Pet Scan And Gynaecological Malignancies: Hospital Sultanah Bahiyah Experience

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SUMMARY

The objective of this study was to evaluate the role of PET/CT in diagnosing and evaluating patients with suspected gynaecological tumour recurrence and persistent disease following treatment. This cross-sectional study involving 26 patients with gynaecological malignancies was carried out at Hospital Sultanah Bahiyah between 2006 and 2008. The standard imaging modalities disclosed possible tumour recurrence or persistent disease in 24 of the 26 patients (92.3%). Two patients with negative CT were subjected to PET/CT due to persistently elevated serum tumour markers. PET/CT confirmed tumour recurrence in 9 (34.6%) patients and was inconclusive in 2 (7.7%) patients. No abnormal uptake was observed in 15 (57.7%) patients. Of the 9 patients with positive PET/CT, 7 (77.8%) had a repeat PET/CT and 2 (22.2%) had a CT following subsequent treatment which confirmed no further evidence of disease. Patients with negative or inconclusive PET/CT were either continued with routine follow-up or had a close monitoring by either CT or serum tumour markers. With the availability of PET/CT, almost two-third of patients did not have to undergo unnecessary chemotherapy or radiotherapy. Integrated PET/CT imaging offers beneficial effects in both diagnosing and evaluating suspected tumour recurrence and persistent disease in gynaecological malignancies.

KEY WORDS:
PET/CT Scan, Gynaecological Malignancies

INTRODUCTION

In the last two decades, the invention of positron emission tomography (PET) using the radionuclide-labeled analogue of glucose "2- [18F]fluro-2-deoxy-D-glucose (18F-FDG)", which is one of the major source of energy in cancer cells, makes possible for us to detect regional metabolism in metabolically active tumour foci more accurately than with that of morphologic imaging techniques [1,2]. As PET alone lacks in its ability to give precise anatomical information, recently, combined PET and computed tomography (CT) integrating morphologic data of CT and functional data of PET has been widely used to evaluate loco-regional and distant spreads in many different types of malignancies.

The role of PET/CT in gynaecological malignancies have been promising though limited studies are available on their accuracies [2]. There are many circumstances whereby asymptomatic patients had an abnormal biochemical markers or inconclusive CT or magnetic resonance imaging (MRI) post-treatment. It is certainly not justified to subject these patients with unnecessary invasive procedures, more so when the lesion is not well-defined. This is when ^{18}F-FDG appears to have potential roles, not just in assessing response to treatment and forecasting prognosis, but also in detecting lesions in the setting of post-treatment unexplained tumor-markers elevation.

In Malaysia, PET/CT Scanners have been available since January 2005. The facilities are available in two government hospitals, one at the Department of Nuclear Medicine of Hospital Pulau Pinang and the other is located at the Department of Nuclear Medicine of Hospital Putrajaya. In addition, a few PET Scanners are available in private hospitals throughout the country. However, the indications for PET/CT in this country are still restricted to selected patients and for limited indications.

Hospital Sultanah Bahiyah is a recognized Gynaecology Oncology Centre under the Ministry of Health, Malaysia. The Gynaecology Oncology Unit of this hospital was established in 2003 and comprises of three qualified Gynaecological Oncologists and one trainee. The unit provides gynaecology oncology services for the northern part of West Malaysia with a total of 150 to 200 new cases seen annually, which include 60 to 80 ovarian cancers, 40 to 60 cervical cancers, 20 to 30 uterine cancers and about 5 vulva cancers. In 2008, there were a total of 1334 follow-up visits made to the Gynaecology Oncology Clinic.

The objective of the present study was to evaluate the role of PET/CT in diagnosing and evaluating patients with suspected gynaecological tumour recurrence and persistent disease following treatment at Hospital Sultanah Bahiyah.

PATIENTS AND METHODS

Patients

This was a cross-sectional study carried out at the Gynaecology Oncology Unit of Hospital Sultanah Bahiyah, Alor Setar, Kedah. All patients with proven gynaecological malignancies subjected to PET/CT between 1 January 2006 and 31 December 2008 were included in the study. Each patient had their malignancies treated either surgically with or without adjuvant treatment or received radiation therapy or concurrent chemoradiation as primary treatment.

Inclusion criteria: The decision for PET/CT was made when there were suspicious or inconclusive lesions on CT, in the

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Table I: Primary Tumour Sites

Primary Tumour	Number (n)	%
Ovary	16	61.7
Cervix	6	23.1
Endometrium	1	3.8
Vulva	1	3.8
Peritoneal	1	3.8
GTN	1	3.8
Total	26	100

GTN = Gestational Trophoblastic Neoplasia

Table II: Site of Possible Tumour Recurrence

Site of Possible Tumour Recurrence as Reported by CT	Number (n)	%
Pelvis / Pelvic Nodes	6	23.1
Liver	3	11.5
Lungs	3	11.5
Adrenal Gland	1	3.8
Para-Aortic Nodes	1	3.8
Mesentery	1	3.8
Multiple Sites	8	30.8

Table III: Indications for PET/CT

Indications for PET/CT	Number (n)	%
Evaluation of Suspicious Lesion on CT after completion of First Line Chemotherapy	6	23.1
Evaluation of Suspicious Lesion on CT for suspected Tumour Recurrence	11	42.3
Evaluation of Suspicious Lesion on CT after completion of treatment for Tumour Recurrence	7	26.9
Persistently Abnormal Tumour Markers	2	7.7
Total	26	100

Table IV: PET/CT for Suspected Tumour Recurrence

Case No.	Primary Tumour	Evidence of Pelvic or Distant Recurrence		Further Management
		Standard Imaging	PET/CT	
1	Peritoneal	+	+	Rechallenge Chemotherapy
2	Ovary	+	-	Routine Follow-Up
3	Ovary	-	-	Close Observation – AFP
4	Ovary	+	-	Routine Follow-Up
5	Ovary	+	-	Routine Follow-Up
6	Cervix	+	+/-	Close Observation – PET / Vault
7	Ovary	+	-	Routine Follow-Up
8	Uterus	+	-	Routine Follow-Up
9	Cervix	+	-	Routine Follow-Up
10	Cervix	+	+	Palliative Chemotherapy
11	Cervix	+	-	Routine Follow-Up
12	Ovary	+	-	Close Observation – CT
13	GTN	+	-	Close Observation – βHCG
14	Ovary	+	+/-	Close Observation – PET / Ca 125
15	Ovary	+	+	Rechallenge Chemotherapy
16	Ovary	+	-	Close Observation – Ca 125
17	Ovary	-	-	Close Observation – Ca 125
18	Vulva	+	+	Debulking, then EBRT
19	Ovary	+	+	Rechallenge Chemotherapy
20	Ovary	+	-	Routine Follow-Up
21	Ovary	+	+	Rechallenge Chemotherapy
22	Ovary	+	+	Rechallenge Chemotherapy
23	Cervix	+	+	Palliative Chemotherapy
24	Cervix	+	-	Routine Follow-Up
25	Ovary	+	+	Second-Look, then Chemo
26	Ovary	+	-	Routine Follow-Up

Table V: Percentage of Tumour Recurrence According to Primary Tumour as Confirmed by PET/CT

Primary Tumour	Number (n)	%
Ovary	5 of 16	31.3
Cervix	2 of 6	33.3
Uterus	0 of 1	0
Vulva	1 of 1	100
Peritoneal	1 of 1	100
GTN	0 of 1	0

GTN = Gestational Trophoblastic Neoplasia

absence of clinical findings with normal serum tumour markers or when there were persistently raised serum tumour markers in the presence of negative clinical findings or CT.

Twenty-six patients were included in the study. Each patient had undergone a comprehensive evaluation of her clinical status. She was either on routine follow-up after completion of treatment or being followed-up for suspected tumour recurrence. Tumour markers (Ca 125, CEA and Ca 19.9) were taken when applicable. CT Scan was performed to monitor the disease and this was compared with previous films.

PET/CT Scan
All patients were referred to the Nuclear Medicine Department of Hospital Pulau Pinang for PET/CT. At the time of the study, the waiting list was approximately three to four weeks. Patients were instructed to fast at least six hours before an intravenous injection of 10.43 mCi ^{18}F-FDG. Patients voided prior to administration of ^{18}F-FDG and over again prior to image obtaining. ^{18}F-FDG was given intravenously followed by a tracer uptake of approximately 60 minutes. After injection, patients were kept lying comfortably.

The scanned regions encompassed the neck, thorax, abdomen and upper thigh. A contemporaneous non-contrast CT scan was performed for the purposes of attenuation correction and anatomical correlation. All PET/CT images were evaluated by visual interpretation by an experienced nuclear medicine and radiology physician.

Analysis
The accuracy of the imaging studies were confirmed by histology (obtained during second-look laparotomy or guided biopsies), by clinical (if any) or radiological outcomes after subsequent management.

RESULTS

Profile of Patients: The mean + SD age of the study cohort was 50.31 + 12.71 (range 24 – 71) years. The primary tumours are as shown in Table I. Twenty-three of the 26 patients (88.5%) had surgical intervention as primary treatment and of this, 21 (91.3%) received adjuvant chemotherapy and 2 (8.7%) received adjuvant radiotherapy. Two (7.7%) patients had primary chemoradiation as primary treatment and one (3.8%) which was a case of choriocarcinoma had chemotherapy as primary treatment. The response to treatment was assessed clinically, biochemically and radiologically. The standard imaging modalities disclosed possible tumour recurrence or persistent disease in 24 of the 26 patients (92.3%). The sites of possible recurrence in these patients are shown in Table II. Two patients with negative CT were also subjected to PET/CT due to persistently elevated serum tumour markers.

The indications for PET/CT are shown in Table III. The PET/CT confirmed tumour recurrence in 9 of the 26 patients (34.6%). PET/CT was inconclusive in 2 (7.7%) patients. PET/CT did not show any abnormal uptake for the rest of the patients.

Outcome: Table IV summarizes the 26 patients who underwent PET/CT. Case #18 and #25 had histological confirmation of tumour recurrence following PET/CT via groin nodes debulking and second-look laparotomy respectively. Case #18 subsequently had external beam radiotherapy (EBRT) and Case #25 had a second line chemotherapy. Seven (77.8%) of the 9 patients whom had confirmation of tumour recurrence by PET/CT, had a repeat PET/CT following subsequent treatment which confirmed no further evidence of disease. Another two patients were assessed by conventional imaging (CT Scan) due to a long waiting list for PET/CT.

In this study, one-third cervical carcinoma patients with inconclusive CT had abnormal uptake of 18F-FDG. Case #10 (refer Table IV) had adjuvant chemotherapy after Radical Hysterectomy (refused radiation therapy) and had abnormal uptake in the right adrenal gland. Case #23 had primary chemoradiation therapy and had abnormal uptake at multiple sites in the pelvis and abdomen. Both patients were subjected to palliative chemotherapy, and one is still alive at present.

Case #2 had advanced ovarian carcinoma which was debulked surgically followed by adjuvant chemotherapy. CT post-chemotherapy showed an inconclusive lesion in the liver which was not feasible for biopsy. PET/CT performed showed no abnormal uptake and patient was subsequently managed conservatively and remained in remission. Case #3 was an ovarian carcinoma which was operated, also followed by adjuvant chemotherapy. Her serum tumour marker remained elevated post-treatment and repeated CT remained negative. She was then subjected to PET/CT which also showed no abnormal uptake, and she was subsequently continued with routine follow-up.

The two patients with inconclusive PET/CT were monitored closely with repeat PET/CT and vault smear and serum Ca 125 respectively. The other 15 (57.7%) patients with negative PET/CT were either continued with routine follow-up or had a close monitoring by either CT or serum tumour markers.
As the entire study group except for two consisted of patients with inconclusive CT requiring confirmation by PET/CT for persistent disease or recurrent tumour, it was not possible to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the PET/CT versus the standard imaging procedures. Table V showed the percentage of tumour recurrence confirmed by PET/CT according to gynaecological organs.

The current status of the patients included in this study, as of November 2010, is shown in Table VI. All patients with no abnormal uptake on PET/CT were alive and well except for two which were lost to follow-up. Seven of nine (77.8%) patients with positive PET/CT had died and the only patient with inconclusive PET/CT was lost to follow-up.

DISCUSSION

Previously, CT Scan and to a lesser extent, MRI has been the most commonly used imaging techniques in the routine management of cancer patients. CT detection of a tumour is based primarily on the presence of abnormal mass or organs enlargement.

PET Scan has been useful in differentiating benign tumours from malignant tumours and in evaluating metastases and tumour recurrence. Its value has been demonstrated in a wide variety of malignancies, including ovarian, cervical, colo-rectal, lungs, breast and lymphoma. Detection of tumour tissues by PET Scan does not require the presence of a mass and thus may provide definitive information much earlier than the anatomic imaging modalities such as CT and MRI.

For cervical carcinoma, PET/CT has proven useful in both the staging of untreated advanced cervical cancer and restaging of the disease. Yildrim et al,1 found that PET/ CT is an effective imaging technique in the evaluation of locally advanced cervical carcinoma with negative CT findings. The accuracy, sensitivity, specificity, PPV and NPV of PET/CT were 75%, 50%, 83.3%, 50% and 83.3% respectively. In this study, one-third cervical carcinoma patients with inconclusive CT had abnormal uptake of ^{18}F-FDG.

Grigsby, *et al*,[3] and Kerr, *et al*,[4] found that FDG-PET is a sensitive method for detecting regional and distant metastases in patients with cervical carcinoma and has the potential to replace conventional imaging studies and allow more appropriate treatment planning strategies. The former examined the accuracy of FDG-PET for detecting disease activity in 23 women with carcinoma of the cervix at primary and metastatic sites. Increased FDG uptake was observed in the primary tumor in 10 of 11 patients with newly diagnosed disease. Additional sites of FDG uptake were identified in pelvic lymph nodes in eight, in extrapelvic lymph nodes in five and at distant metastatic sites in three patients. FDG uptake was present in 11 out of 12 patients with suspected recurrent disease. For both patient groups, FDG-PET demonstrated more sites of tumour metastasis than conventional imaging studies[3].

Another role of PET/CT in cervical cancer that is being evaluated is its value in monitoring the patients post-treatment. Though limited data are currently available, Schwartz, *et al*,[5] in their prospective study on 92 patients after chemoradiation showed that the 3-year progression-free survival rates, according to the metabolic response, were 78% for a complete response, 33% for partial response and 0% for progressive disease, and in the analysis of outcome-predictive factors, only post-therapy metabolic response and pre-treatment lymph nodes status, assessed by ^{18}F-FDG, predicted progression-free survival.

The chief field of ^{18}F-FDG PET and PET/CT imaging application in cervical cancer is the diagnosis of relapse. Yen, et al,6 compared PET findings with histopathology or follow-up, in 58 patients with biopsy-proven, 52 patients with CT or MRI-proven relapse and 40 patients with complete remission, and found that ^{18}F-FDG PET provided an important added value over conventional imaging in 73.8% of patients, mainly in detecting distant metastases. Another group, Liu, *et al*,[7] aiming to evaluate ^{18}F-FDG PET efficacy versus CT and MRI in detecting bony metastasis in more than 200 patients with advanced cervical cancer, both primary or tumour recurrence, found that PET was more sensitive than CT and more specific than MRI.

Overall, there have been a growing number of investigations being done directly aimed at comparing PET and PET/CT to conventional imaging in each step of cervical cancer from diagnosis to staging to treatment planning and to assess response to treatment as well as detection of recurrent and prognostication. Unfortunately, until more scanners are available, the role of PET/CT in our setting is limited to those patients with inconclusive CT or MRI.

Radiological imaging has always been one of the important aspects in monitoring response to therapy in patients with known malignancies. However, a residual mass is not necessarily a residual tumour since it may compose of fibrotic or reactive tissues. Fused PET/CT images allow determination of the presence or absence of tumour, differentiation between fibrotic and necrotic regions and remnants of tumour within the residual mass detected on CT[2].

PET is of great benefit as a diagnostic tool in ovarian carcinoma when there is an increase in serum Ca 125 and CT/MRI or conventional imaging are inconclusive or negative. Case #2 and #3 demonstrated the benefit of PET/CT in cases where conventional imaging technique, CT Scan in this study, fails to detect disease recurrence despite raising Ca 125 levels. CT, MRI and Ultrasound lack the sensitivity to consistently detect recurrence of ovarian cancer[8]. Though PET/CT has proven beneficial in detecting recurrent peritoneal and ovarian cancers as in the cases above, PET alone has been shown to have low sensitivity and specificity in detecting recurrent ovarian cancer. Rose, *et al*,[9] found that the sensitivity of PET for small-volume disease (less than 1 cm) is low compared with that of second-look laparotomy among patients with ovarian of peritoneal cancers with normal CT findings. This may be due to the difficulty in imaging the abdomen and pelvis with ^{18}F-FDG PET interpretation alone due to physiological uptake of ^{18}F-FDG PET in intestines and bladder.

Nanni, *et al*,[10] demonstrated that fused PET/CT is capable of detecting recurrent ovarian carcinoma with high sensitivity and specificity and recommended its usage for patients' follow-up in the presence of high risk disease relapse, equivocal findings at conventional radiologic imaging and increased serum Ca 125 levels. In addition, Simcock, *et al*[11] found that PET/CT significantly modifies the assessment of the distribution of recurrent ovarian tumour and alters patients' management in a substantial portion of patients (58%). They also observed that patients with localized disease in PET/CT have a better prognosis than the group with a systemic recurrence.

There has been a growing interest on the application of ^{18}F-FDG PET or PET/CT for therapy monitoring in ovarian carcinoma. Picchio, *et al*,[12] demonstrated the beneficial role of PET/CT in assessing tumour response after primary treatment, with the major advantage over CT alone in excluding the presence of residual viable lesions after treatment. The overall lesion-based sensitivity, specificity and accuracy of PET/CT in this study were 82.6%, 91.67% and 85.71% versus 69.59%, 83.33% and 74.28 of CT alone. As for now, the use of PET/CT as part of therapy monitoring for ovarian carcinoma in our unit is only reserved for those with inconclusive CT.

A more interesting application is interim PET/CT during therapy, in order to identify non-responder patients who could benefit from other therapeutic approaches, thus reducing toxicity and costs. However, only few publications are available on this, and all are on PET alone. Avril, *et al*,[13] in their study of 33 patients receiving 6 cycles of chemotherapy found that a maximum Standardized Uptake Value (SUV_{max}) reduction of 20% after the first cycle was more accurate by PET than clinical or histopathological response criteria, which included Ca 125 levels, in predicting tumour response and survival. Nishiyama, *et al*,[14] with 13 patients with ovarian cancer showed that SUV after therapy in responders was significantly lower than in non-responders, and percent change value in responders was significantly higher than that in non-responders. Both studies demonstrated that PET was of value in predicting and evaluating the response of primary tumour to neoadjuvant therapy; especially percent change value may have a major impact on the design of future therapy monitoring protocols in patients with advanced ovarian cancer. Further studies are needed on the role of PET/CT during treatment for ovarian carcinoma.

There was only one patient with uterine malignancy in this study. She had Uterine Papillary Serous Carcinoma (UPSC) of the endometrium and had a surgical intervention which was followed by chemotherapy. A PET/CT performed for the possibility of recurrent tumour did not show any abnormal uptake. The role of PET/CT in endometrial carcinoma is mainly in the setting of post-therapy surveillance of the disease. In a limited series, it also appears to give additional information in the pre-treatment states, hence helping in identifying which patient would require pelvic lymphadenectomy. Kitajima, *et al*,[15] assessed the value of PET/CT over conventional imaging in the pre-operative staging of lymph nodes of 40 patients and found only moderate sensitivity in predicting pre-operative lymph nodes metastasis. The overall node-based sensitivity, specificity, and accuracy of PET/CT for detecting nodal metastases in their study were 53.3%, 99.6% and 97.8% respectively.

PET may be of value in detecting the extra-uterine lesions that are not visualized with CT/MRI particularly in evaluation of tumour recurrence. Chung, *et al*,[16] investigated the ability of PET/CT in detection of recurrent endometrial carcinoma in 31 patients, and found that this technique had sensitivity, specificity and accuracy of 100%, 94.7% and 92.3%, respectively, and it changed the management of 22.6% patients. As the number of patients in most studies is small, there is still insufficient information to conclude the role of PET/CT in endometrial carcinoma, though both studies quoted above proved its benefit pre- and post-operatively.

Data on the role of PET imaging on the management of vulva and vaginal cancer are relatively sparse at this time but the modality appears to be of value in staging of the disease and is more effective than conventional diagnostic modalities with respect to detecting nodal metastasis in both malignancies. There was only one case of vulva carcinoma in this study and PET/CT had proven useful in confirming a recurrent tumour in the obturator nodes. Grisaru, *et al*,[2] only had one patient with vulva carcinoma in their series which had a positive lymph node on PET/CT which was not detected on CT alone. There have been multiple case studies in the literature describing the utility of PET and/or PET/CT in metastatic vulva deposits, either in detecting the secondary deposit in the vulva in a known primary or finding out the primary site in a known metastatic vulva disease[17,18].

Patients with vulva carcinoma are usually surgically staged and have had undergone some form of imaging as a routine disease-staging procedure. Whole-body FDG-PET imaging has the potential to address all these issues in a single non-invasive examination. Cohn, *et al*,[19] carried out a prospective study, evaluating the role of FDG-PET in staging disease with respect to groin nodes metastasis. The study found a sensitivity of 80%, specificity of 90%, PPV of 80% and NPV of 90% for detection of nodal metastases on a patient specific analysis. The similar figures for lesion-specific analysis were 67%, 95%, 86% and 86%, respectively, while for detection of extranodal disease, FDG-PET demonstrated high specificity and accuracy. It appears from here that PET is of value and more effective than conventional imaging with respect to detecting nodal as well as distant metastasis for vulva carcinoma.

There was also one patient with Gestational Trophoblastic Neoplasia (GTN) in this study and PET/CT showed no abnormal uptake for recurrence of disease. There was hardly any literature available on the role of PET/CT in GTN. Grisaru, *et al*,[2] also only had one patient in his study who had a false positive PET/CT. Therefore, as for now, no recommendation can be made on the role of this imaging modality in patients with GTN.

There were also two cases of inconclusive PET/CT in this study. In both cases, the patients were asymptomatic and there were no abnormal clinical findings. The initial PET/CT showed some abnormal activities in the lungs which were not amenable to biopsy. As both patients were completely asymptomatic, decision was made to follow them up with a repeat PET/CT. The cervical carcinoma patient had a repeat PET/CT and vault smear after three months, which did not show any abnormal uptake. The ovarian carcinoma patient also had a repeat PET/CT after three months, which were negative for abnormal uptake and her Ca 125 remained normal.

At the end of this study, only one of the patients who had recurrent tumour confirmed by PET/CT died, whereas two were lost to follow up. Although this does not translate into any meaningful sensitivity, specificity, PPV and NPV, with the availability of PET/CT, almost two-third of patients did not have to undergo unnecessary chemotherapy or radiotherapy.

CONCLUSION

Intergrated PET/CT imaging offers high diagnostic accuracy both at diagnosis and in the evaluation of suspected tumour recurrence and persistent disease in selected cases. In addition, it provides high management impact and superior prognostic stratification compared with conventional techniques in the restaging of a range of malignancies.

Based on the literatures reviews available to date, the potential use of PET/CT appears promising in several decision making steps in the management of patients with gynecological malignancies. Newer PET tracers such as ^{11}C-Choline and others that are on the horizon open up newer possibilities that might further enhance the role of PET in gynaecological malignancies [20].

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