Efficacy of 18-FDG PET-CT Dual-phase Scanning for Detection of Lymph Node Metastasis in Gynecological Cancer

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Abstract. *Aim: This study investigated whether dual-phase scanning (DPS) with 18-fludeoxyglucose positron emission tomography -computed tomography (FDG PET-CT) improves diagnosis of lymph node metastasis (LNM) in gynecologic malignancies, compared to mono-phase scanning (MPS). Patients and Methods: The study included 139 patients who underwent PET-CT followed by systemic lymph node dissection. PET-CT scans were obtained twice. The maximum standardized uptake value (SUVmax) was measured and the retention index (RI) was calculated as the % change from the early to the delayed scan. The optimal threshold of RI was determined using a receiver operating characteristic (ROC) curve. Diagnostic efficacies were calculated for MPS and DPS using pathological results. Results: In total, 1,879 regions were dissected. The optimal RI was 9%. The sensitivity, specificity and accuracy were 35.8%, 99.0% and 96.8% for MPS and 26.9%, 99.6% and 97.0% for DPS, respectively. Specificity was significantly improved by DPS and accuracy was also improved, but not significantly. Conclusion: DPS had an unsatisfactory impact on the diagnostic efficacy for LNM.*

In positron emission tomography (PET)-computed tomography (CT), images from CT are overlaid on those from PET to improve anatomical accuracy. This approach has become more common for gynecological cancer in which lymph node metastasis (LNM) is a major factor in treatment planning and prediction of prognosis. PET-CT imaging should allow accurate detection of LNM based on metabolic changes and anatomical precision. However, there are few studies on the diagnostic accuracy of PET-CT for detection of LNM and the available results show variable accuracy (1).

Most studies of PET-CT for the detection of LNM in gynecological cancer have been based on mono-phase scanning (MPS) (2-5). A malignant lesion shows elevation of the maximum standardized uptake value (SUVmax) in the delayed phase, in contrast to other lesions, such as those due to inflammation (6). The efficacy of dual-phase scanning (DPS) for detecting LNM has been shown in several cancers (7-9); however, DPS has not been widely studied in gynecological cancer. There is only one report with cervical cancer, which did not use pathological confirmation as standard reference (10). We retrospectively examined the accuracy of PET-CT DPS for the detection of LNM based on elevation of SUVmax, with comparison to findings in the final pathological diagnosis. To the best of our knowledge, this is the first report for the utility of this method in gynecological cancer.

Patients and Methods

Subjects. The subjects were consecutive patients with a clinical diagnosis of gynecological cancer who underwent preoperative PET-CT and surgery, including lymph node dissection, in the gynecological department of our Hospital from September 2012 to March 2014. Cases of cervical cancer, endometrial cancer, ovarian cancer, fallopian tubal cancer and primary peritoneal cancer were included in the study; cervical cancer and endometrial cancer required preoperative pathological diagnosis. Patients were excluded if the final pathological evaluation showed a benign tumor or a borderline malignancy, if they did not undergo surgery, including lymph node dissection, moved to another institute or joined another clinical trial on LNM. Informed consent was not obtained from each patient because of the retrospective study design. Instead, the study was disclosed *via* a website and patients could refuse to participate. Those who did not do so were considered to be voluntary participants. The study was conducted with approval of the ethics committee of our university (approval number: 20130289).

The study included 70 patients with cervical cancer, 53 with endometrial cancer, 15 with ovarian cancer and 1 with fallopian tubal

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Key Words: Positron emission tomography, diagnostic imaging, lymphatic metastasis, gynecology, clinical oncology.

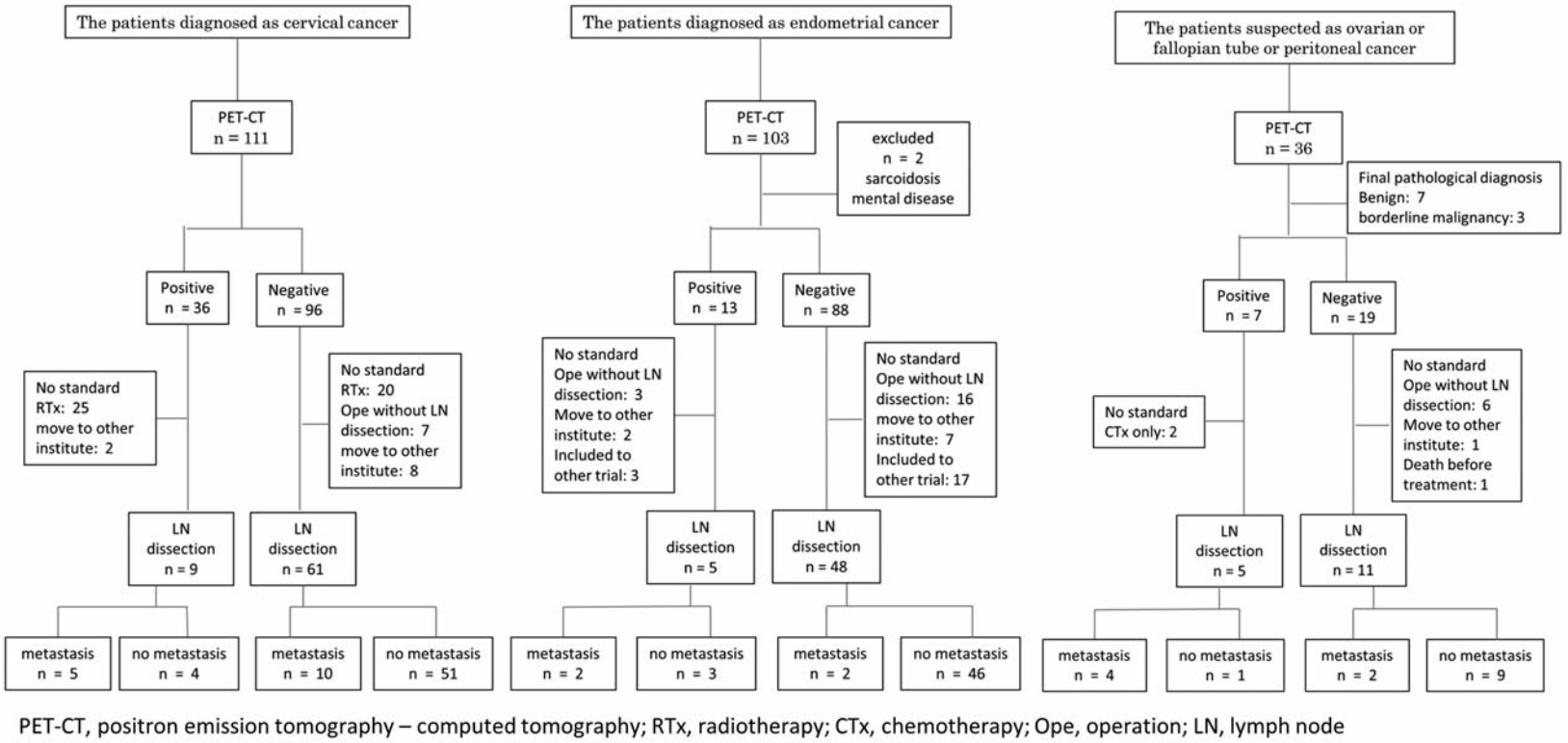


Figure 1. *Flow diagram of cases of cervical, endometrial, ovarian and fallopian tube cancers examined in the study.*

cancer. There was no case with peritoneal cancer. In the endometrial cancer group, one patient with a history of sarcoidosis and one patient who could not complete PET-CT due to mental illness were excluded. A flow diagram of the study is shown in Figure 1.

The characteristics of the patients are shown in Table I. For patients with cervical cancer, the mean age was 38.8±8.5 years, the pathological type was mainly squamous cell carcinoma (SCC) (58.6%) and the common FIGO 2008 stage was IB1 (74.3%). For those with endometrial cancer, the mean age was 58.7±11.4 and the main histological type, grade and stage were endometrioid adenocarcinoma (83.0%), grades 1 and 2 (30.1% each), and IA (47.2%), respectively. For those with ovarian and fallopian tube cancer, the mean age was 59.4±8.6, the main pathological type was clear cell carcinoma (43.8%) and the common FIGO 1988 stage was IIIc (43.8%).

PET-CT protocol. The PET-CT device in our institute is a Biograph mCT (Siemens Medical Solutions, Knoxville, TN, USA). Patients were administered 3.7 MBq/kg of 18-fludeoxyglucose (FDG) and received routine PET-CT DPS at one hour and two hours after administration. Data were analyzed on an AZE workstation (AZE Ltd, Tokyo, Japan). A PET-CT-positive region was defined as a region with abnormal FDG uptake, regardless of the size of lymph nodes in CT images, as in previous studies (2-5). The diagnosis of abnormal uptake was made by radiologists, using the normal uptake of FDG in contralateral lymph node region and the background as a reference. Regarding anatomical position, CT image helped differentiate lymph node metastasis from peritoneal dissemination, urine tract or ovary. A PET-CT-positive region in MPS was defined by only early phase scanning and SUVmax of these regions were determined in the early (SUVe) and delayed (SUVd) phases. The retention index (RI) was defined as the % change of SUV from the early to the delayed scan: RI=(SUVd-SUVe)/SUVe×100%. Abnormal FDG uptake in the lymph node areas was evaluated by general radiologists with >8 years of experience and the findings were reviewed retrospectively by a radiologist specialized in nuclear medicine imaging with 28 years of experience who was blinded to the pathological findings. There were no adverse events associated with PET-CT.

Surgery. The range of lymph node dissection was determined according to our institute's criteria. In cervical cancer, cases of stage IA2-IIB1 in FIGO clinical staging underwent pelvic lymph node dissection. In endometrial cancer, pelvic and paraaortic lymph node dissection was performed in cases with a high risk of recurrence; these included cases with >50% myometrial invasion or a histopathological type of serous, clear cell, grade 3 endometrioid adenocarcinoma and carcinosarcoma. Patients with an intermediate risk of recurrence underwent pelvic dissection only. Patients with ovarian cancer and fallopian tube cancer underwent pelvic and paraaortic lymph node dissection in staging laparotomy.

Lymph nodes were dissected separately by region (Figure 2). Pelvic nodes were divided into 13 regions: bilateral common iliac, external iliac, suprainguinal, internal iliac, obturator, parametrial and sacral nodes; and paraaortic nodes were divided into 6 regions: 3 columns divided by the right and left edges of the aorta and 2 rows divided at the height of the inferior mesenteric artery. The coincidence of regions with dissected tissue and images showing elevated uptake was determined based on clinical records, surgical records and pictures mapping dissected nodes; these findings were reviewed by a gynecological oncologist with 21 years of experience.

Pathological evaluation. Dissected lymph nodes were fixed and stained with hematoxylin and eosin. The presence of LNM was determined using a standard pathological evaluation of lymph nodes based on one or two sections (11). Two experienced general pathologists made the diagnosis and one pathologist with 8 years of experience in gynecological tumors reviewed the results retrospectively, while blinded to the PET-CT findings.

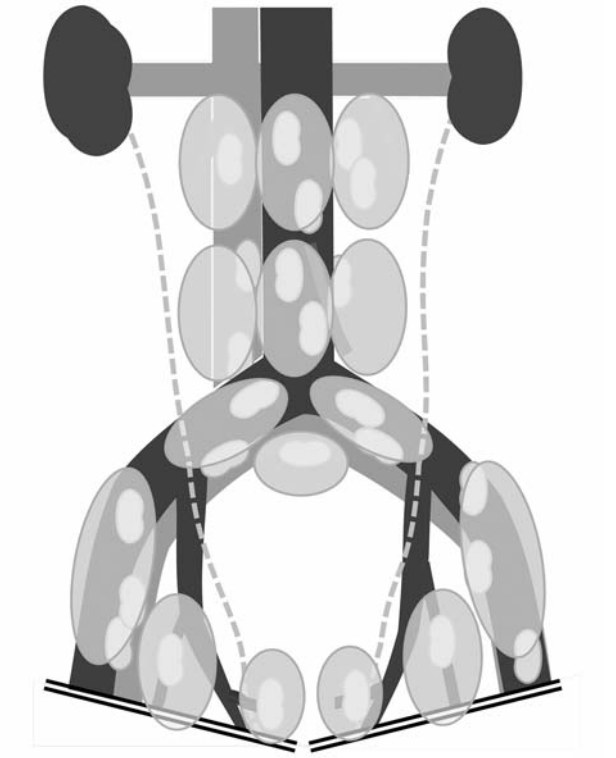


Figure 2. *Map of the pelvic and paraaortic lymph nodes. Pelvic nodes were divided into 13 regions: bilateral common-iliac, external-iliac, suprainguinal, internal-iliac, obturator, parametrial and sacral nodes; and paraaortic nodes were divided into 6 regions: 3 columns divided by the right and left edges of aorta and 2 rows divided by the height of inferior mesenteric artery.*

Statistical analysis. The diagnostic accuracy for detection of LNM was calculated with 95% confidence intervals determined by the Clopper-Pearson (exact) method. Sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR^+) and negative likelihood ratio (LR^-) were calculated in this analysis. The optimal RI was obtained using a receiver operating characteristic (ROC) curve. Diagnostic efficacies of DPS with the obtained RI and MPS were compared using the McNemar test. All analyses were performed using the SPSS software, ver.22 (IBM, New York, NY, USA).

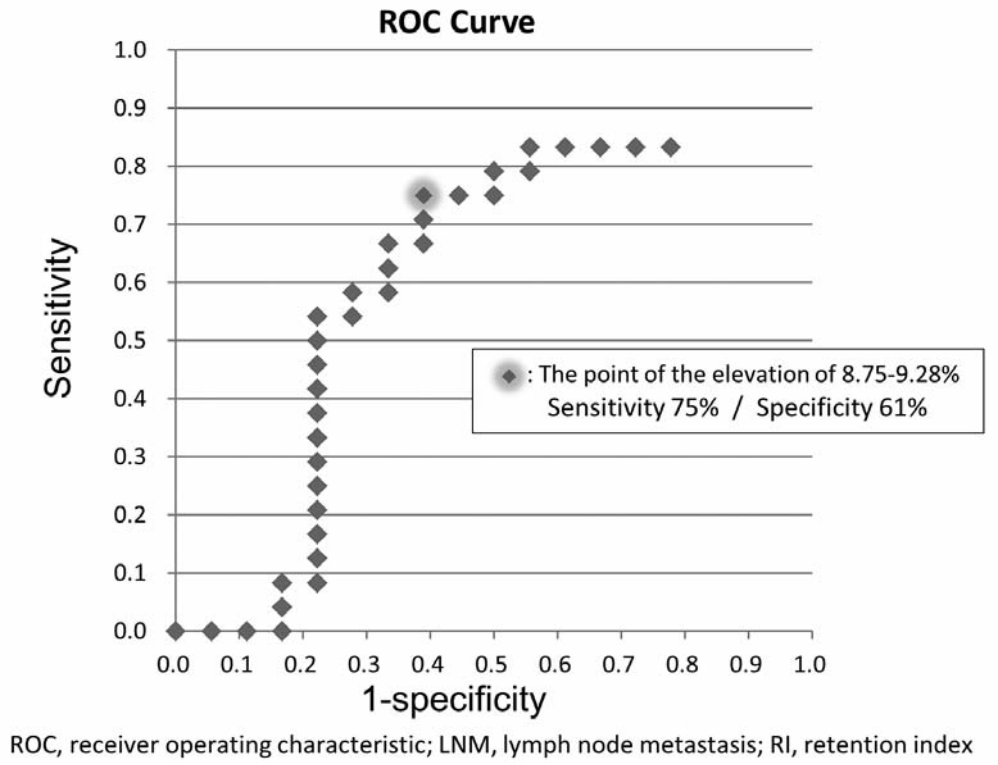
Results

In total of 139 cases, 1,879 lymph node areas were dissected. Among these, 42 regions indicated abnormal FDG uptake in early phase. There was no region indicating abnormal FDG uptake only in delayed phase. Twenty five of 139 cases had LNM and 67 of 1,879 regions had LNM pathologically.

Table I. *Patients' characteristics*.

			Cervical cancer		Endometrial cancer		Ovarian and fallopian tubal cancer	
Number	Cases		70		53		16	
Age	Years old, mean±SD		38.8±8.5		58.7±11.4		59.4±8.6	
Histological type		Squamous cell carcinoma	41 (58.6%)	Emdometrioid adenocarcinoma	grade1 16 (30.1%)	Emdometrioid adenocarcinoma	grade1 1 (6.3%)	
	Cases(%)	Mucinous adenocarcinoma	20 (28.6%)		grade2 16 (30.1%)		grade2 1 (6.3%)	
		Adenosquamous cell carcinoma	2 (2.9%)		grade3 12 (22.6%)		grade3 1 (6.3%)	
		Emdometrioid adenocarcinoma	3 (4.3%)	Serous papillary adenocarcinoma	2 (3.8%)	Serous papillary adenocarcinoma	6 (37.5%)	
		Glassy cell carcinoma	2 (2.9%)	Clear cell carcinoma	3 (5.7%)	Clear cell carcinoma	7 (43.8%)	
		Serous adenocarcinoma	1 (1.4%)	Carcinosarcoma	4 (7.5%)	Carcinosarcoma	0 (0%)	
		Emdometrioid+1 clear cell carcinoma	(1.4%)	Undifferentiated	0 (0%)	Undifferentiated	0 (0%)	
		Undifferentiated	0 (0%)					
FIGO Stage								
	Included patients							
		IA1	4 (5.7%)	IA	25 (47.2%)	Ia	2 (12.5%)	
		IA2	1 (1.4%)	IB	11 (20.8%)	Ib	0 (0%)	
		IB1	52 (74.3%)	II	5 (9.4%)	Ic	4 (25.0%)	
		IB2	10 (1.4%)	IIIA	4 (7.5%)	IIa	0 (0%)	
		IIA1	2 (2.9%)	IIIB	2 (3.8%)	IIb	0 (0%)	
		IIA2	0 (0%)	IIIC1	1 (1.9%(	IIc	1 (6.3%)	
		IIB	1 (1.4%)	IIIC2	3 (5.7%)	IIIa	0 (0%)	
				IVA	0 (0%)	IIIb	2 (0%)	
				IVB	2 (3.8%)	IIIc	7 (43.8%)	
						IV	0 (0%)	
	Excluded patients							
		IA1	6 (9.7%)					
		IA2	0 (0%)					
		IB1	17 (27.4%)					
		IB2	7 (11.3%)					
		IIA1	7 (11.3%)					
		IIA2	2 (3.2%)					
		IIB	15 (24.2%)					
		IIIA	0 (0%)					
		IIIB	5 (8.1%)					
		IVA	0 (0%)					
		IVB	2 (3.2%)					
		Unclassified	1 (1.6%)					
Period between PET-CT and surgery(days, mean±SD)								
			True positive	35.2±17.8				
			False negative	32.4±16.6	p=0.037 by ANOVA			
			False positive	40.4±16.6				
			True negative	48.0±23.8				

PET-CT, Positron emission tomography-computed tomography; ANOVA, analysis of variance.



ROC, receiver operating characteristic; LNM, lymph node metastasis; RI, retention index

Figure 3. *ROC curve for the detection of LNM according to RI. The optimal cutoff of RI to maximize sensitivity and specificity was 9%.*

The diagnostic accuracies of PET-CT MPS for the detection of LNM are shown in Table II, calculated by cases and by region for all cancers. The sensitivity and specificity were 44.0% and 93.0% by cases and 35.8% and 99.0% by regions, respectively.

To evaluate the effect of DPS on improvement of diagnostic efficacy, the SUVmax of regions with abnormal uptake in MPS was recorded in early and delayed PET-CT scans and RI was calculated for each positive region. Regions indicated to be positive in early phase PET-CT were switched to negative if elevation of SUVmax in the delayed phase did not reach a certain RI. Sensitivities and specificities for each RI were calculated using an ROC curve, with the goal of determining the optimal cutoff for RI (Figure 3). A RI of 9% gave the maximum sensitivity and specificity.

The efficacies of DPS for all cases and all regions are shown in Table III, based on the definition of a PET-CT-positive region as abnormal FDG uptake plus a 9% elevation of SUVmax in the delayed phase. Analyzed by cases, the McNemar test using the DPS criteria did not show a significant change in sensitivity and specificity, compared to MPS. Analysis by region showed that specificity increased (p=0.001) but sensitivity decreased significantly (p=0.008). Accuracy by region also increased, but the change was not significant (p=0.33).

Discussion

The diagnostic efficacy of PET-CT for the detection of LNM in gynecological cancers has varied in several reports and is lower than expected (1, 12). These findings indicate the need to improve the diagnostic efficacy of PET-CT. A malignant lesion shows SUV elevation in the delayed phase in DPS, in contrast to lesions due to inflammation or other conditions. The utility of DPS has been shown in some cancers, including cervical cancer (10), but less than 30% of cases judged to have metastasis in imaging were confirmed pathologically. The utility of DPS for the detection of LNM in gynecological cancer has not been examined prior to the current study.

In our hospital, all cases of cervical or endometrial cancer or suspected ovarian, fallopian tubal or peritoneal cancer undergo preoperative PET-CT, provided that there is no medical contraindication. However, a standard pathological evaluation by systemic lymph node dissection was not performed for all cases. Radiotherapy or chemotherapy may be selected as initial treatment for cases at a higher stage, which have a high risk of LNM. Therefore, the cases included in this study may have had a lower incidence of LNM and this may have influenced the resultant predictive value.

Table II. *The diagnostic efficacy of MPS PET-CT for detecting lymph node metastasis, by cases and by regions.*

		Pathological evaluation									
		Lymph node metastasis	No metastasis	Total	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR^+ (95% CI)	LR^- (95% CI)
	PET-CT										
By caces	+	11	8	19	44.0	93.0	84.2	57.9	83.3	6.27	0.60
	–	14	106	120	(24.4-65.1)	(86.4-96.9)	(77.0-89.8)	(33.5-79.7)	(81.2-93.5)	(2.81-14.0)	(0.42-0.86)
	Total	25	114	139							
By regions	+	24	18	42	35.8	99.0	96.8	57.1	97.7	36.1	0.65
	–	43	1794	1837	(24.5-48.5)	(98.4-99.4)	(95.8-97.5)	(41.0-72.3)	(96.9-98.3)	(20.6-63.2)	(0.54-0.76)
	Total	67	1812	1879							

MPS, Mono-phase scanning; PET-CT, positron emission tomography-computed tomography ; PPV, positive predictive value; NPV, negative predictive value; LR^+, likelihood ratio positive; LR^-, likelihood ratio negative; CI, confidence interval.

Table III. *Comparison of the diagnostic efficacy of PET-CT for detecting lymph node metastasis between MPS and DPS, by cases and by regions.*

			Pathological evaluation									
			Lymph node metastasis	No metastasis	Total	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR^+ (95% CI)	LR^- (95% CI)
		PET-CT										
By caces	MPS	+	11	8	19	44,0	93,0	84,2	57,9	83,3	6,27	0,60
		–	14	106	120	(24.4-65.1)	(86.4-96.9)	(77.0-89.8)	(33.5-79.7)	(81.2-93.5)	(2.81-14.0)	(0.42-0.86)
		Total	25	114	139							
	DPS	+	9	4	13	36,0	96,5	85,6	69,2	87,3	10,26	0,66
		–	16	110	126	(18.0-57.5)	(91.3-99.0)	(78.7-91.0)	(38.6-90.9)	(80.2-92.6)	(3.43-30.7)	(0.49-0.89)
		Total	25	114	139							
	McNemer test					p=0.50	p=0.13	p=0.69				
By regions	MPS	+	24	18	42	35,8	99,0	96,8	57,1	97,7	36,1	0,65
		–	43	1794	1837	(24.5-48.5)	(98.4-99.4)	(95.8-97.5)	(41.0-72.3)	(96.9-98.3)	(20.6-63.2)	(0.54-0.76)
		Total	67	1812	1879							
	DPS	+	18	7	25	26,9	99,6	97,0	72,0	97,4	69,5	0,73
		–	49	1805	1854	(16.8-39.1)	(99.2-99.8)	(96.1-97.7)	(50.6-87.9)	(96.5-98.0)	(30.1-160)	(0.63-0.85)
		Total	67	1812	1879							
	McNemer test					p=0.008	p=0.001	p=0.33				

MPS, Mono-phase scanning; PET-CT, positron emission tomography-computed tomography ; PPV, positive predictive value; NPV, negative predictive value; LR^+, likelihood ratio positive; LR^-, likelihood ratio negative; MPS, mono-phase scannnig; DPS, dual-phase scanning; CI, confidence interval.

The period from PET-CT to surgery (Table I) also differed based on PET-CT findings of true positive, false positive, true negative and false negative. However, this period was significantly longer in true negative cases than in false negative cases. Since a longer period should increase the possibility of a false negative finding, we believe that the differences in times from PET-CT to surgery had little influence on the results.

The findings of the study showed that an elevation of SUVmax of >9% was optimal as a cutoff for detecting LNM. Previous studies in other cancers have found a similar cutoff of 10%. PET-CT criteria defined by the absolute value of SUVmax have also been proposed (9), but this value can vary due to factors, such as the scanning protocol, scanning device and workstation software. The change in SUVmax might also be influenced by these factors, but is likely to be more universally applicable than the absolute value, especially with the current development of new devices and protocols.

Generally, we would expect an increase of sensitivity to DPS, which scan twice. However as a result, DPS increase only specificity by reducing false positives by checking the trend of FDG uptake, because there was no region indicating positive in only the delayed phase. In order to detect new abnormal uptake in the delayed phase to lymph node area, the two-hour period to scanning may need to be shortened.

By adding a certain condition, such as SUV elevation in the delayed phase, to the definition of test-positive, an abnormal uptake in the early phase, the relationship between sensitivity and specificity becomes a trade-off. Indeed, our analysis by regions indicated that specificity increased and sensitivity decreased with DPS compared to MPS, while accuracy was also increased, but not significantly. These results do not indicate a markedly improved efficacy of DPS for detecting LNM, but the increased specificity is of note, whereas sensitivity may be increased by administration of a higher dose of FDG or use of a longer scanning time. However, these changes will increase the use of medical resources and the patient's waiting time.

Also of note that the current study only examined the effect of DPS for the detection of LNM. However, DPS can also be useful when examining digestive and urinary tract, both of which move during intervals, to differentiate between abnormal uptake and physiological accumulations. Additionally, the accuracy of DPS for other factors, such as malignancy of the primary tumor or distant metastasis, will have to be examined separately in future studies.

Conclusion

The present study is the first report comparing between PET-CT MPS and DPS for the detection of LNM in gynecological cancer. The results indicated an optimal cutoff for RI of 9%. Using this criterion, DPS had an unsatisfactory impact in the improvement of detection and was judged as a not definitive method. DPS exhibited increased specificity for detecting LNM compared to MPS but further modifications may be required to improve the sensitivity of this diagnostic approach.

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Received January 10, 2015
Revised January 24, 2015
Accepted January 27, 2015