful for the evaluation of recurrent cervical cancer, both on a per-patient and per-lesion analysis. These findings further support the hypothesis that PET/CT should have an integral role, along with conventional imaging and bio-markers (especially SCC-Ag), in the evaluation of patients with recurrent cervical cancer. Additional prospective studies, with larger cohorts of patients, would add further value to research in this area.

Acknowledgments

This research was supported in part by NCI ICMIC CA114747 (SSG) and the clinical studies were supported in part by the Doris Duke Foundation and Canary Foundation (SSG).

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Fig. 1. PET/CT scan of a 60-year-old woman with cervical cancer. Maximum intensity projection (MIP, **a**), as well as transaxial CT (**b**), PET (**c**), and fused (**d**) images show the primary lesion. Widespread pulmonary, mediastinal, and hilar lymph node metastases are also seen on the MIP image. Of note, radiation treatment planning markers are also seen on the MIP image

Fig. 2.

A 36-year-old woman with cervical carcinoma. Focal uptake in the region of the uterine cervix is worrisome for residual/recurrent disease. However, pathologic assessment subsequently showed granulation tissue. As such, this is an example of a false-positive finding with PET/CT

Fig. 3.

Box-and-whiskers plot of the SUV_{max} values at the primary site and in distant metastases.

Upper line upper limit, light grey box 75th percentile, black line 50th percentile, dark grey box 25th percentile, lower line lower limit. The median SUV_{max} of the metastases were significantly different from the SUV at the primary site (p value=0.04). Other comparisons were not significantly different

Fig. 4.

Comparison of the sensitivity and specificity of PET/CT for the evaluation of recurrent cervical cancer from this and other published reports

Table 1International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical carcinomas^a

Stage	Description
I	Carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded.
IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
IA-1	Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm diameter.
IA-2	Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
IB	Clinical lesions confined to the cervix or preclinical lesions greater than stage IA. All gross lesions even with superficial invasion are stage IB cancers.
IB-1	Clinical lesions no greater than 4 cm in size.
IB-2	Clinical lesions greater than 4 cm in size.
II	Carcinoma that extends beyond the cervix, but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.
IIA	No obvious parametrial involvement. Involvement of up to the upper two thirds of the vagina.
IIB	Obvious parametrial involvement, but not into the pelvic sidewall.
III	Carcinoma that has extended into the pelvic sidewall and involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney are stage III.
IIIA	No extension into the pelvic sidewall but involvement of the lower third of the vagina.
IIIB	Extension into the pelvic sidewall or hydronephrosis or non-functioning kidney.
IV	Carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
IVA	Spread of the tumor into adjacent pelvic organs.
IVB	Spread to distant organs.

^a <http://screening.iarc.fr/viaviliappendix1.php>

Table 2

Distribution of patients according to clinical stage and histological diagnosis

FIGO classification ^a	Histological diagnosis			Total
	Squamous cell carcinoma	Adenocarcinoma	Other ^b	
IB-2	2	0	0	2 (7%)
IIA	2	1	1	4 (13%)
IIB	7	2	1	10 (33%)
IIIA	1	0	0	1 (3%)
IIIB	8	2	1	11 (37%)
IVA	2	0	0	2 (7%)
Total	22 (73%)	5 (17%)	3 (10%)	30

^aSee Table 1 for staging system^bOther histological findings primarily include papillary squamous carcinoma and adenosquamous carcinoma

Table 3

Positive PET/CT results by patient and lesion

	Number of patients	Number of lesions
Local recurrence only	5	8
Distant disease only	4	38
Local+distant disease	13	79 (18+61)

Table 4

Location of distant metastases by frequency

Location	Number
Para-aortic lymph nodes	26
Iliac chain lymph nodes	17
Pelvic nodes	16
Liver	12
Abdominopelvic masses (i.e., peritoneal metastases)	9
Other retroperitoneal lymph nodes	7
Pleura	6
Neck or chest lymph nodes	5
Spleen	1

Table 5

Comparison of PET/CT and histology/clinical follow-up for local and distant disease

Local (primary) site			
	Histology/clinical follow-up		
PET/CT	Positive	Negative	Total
Positive	13	2	15
Negative	1	26	27
Total	14	28	42
Distant (metastatic) sites			
	Histology/clinical follow-up		
PET/CT	Positive	Negative	Total
Positive	22	1	23
Negative	1	18	19
Total	23	19	42