Nuclear Science and Techniques **23** (2012) 305–311

Preoperative detecting metastases of cervical cancer in pelvic and para-aortic lymph nodes: comparison of integrated ^{18}F-FDG PET/CT with or without contrast enhancement

XING Yan ZHAO Jinhua* SONG Jianhua CHEN Xiang QIAO Wenli

Department of Nuclear Medicine, Shanghai First People's Hospital, Shanghai Jiao Tong University, Shanghai 200080, China

Abstract **Purpose:** Compared the performance of contrast-enhanced PET/CT and non-enhanced PET/CT for preoperatively detecting pelvic and para-aortic lymph node metastases in patients with cervical cancer. **Methods:** This prospective study included 72 patients with clinically M0 cervical cancer. They underwent surgery within two weeks of PET/CT imaging. Imaging consisted of a whole-body PET/CT protocol without intravenous contrast, followed by abdominal and pelvic PET/CT protocol including contrast-enhanced CT. We compared the diagnostic efficiency between the methods on per-patient and per-lesion basis. **Results**: Patient-based analysis showed that the sensitivity, specificity, and accuracy of contrast-enhanced PET/CT were 63.6% (14/22), 94.0% (47/50), and 84.7%(61/72), respectively, whereas those of non-enhanced PET/CT were 54.5% (12/22), 88.0% (44/50), and 77.8% (56/72), respectively, and those of enhanced CT alone were 36.4% (8/22), 80.0% (40/50), and 66.7% (48/72), respectively. Lesion-based analysis showed that the sensitivity, specificity, and accuracy of contrast-enhanced PET/CT were 77.7% (87/112), 98.7%(938/950), and 96.5% (1025/1062), respectively, whereas those of non-enhanced PET/CT were 69.6% (78/112), 97.5% (926/950), and 94.5% (1004/1062), respectively, and those of enhanced CT were 54.4% (61/112), 96.1% (913/950), and 91.7% (974/1062), respectively. Contrast-enhanced PET/CT had the best sensitivity, specificity and accuracy. Although patient-based analysis showed no significant difference between contrast-enhanced PET/CT and non-enhanced PET/CT (p =0.540, 0.295 and 0.286), the specificity and accuracy of these two methods were significantly different on lesion-based analysis (p =0.043 and 0.027).

Key words Uterine cervical cancer, Nodal staging, FDG, PET/CT, Contrast enhanced CT

1 Introduction

Worldwide, cervical cancer is one of the most common malignant tumour in women and a major cause of morbidity and mortality[1,2]. Accurate staging is necessary for optimal treatment planning and prognosis. The most widely used staging classification of cervical cancer is that of the International Federation of Gynecology and Obstetrics (FIGO) staging system. The FIGO staging system has undergone several revisions over the past few decades, most recently in 2009[3,4]. This clinical staging system relies primarily on physical examination. As a result, it has inherent deficiencies in evaluating some important parameters such as the invasion of parametrial and pelvic sidewall and the metastases of pelvic and para-aortic lymph nodes. The accurate pretreatment evaluation of lymph node (LN) status is not only important for prognosis but also for determining the proper treatment strategies. Survival rates for cervical cancer patients with positive pelvic LNs were reported to be about 50% lower than those who with negative pelvic LNs[5] and the survival rate of patients with positive para-aortic LNs is about 30%[6]. The introduction in clinical practice of a non-invasive modality that allows an accurate staging of cervical cancer would be essential in the surgical decision making. The FIGO staging committee has, for the first time, encouraged the incorporation of imaging methods into the evaluation and treatment planning of

* Corresponding author. *E-mail address:* zjh1963@gmail.com

Received date: 2012-03-31

patients with cervical cancer[4]. However, computed tomography (CT) and magnetic resonance imaging (MRI) which are size-based characterization system proved to be suboptimal in evaluating lymph nodes metastases[7,8].

Positron emission tomography, using the radiolabeled glucose analogue 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG), is a functional diagnostic technique based on the detecting of the increased glucose metabolism of malignant tumors. ^{18}F-FDG-PET imaging has proven to be valuable for staging, re-staging, planning and monitoring therapy in different cancer[9,10]. Nevertheless, PET does not provide anatomical information; as a result, the precise localization of any suspicious lesions may be difficult. Recently the combination of two imaging techniques, i.e. Positron Emission Tomography and Computed Tomography (PET/CT), has been introduced in clinical practice with the advantage over PET alone. The integrated PET/ CT scanners can often detect metastatic LNs that are not enlarged (i.e. <1 cm). Previous studies have investigated LN assessment by PET/CT in patients with cervical cancer[11,12]. Their results suggested that integrated PET/CT was an effective imaging technique in predicting pelvic or para-aortic LN metastasis in preoperative staging of cervical cancer.

The PET/CT scanning includes two different methods: first, CT is used for attenuation correction and approximate anatomical mapping and is performed with a low radiation dose ("low-dose non-enhanced CT"). Second, CT is used for diagnostic purposes and is performed with a standard radiation dose and administration of intravenous contrast agent ("full-dose contrast-enhanced CT"). This prospective study was to compare the performance of PET/ full-dose contrast-enhanced CT and PET/low-dose non-enhanced CT for preoperatively detecting pelvic and para-aortic lymph node metastases in patients with cervical cancer, and to investigate the clinical value of intravenous contrast agent in the PET/CT scan.

2 Materials and methods

2.1 Patients

Seventy-two patients with histologically proven cervical cancer were enrolled into this study. All consecutive patients underwent ^{18}F-FDG PET/CT imaging and then surgical treatment at Shanghai First People's Hospital, Shanghai Jiaotong University. Exclusion criteria included the presence of known or suspected distant metastatic disease at the time of diagnosis, and inability of the patient to undergo both the whole-body (WB) PET/CT and contrast-enhanced CT. Patients were also excluded if they had received chemotherapy or radiotherapy during the 4-8 weeks before PET/CT or during the interval between PET/CT and surgery. Informed consents were obtained from all subjects before being enrolled into the study. This study was approved by the ethics committee of Shanghai First People's Hospital.

2.2 PET/CT Protocol

After patients had fasted for at least 6 hours, their serum blood glucose level was measured and found to be less than 1.7×10^3 mg·L^{-1} in all cases. ^{18}F-FDG (4.4～5.6 MBq/Kg) was injected intravenously 60 min before the start of the first PET/CT scan. During the uptake interval, patients rested comfortably at a quiet room and were encouraged to minimize physical activity, talking, and chewing. To avoid artifacts caused by the urinary tract, patients were asked to drink 500 ml of water after injection, and to void just before the start of acquisition. No urinary bladder catheterization was used. All patients were performed on a commercial combined 16-slice PET/CT scanner (Discovery STE; GE Medical Systems, Milwaukee, WI). Two sequential image acquisition protocols were performed for each patient. At 60 min after injection of ^{18}F-FDG, a WB PET/CT acquisition protocol was performed. For this examination, low-dose non-enhanced CT was performed at 140 kV and 160 mA with a 3.75-mm slice thickness. After the WB PET/CT, patients were allowed 10 min break and a contrast enhanced PET/CT acquisition was started at about 100 min after the injection. The diagnostic full-dose contrast enhanced CT was performed at 120 kV and 220 mA, with a 2.5-mm slice thickness. At 60 seconds before the CT acquisition, an intravenous bolus of 100-ml iohexol (Omnipaque 300; GE Healthcare) iodinated contrast was administrated *via* a power injection at a rate of 3.0 mL/s.

2.3 Image Interpretation

CT and PET/CT images were evaluated on a commercially available computer workstation (xeleris 1.0 and aw 4.3，GE Healthcare). Non-enhanced PET/CT images were interpreted in consensus by two experienced radiologists who had knowledge of neither the other imaging results nor the clinical information. Enhanced PET/CT images were reviewed in consensus by two other experienced radiologists who had knowledge of neither the other imaging results nor the clinical information. Image analysis was performed as follows: PET images, non-contrast enhanced CT or contrast enhanced CT images and co-registered fused images. The para-aortic lymph nodes and pelvic lymph nodes, including common iliac, external iliac, internal liliac and obturator lymph nodes, were considered for the analysis. The diagnosis of metastatic lymph node on PET/CT images was based on the presence of focal increased tracer uptake on PET images, corresponding to lymph-nodal chains on CT images, independently on the LN size on CT. Conversely, lymph nodes with no detectable tracer uptake were reported as benign, without considering their size on CT images.

2.4 Surgical procedures

Twenty patients underwent total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy with para-aortic lymphadenectomy. Fifty-two patients underwent total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy without para-aortic lymphadenectomy. The pelvic lymph nodes dissected included the common iliac, external iliac, internal liliac and obturator lymph nodes on both sides. The time interval between PET/CT scan and surgical treatment was 4–14 days (mean, 9 days). The gold standard for the presence or absence of tumor was histopathology.

2.5 Statistical analysis

We performed patient-based and lesion site-based analysis of contrast enhanced PET/CT in comparison with non-enhanced PET/CT and enhanced CT alone. Sensitivity, specificity, accuracy were calculated by standard statistical formula. Differences in assessment among three imaging procedures were tested for significance by $\chi 2$ test with SPSS 16.0 and p values less than 0.05 were considered statistically significant.

3 Results

3.1 Patient characteristics

From September 2009 to August 2011, 72 consecutive patients were enrolled into this study and were performed on ^{18}F-FDG PET/CT and contrast-enhanced PET/CT. The median age was 49.1±9.8 years (range 34 –67 years). The characteristics of patients are shown in Table 1.

Table 1 Characteristics of patient with cervical cancer (n=72)

Characteristics	Values
Age(years)	
Mean±SD	49.1±9.8
Range	34-67
Age groups, *n*(%)	
＜45 years	30(41.7%)
≥45 years	42(58.3%)
Histology, *n*(%)	
Squamous carcinoma	51(70.8%)
Adenocarcinoma	18(25.0%)
Clear cell	3(4.2%)
FIGO stage, *n*(%)	
Ia1	4(5.6%)
Ia2	10(13.9%)
Ib1	19(26.4%)
Ib2	13(18.1%)
IIa	22(30.6%)
IIb	4(5.6%)

3.2 Patient-based analysis

At histopathological examination, 22 (30.6%) of the 72 patients had one or more lymph nodes with metastases and 50 (69.4%) had no nodal metastases. Contrast-enhanced PET/CT was true positive for nodal metastases in 14 of 22 patients with lymph node metastases and true-negative in 47 of 50 patients without lymph node metastases. Non-enhanced PET/CT gave a true-positive result for nodal metastases in 12 of 22 patients with LN metastases and a true-negative result in 44 of 50 patients without LN metastases. Enhanced CT gave a true-positive

result for nodal metastases in 8 of 22 patients with LN metastases, and a true-negative result in 40 of 50 patients without LN metastases. As shown in Tables 2 and 3, patient-based analysis revealed no significance between contrast-enhanced PET/CT and non-enhanced PET/CT in terms of sensitivity, specificity and accuracy. Otherwise, the specificity and accuracy of contrast-enhanced PET/CT were significantly better than those of enhanced CT alone.

Table 2 Patient-based diagnostic results of contrast-enhanced PET/CT, non-enhanced PET/CT, and enhanced CT alone

Modality	Sensitivity	Specificity	Accuracy
Contrast-enhanced PET/CT	63.6%(14/22)	94.0%(47/50)	84.7%(61/72)
Non-enhanced PET/CT	54.5%(12/22)	88.0%(44/50)	77.8%(56/72)
Enhanced CT alone	36.4%(8/22)	80.0%(40/50)	66.7%(48/72)

Table 3 Comparison of the diagnostic efficiency of the three imaging modalities on patient-based analysis

Comparison	Sensitivity		Specificity		Accuracy	
	χ^2 value	p value	χ^2 value	p value	χ^2 value	p value
Contrast-enhanced PET/CT *vs.* Non-enhanced PET/CT	0.376	0.540	1.099	0.295	1.140	0.286
Non-enhanced PET/CT *vs.* enhanced CT alone	1.467	0.226	1.190	0.275	2.215	0.137
Contrast-enhanced PET/CT *vs.* enhanced CT alone	3.273	0.070	4.332	0.037	6.379	0.012*

*p value <0.05

3.3 Node-based analysis

At surgical and histopathological analysis, a total of 1062 lymph nodes were sampled and 112 lymph nodes proved to be positive for metastases. These 112 metastatic nodes consisted of 21 para-aortic lymph nodes and 91pelvic lymph nodes: common iliac (n=20), internal iliac (n=31), obturator fossa (n=17) and external iliac (n=23). For pelvic and para-aortic lymph node metastases, contrast-enhanced PET/CT was true-positive in 87 of the 112 metastatic nodes and true-negative in 938 of the 950 non-metastatic nodes. Non-enhanced PET/CT was true-positive in 78 of the 112 metastatic nodes and true-negative in 926 of the 950 non-metastatic nodes. Enhanced CT was true-positive in 61 of the 112 metastatic nodes and true-negative in 913 of the 950 non-metastatic nodes. As shown in Tables 4 and 5, contrast-enhanced PET/CT had the best sensitivity, specificity, and accuracy among these three imaging methods. The specificity and accuracy of contrast-enhanced PET/CT were superior to non-enhanced PET/CT and the difference was significant. Both contrast-enhanced PET/CT and non-enhanced PET/CT were significantly better than enhanced CT alone. Representative cases are shown in Figs.1 and 2.

Table 4 Node-based diagnostic results of contrast-enhanced PET/CT, non-enhanced PET/CT, and enhanced CT alone

Modality	Sensitivity	Specificity	Accuracy
contrast-enhanced PET/CT	77.7%(87/112)	98.7%(938/950)	96.5%(1025/1062)
non-enhanced PET/CT	69.6%(78/112)	97.5%(926/950)	94.5%(1004/1062)
enhanced CT alone	54.5%(61/112)	96.1%(913/950)	91.7%(974/1062)

Table 5 Comparison of the diagnostic efficiency of the three imaging modalities on node-based analysis

Comparison	Sensitivity		Specificity		Accuracy	
	χ^2 value	p value	χ^2 value	p value	χ^2 value	p value
Contrast-enhanced PET/CT *vs.* non-enhanced PET/CT	1.864	0.172	4.077	0.043*	4.859	0.027
Non-enhanced PET/CT vs. enhanced CT alone	5.479	0.019*	2.862	0.091	6.619	0.010
Contrast-enhanced PET/CT vs. enhanced CT alone	13.462	0.000*	13.093	0.000*	22.109	0.000

*p value <0.05

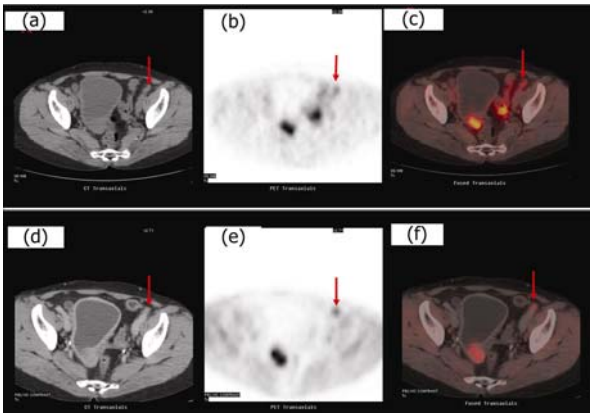

Fig.1 A 55-year-old woman with pelvic LN metastasis. (a) Non-enhanced CT shows no abnormal findings, (b) ^{18}F-FDG PET shows mild FDG uptake (arrow) in the left pelvic region, SUV_{max}=2.2, (c) Non-enhanced PET/CT shows the hot-spot in the left external iliac area suspected to be physiological uptake by vessels, (d) Enhanced CT shows a left external iliac LN measuring 9×6mm (arrow), which does not indicate LN metastasis on the basis of the size, (e) PET shows mild FDG uptake (arrow) in the left pelvic region, SUV_{max}=2.9 and (f) Contrast-enhanced PET/CT shows the abnormal FDG uptake corresponding to left external iliac LN (arrow) suggesting metastasis. Histopathological examination confirmed cancer involvement in this node.

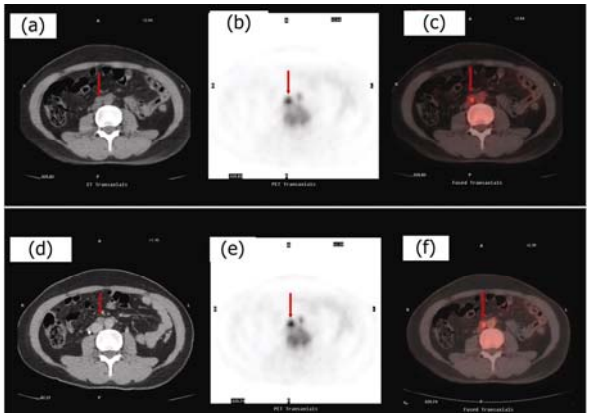

Fig.2 A 46-year-old woman with para-aortic LN metastasis. (a) Non-enhanced CT show a para-aortic LN measuring 9×8mm (arrow), which does not indicate LN metastasis on the basis of the size, (b) ^{18}F-FDG PET shows intensive FDG uptake (arrow) around the aorta, SUVmax=4.8, (c) Non-enhanced PET/CT shows abnormal FDG uptake corresponding to a para-aortic LN measuring 9×8mm, suggesting the presence of metastasis, (d) Enhanced CT shows a para-aortic LN (arrow) which does not indicate LN metastasis on the basis of the size, (e) ^{18}F-FDG PET shows intensive FDG uptake (arrow) around the aorta, SUVmax=5.0 and (f) Contrast-enhanced PET/CT shows abnormal FDG uptake in a para-aortic LN (arrow) suggesting the metastasis. Histopathological examination findings confirmed cancer spread in this lymph node.

4 Discussion

Accurate assessment of para-aortic and pelvic lymph node metastases in patients with cervical cancer is beneficial for selecting the appropriate treatment strategies and improving patient survival. Unfortunately, clinical staging does not provide accurate information about tumor involvement of para-aortic and pelvic lymph node. Therefore, surgical staging has been suggested as a gold standard for the evaluation of LN metastases[13]. However, the routine use of surgical staging before radiotherapy has been challenged because it has significant adverse effects[14-16]. A non-invasive method that accurately detects LN metastases in cervical cancer is crucial for improving treatment management.

MRI or CT has been used to determine the lymph nodes staging of the disease. The recent meta-analysis indicates that both MRI and CT have low sensitivity (55.5% and 57.5%, respectively). This low sensitivity seriously hampers the overall diagnostic accuracy in the detection of nodal metastases. Both MRI and CT have negative likelihood ratio (LR) greater than 0.5; thus, these tests cannot be used to confirm the absence of nodal metastases[17].

Because ^{18}F-FDG PET can demonstrate metabolically active sites of tumor spread, it has been shown to have some promise in detecting lymph node metastases in the pelvis and retroperitoneum. Several previous studies have carried out LN assessment by PET/CT in patients with uterine cervical cancer and these studies reported that the sensitivity, specificity and accuracy on a patient basis were 41–100%, 56–99% and 68–99%, respectively, whereas those on a region-site basis were 36–72%, 93–99% and 85–99%, respectively[12,18-23].

There is debate regarding the value of intravenous contrast agents in PET/CT. Some researchers believed that CT imaging data should be used only for attenuation correction of PET and localization of hypermetabolic lesions with a low radiation dose[24], whereas other researchers advocated the need to perform full-dose, contrast-enhanced and high-resolution CT[25].

Recently, some researchers have studied the clinical usefulness of iodine contrast material for PET/CT scanning. Several reports have demonstrated the superiority of contrast-enhanced PET/CT over non-enhanced PET/CT for the staging of malignant lymphoma[26], staging and therapy planning for non-small cell lung cancer[27], preoperative staging of

primary squamous cell carcinoma of the head and neck[28], evaluation of the nodal status of the pelvic and retroperitoneal lymphatic pathways in malignant lymphoma[29], and the restaging of uterine cancer[30].

Kitajima K, *et al*[31] have recently investigated the additional diagnostic value of PET/ceCT over PET/ldCT for the detection of pelvic and para-aortic LN metastases in patients with uterine cancer. They found that although PET/ceCT had better sensitivity and accuracy than PET/ldCT, the differences between the two imaging methods did not reach statistical significance. The number of patients in this study was relatively small (40 patients including both uterine cervical and endometrial cancer). They assumed that a significant difference might emerge if a larger population is studied.

This study was the largest prospective study focusing on the value of intravenous contrast medium in PET/CT examinations for the detecting of pelvic and para-aortic LN metastases in patients with cervical cancer. Although there was no significant difference in the diagnostic efficiency between contrast-enhanced PET/CT and non-enhanced PET/CT on patient-based analysis, we found that there were significant difference in specificity and accuracy between contrast-enhanced PET/CT and non-enhanced PET/CT on lesion-based analysis. We also found that both contrast-enhanced PET/CT and non-enhanced PET/CT were significantly better than enhanced CT alone. When PET reveals a suspicious uptake of FDG in the pelvic LN areas, contrast-enhanced and high-dose CT with inline PET/CT may accurately differentiate pathological LN uptake from physiological uptake by vessels, bowels, or the ureter, in comparison with non-contrast and low-dose CT.

Our study showed the sensitivity of both contrast-enhanced PET/CT and non-enhanced PET/CT was relatively low (54.5%~77.7%). This result is similar to that of Kitajima K[31]. Because small lymph nodes accounted for most false-negative nodes by both the contrast-enhanced and non-enhanced PET/CT protocol, PET or PET/CT can only detect lesions with a certain number of malignant cells sufficient to change the observed glucose metabolism. And neither of these imaging modalities can detect micro-metastases. Furthermore, the mean value of spatial resolution of the PET components is 5 mm (range 4–6 mm), so the presence of metastases in small lymph nodes is hardly detectable.

Because the contrast-enhanced PET/CT was performed 30-40 min after the non-enhanced PET/CT, there was higher tumor uptake due to more uptake phase time in comparison to the first PET imaging acquisition. In our study, the SUVs of true-positive lymph nodes of contrast-enhanced PET/CT were mostly higher than those of non-enhanced PET/CT.

Although this study still has some limitations. Firstly, the surgeons were guided by the preoperative PET/CT findings, which may have resulted in verification bias. Secondly, the relatively small amount of our patient is only 22/72 (30.6%) patients with nodal metastases at histology. It is difficult to draw definitive conclusions regarding the value of positive PET/CT findings, and it should be confirmed in the future.

5 Conclusion

In this study, we clarified both contrast-enhanced PET/CT and non-enhanced PET/CT outperform enhanced CT alone in the identification of pelvic and para-aortic lymph nodes metastases. The contrast-enhanced PET/CT protocol demonstrates a significantly better performance than non-enhanced PET/CT on a per-lesion based analysis. However, further studies are needed to verify it.

References

1 Parkin D M, Bray F I, Devesa S S. Eur J Cancer, 2001, **37:** S4−S66.

2 Parkin D M, Bray F, Ferlay J, *et al.* CA Cancer J Clin, 2005, **55:** 74−108.

3 Pecorelli S. Int J Gynaecol Obstet, 2009, **105:** 103−104.

4 Pecorelli S, Zigliani L, Odicino F. Int J Gynaecol Obstet, 2009, **105:** 107−108.

5 Comerci G, Bolger B S, Flannelly G, *et al.* Int J Gynecol Cancer, 1998, **8:** 23−26.

6 Grigsby P W, Perez C A, Chao K S, *et al.* Int J Radiat Oncol Biol Phys, 2001, **49:** 733−738.

7 Mitchell D G, Snyder B, Coakley F, *et al.* J Clin Oncol, 2006, **24:** 5687−5694.

8 Hricak H, Gatsonis C, Coakley F V, *et al.* Radiology, 2007, **245:** 495−498.

9 Ak I, Stokkel M P, Pauwels E K. J Cancer Res Clin Oncol, 2000, **126:** 560−574.

10 Cermik T F, Mavi A, Basu S, *et al.* Eur J Nucl Med Mol Imaging, 2008, **35:** 475−483.

11 Sironi S, Buda A, Picchio M, *et al.* Radiology, 2006, **238:** 272−279.

12 Loft A, Berthelsen A K, Roed H, *et al.* Gynecol Oncol, 2007, **10:** 29−34.

13 Yildirim Y, Sehirali S, Avci M E, *et al.* Gynecol Oncol, 2008, **108:** 154−159.

14 Weiser E B, Bundy B N, Hoskins W J, *et al.* Gynecol Oncol, 1989, **33:** 283−289.

15 Denschlag D, Gabriel B, Mueller-Lantzsch C, *et al.* Gynecol Oncol,2005, **96:** 658–664.

16 Hasenburg A, Salama J K, Van T J, *et al.* Gynecol Oncol, 2002, **84:** 321−326.

17 Selman T J, Mann C, Zamora J, *et al.* CMAJ, 2008, **178:** 855−862.

18 Choi H J, Roh J W, Seo S S, *et al.* Cancer, 2006, **106:** 914−922.

19 Sironi S, Buda A, Picchio M, *et al.* Radiology, 2006, **238:** 272−279.

20 Amit A, Beck D, Lowenstein L, *et al.* Gynecol Oncol, 2006, **100:** 65−69.

21 Yildirim Y, Sehirali S, Avci M E, *et al.* Gynecol Oncol, 2008, **108:** 154−159.

22 Chung H H, Park N H, Kim J W, *et al.* Gynecol Obstet Invest, 2009, **67:** 61–66.

23 Kitajima K, Murakami K, Yamasaki E, *et al.* Eur Radiol, 2009, **19:** 1529−1536.

24 Coleman R E, Delbeke D, Guiberteau M J, *et al.* J Nucl Med, 2005, **46:** 1225−1239.

25 Antoch G, Freudenberg L S, Beyer T, *et al.* J Nucl Med, 2004, **45:** 56−65.

26 Rodriguez-Vigil B, Gomez-Leon N, Pinilla I, *et al.* J Nucl Med, 2006, **47:** 1643−1648.

27 Pfannenberg A C, Aschoff P, Brechtel K, *et al.* Eur J Nucl Med Mol Imaging, 2007, **34:** 36−44.

28 Rodrigues R S, Bozza F A, Christian P E, *et al.* J Nucl Med, 2009, **50:** 1205−1213.

29 Morimoto T, Tateishi U, Maeda T, *et al.* Eur J Radiol, 2008, **67:** 508−513.

30 Kitajima K, Suzuki K, Nakamoto Y, *et al.* Eur J Nucl Med Mol Imaging, 2010, **37:** 1490−1498.

31 Kitajima K, Suzuki K, Senda M, *et al.* Ann Nucl Med, 2011, **25:** 511−519.