

The diagnostic accuracy of fluorodeoxyglucose-positron emission tomography/computed tomography and sentinel node biopsy in the prediction of pelvic lymph node metastasis in patients with endometrial cancer

A retrospective observational study

Tomohito Tanaka, MD, PhD^{a,*}, Yoshito Terai, MD, PhD^a, Kazuhiro Yamamoto, MD, PhD^b, Takashi Yamada, MD, PhD^c, Masahide Ohmichi, MD, PhD^a

Abstract

According to the sentinel node biopsy (SNB), systematic pelvic lymph node dissection (PLND) may not be needed for patients with early-stage endometrial cancer. On the other hand, imaging technology including fluorodeoxyglucose-positron emission tomography/computed tomography (FDG PET/CT) has been developing worldwide. The aim of this study was to evaluate the combined diagnostic accuracy of FDG PET/CT and SNB in the prediction of pelvic lymph node metastasis in endometrial cancer patients.

One hundred twenty-one patients with endometrial cancer underwent FDG PET/CT before hysterectomy and received SNB followed by systematic PLND. Univariate and multivariate analyses were performed to compare the diagnostic accuracy of FDG PET/CT and SNB in the prediction of pelvic node metastasis to the ultimate histologic status.

FDG PET/CT had lower sensitivity (36.8% versus 57.9%, $P = .1$) and a higher specificity (96.4% versus 84.8%, $P < .01$) than SNB. The kappa statistics of FDG PET/CT and SNB were 0.37 (95% CI, 0.15–0.59) and 0.72 (95% CI, 0.53–0.90), respectively. The sensitivity of SNB was significantly higher than that of FDG PET/CT in all hemi-pelvises (HPs) in which the short axis of the largest metastatic lymph node was <5 mm in diameter (72.7% versus 18.2%, $P = .01$). In contrast, the sensitivity of FDG PET/CT was higher than that of SNB in all HPs in which the short axis of the largest metastatic lymph node was ≥ 5 mm in diameter (62.5% versus 37.5%, $P = .2$); however, the difference was not statistically significant. When the combined diagnosis of FDG PET/CT and SNB was made, the sensitivity and specificity were 84.2% and 82.1%, respectively.

SNB was more useful for detecting lymph node metastasis than FDG PET/CT, especially in patients with small metastatic lymph nodes. The combined diagnosis of FDG PET/CT and SNB improves the sensitivity; PET-positive nodes should be dissected regardless of SNB status and HPs in which SNB was not detected should be dissected systematically regardless of FDG PET/CT status.

Abbreviations: ^{99m}Tc = 99m-Technetium, BMI = body mass index, FDG PET/CT = fluorodeoxyglucose-positron emission tomography/computed tomography, FIGO = International Federation of Gynecology and Obstetrics, H&E = hematoxylin and eosin, HPs = hemi-pelvises, ICG = indocyanine green, IDC = indigocarmine, NCCN = The National Comprehensive Cancer Network, PLND = pelvic lymph node dissection, SLN = sentinel lymph node, SNB = sentinel node biopsy.

Keywords: endometrial cancer, lymph node metastasis, pelvic lymph node, PET, sentinel lymph node

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^a Department of Obstetrics and Gynecology, ^b Department of Radiology,

^c Department of Pathology, Osaka Medical College, Takatsuki, Japan.

* Correspondence: Tomohito Tanaka, Department of Obstetrics and Gynecology, Osaka Medical College, 2-7, Daigaku-machi, Takatsuki, Osaka 569-8686, Japan (e-mail: gyn123@osaka-med.ac.jp).

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1. Introduction

Systematic pelvic lymph node dissection (PLND) remains an important surgical procedure in the treatment of endometrial cancer. This procedure has been needed for correct staging and has resulted in a favorable prognosis in patients with endometrial cancer.^[1–9] However, lymph node metastasis rarely occurs in patients with low-risk cancer.^[10] Furthermore, surgical complications, including nerve or vessel injury and lymph edema may occur.^[11–13] Until now the extent of lymph node dissection has been determined according to the presence or absence of myometrial invasion and the tumor grade on preoperative magnetic resonance imaging (MRI), and the preoperative biopsy and/or intraoperative frozen section diagnosis; however, the accuracy of these examinations is not sufficient for decision-making with regard to systematic PLND.^[14–17] Recently, sentinel

lymph node biopsy (SNB) is considered to be an important procedure for decision-making in relation to systematic PLND. This procedure is now included in The National Comprehensive Cancer Network (NCCN) guidelines for endometrial carcinoma and is supported by category-3 evidence.^[18–20]

Over the last decade, 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has become an increasingly important component of the tumor staging of endometrial cancer by virtue of its ability to identify disease, including lymph node-involving distant disease and recurrent disease. When pelvic lymph node metastasis can be preoperatively or intraoperatively diagnosed by an SNB or fluorodeoxyglucose-positron emission tomography/computed tomography (FDG PET/CT), systematic PLND may not be needed. The aim of this study was to evaluate the diagnostic accuracy of FDG PET/CT and SNB in the prediction of pelvic lymph node metastasis in patients with endometrial cancer.

2. Materials and methods

2.1. Participants

A total of 121 Japanese endometrial cancer patients who underwent preoperative FDG PET/CT and intraoperative sentinel node procedures at Osaka Medical College in Japan between September 2013 and September 2017 were retrospectively reviewed. Patients who met the following criteria were eligible for inclusion in the study:

underwent laparoscopic or abdominal hysterectomy including systematic PLND with bilateral salpingo-oophorectomy;

underwent preoperative FDG PET/CT and intraoperative SNB; and

did not receive any treatment, including chemotherapy and radiotherapy, before surgery. Hysterectomy with systematic PLND was performed regardless of the detection and status of the sentinel lymph nodes (SLNs). The present study was approved by the institutional review board, and the participants gave their written informed consent.

2.2. The SLN mapping procedure

We previously reported the SLN mapping procedure.^[21] Briefly, all of the tracers were sub-mucosally injected in 4 quadrants of the cervix at 0, 3, 6, and 9 o'clock. The cervical injection was approximately 5 mm in all cases, as described previously.^[22–24] On the day before the operation, 2.0 ml of fluid containing 110 MBq 99m-Tc-Technetium (^{99m}Tc)-labeled tin colloids was injected into the patient's cervix. Lymphoscintigraphy was performed within 6 hours, and hot spots—indicating SLNs—were identified. On the day of the operation, 5 ml of indigocarmine (IDC) (2 mg/mL) and/or indocyanine green (ICG) (50 µg/mL) was injected into the cervix at the start of surgery. The same quantity of IDC and/or ICG was also injected into the uterine fundus upon reaching the intraabdominal cavity. The SLNs were detected at 40 minutes after injection of IDC or ICG. Radioactive lymph nodes were located using a gamma-probe (Navigator GPS, RMD). IDC-stained lymph nodes were detected by direct inspection. ICG fluorescence-positive lymph nodes were detected using a color fluorescence camera (Hyper Wye Medical System, MIZUHO Co., for laparotomy; Camera Control Unit JC300, MC Medical Co., for laparoscopy). After SLN biopsy, the area of the pelvic lymph node was surveyed by direct observation, and with a color fluorescence camera or a gamma-probe to confirm

that no radioactive tissue remained. The combination of ^{99m}Tc and IDC was used in the early phase and a combination of 3 tracers was used in the late phase.

2.3. Pathology and the analysis of the SLNs

An intraoperative pathological examination was performed. The SLN was cut in half, parallel to the longest axis to obtain the maximum section area. One half was used to create a frozen section. The specimen was cut every 2 mm into 5-µm-thick sections that were stained with hematoxylin and eosin (H&E). The specimens were evaluated at the time that the frozen sections were obtained. The other half and the non-SLN specimens were fixed in 10% formalin for a permanent section procedure; the specimen was cut parallel to the longest axis every 2 mm. After fixation, the 5-µm-thick sections were stained with H&E and examined.

2.4. FDG PET/CT

All of the patients underwent FDG PET/CT within 4 weeks before surgery. All studies were performed with a PET/CT scanner (Discovery 710; GE Healthcare, Milwaukee, WI). Patients fasted for at least 6 hours before the intravenous administration of 3.7 MBq/kg of ¹⁸F-FDG. The preinjection blood glucose level was measured to ensure that the values were <150 mg/dL. During the distribution phase, the patients lay in the supine position in a quiet room. Combined image acquisition began 60 minutes after tracer injection. The patients were scanned on a flat-panel, carbon-fiber composite table insert. First, an unenhanced CT scan (3.3-mm slice thickness) from the base of the skull to the inferior border of the pelvis was acquired during shallow breathing (140 kV, 60–80 mA). A subsequent PET scan was acquired in 3-dimensional mode, with 3 minutes for each bed position, iterative reconstruction was used (ordered subset expectation maximization) with a 128 × 128 matrix size, attenuation correction, correction for random coincidences, and scatter correction. Attenuation correction was performed based on the computed tomography (CT) scan data.

The image readouts were obtained on a Xeleris Workstation (GE Healthcare), which allows for the visualization of PET, CT, and fused sections in transverse, coronal, and sagittal planes. Images were evaluated in consensus by 2 radiologists (1 was a nuclear medicine physician) who had been informed of the clinical data. The deviation of the focal tracer accumulation from the physiological distribution of each tracer was considered to indicate positivity for disease. A lymph node was considered PET-positive if its FDG uptake was greater than the blood pool activity or the activity of the surrounding background tissue, regardless of its size.

2.5. Sensitivity and specificity

Systematic PLND was carried out bilaterally in the external iliac, internal iliac, common iliac and obturator lymph node areas for all patients: the right and left pelvic regions were analyzed separately. The hemi-pelvis (HP) includes the common iliac nodes, external iliac nodes, internal iliac nodes, and obturator nodes. The HP was considered positive on SNB or final pathological examination if at least 1 of the corresponding 4 sub-regions had metastasis and was considered negative if all 4 regions were negative. The sensitivity was defined as the sum of the HPs with PET-positive nodes and involved SLNs divided by

the total number of HPs with positive nodes. Specificity was defined as the sum of the HPs with PET-negative nodes or no involved SLNs divided by the total number of HPs without nodal metastasis.

2.6. Statistical analyses

All of the statistical analyses were performed using the JMP software program (version. 13.1.0). Continuous variables were expressed as the mean \pm standard deviation (SD). The Mann-Whitney *U* test was used to compare continuous variables, and Fisher exact test was used to compare frequencies. *P* values of $<.05$ were considered to indicate statistical significance.

3. Results

There were 121 patients with endometrial cancer who underwent preoperative FDG PET/CT and intraoperative SNB. The mean age of the patients was 57.1 ± 10.6 years, and the mean body mass index (BMI) was 23.7 ± 4.8 . Thirty-six (29.8%) patients were nulliparous. A total of 82 (67.8%) patients had International Federation of Gynecology and Obstetrics (FIGO) stage IA disease, 16 (13.2%) had stage IB disease, 1 (0.8%) had stage II disease, 8 (6.6%) had stage IIIA disease, 1 (0.8%) had IIIB disease, 9 (7.4%) had stage IIIC disease, and 4 (3.3%) had stage IV disease. Histologically, 94 (77.7%) patients had endometrioid carcinoma of grade 1 or 2, 12 (9.9%) had endometrioid carcinoma of grade 3, 7 (5.8%) had serous carcinoma, 3 (2.5%) had clear cell carcinoma, and 5 (4.1%) had carcinosarcoma. Ninety-eight (81.0%) patients underwent laparoscopic surgery; 23 (19.0%) patients underwent laparotomy. All patients underwent systematic PLND after SLN biopsy. Thirty-two (26.7%) patients underwent systematic para-aortic lymphadenectomy. The para-aortic lymph node was resected as the SLN in the biopsies of 8 (6.6%) patients. Eleven patients (9.1%) had lymph node metastasis. The total number of resected lymph nodes was 43.1 ± 18.6 (Table 1). The SLN procedure was performed with ^{99m}Tc in 113 (93.4%) patients, IDC in 114 (94.2%) patients, and ICG in 110 (90.9%) patients. No patient received a single tracer. The mean number of detected SLNs per HP was 2.8 ± 1.7 . The detection rate was 84.3%.

Among 121 patients with endometrial cancer, 19 HPs in 11 patients had lymph node metastasis. In these cases, FDG PET/CT predicted 7 HPs, making the sensitivity 36.8% (7/19). In contrast, SNB predicted 11 HPs (sensitivity, 57.9% [11/19]). Among the other 8 HPs, the SLN could not be detected in 4 HPs. Lymph node metastasis was identified without SLN metastasis in 4 HPs. There was no metastasis in the remaining 223 HPs. FDG PET/CT predicted metastasis in 8 HPs and did not predict the metastasis in 215 HPs; the specificity, false-positive rate, false-negative rate, positive predictive value and negative predictive value were 96.4% (215/223), 3.6% (8/223), 63.2% (12/19), 46.7% (7/15), and 94.7% (215/227), respectively. In these 223 HPs without metastasis, SNB detected no metastasis in 189 HPs (specificity, 84.8% [189/223]; negative predictive value, 97.9% [189/193]) (Fig. 1). Table 2 shows the comparison of the accuracy of FDG PET/CT and SNB in the prediction of pelvic lymph node metastasis. FDG PET/CT had lower sensitivity (36.8% versus 57.9%, $P=.1$) and a lower negative predictive value (94.7% versus 97.9%, $P=.08$) than SNB; however, the difference was not statistically significant. The specificity of FDG PET/CT was significantly higher than that of SNB (95.5% versus 84.8%, $P<.01$). The mean diameter of the short axis of the largest

Table 1

The characteristics of the endometrial cancer patients who underwent preoperative FDG PET/CT and intraoperative sentinel lymph node biopsy.

Total number of patients	121
Age*, years	57.1 \pm 10.6
BMI	23.7 \pm 4.8
Nulliparous (%)	36 (29.8)
FIGO stage (%)	
IA	82 (67.8)
IB	16 (13.2)
II	1 (0.8)
IIIA	8 (6.6)
IIIB	1 (0.8)
IIIC	9 (7.4)
IVB	4 (3.3)
Histological type (%)	
Endometrioid carcinoma G1 or G2	94 (77.7)
Endometrioid carcinoma G3	12 (9.9)
Serous carcinoma	7 (5.8)
Clear cell carcinoma	3 (2.5)
Carcinosarcoma	5 (4.1)
Surgical method (%)	
Laparoscopy	98 (81.0)
Laparotomy	23 (19.0)
Systematic PAND	32 (26.7)
PAN biopsy as SLN	8 (6.6)
Pelvic node metastasis	11 (9.1)
Resected Lymph nodes*	43.1 \pm 18.6

^{99m}Tc = 99m -technetium-labeled tin colloid. FDG PET/CT= fluorodeoxyglucose positron emission tomography/computed tomography, ICG=indocyanine green, IDC=indigo carmine, PAND= paraaortic lymph node dissection, PLND=pelvic lymph node dissection.

*According to analysis of variance (ANOVA) (mean \pm SD).

metastatic lymph node was 5.4 ± 2.6 mm. The sensitivity of SNB was significantly higher than that of FDG PET/CT in each HP in which the short axis diameter of the largest metastatic lymph node was <5 mm (72.7% versus 18.2%, $P=.01$). In contrast, the sensitivity of FDG PET/CT was higher than that of SNB in each of the HPs in which the short axis diameter of the largest metastatic lymph node was ≥ 5 mm (62.5% versus 37.5%, $P=.2$); however, the difference was not statistically significant. The kappa statistics of FDG PET/CT and SNB were 0.37 (95% confidence interval [CI], 0.15–0.59) and 0.72 (95% CI, 0.53–0.90), respectively.

Then the combined diagnosis of FDG PET/CT and SNB was made; HPs with positive FDG PET/CT or positive SNB were considered as positive HPs, in contrast, HPs with both of negative FDG PET/CT and negative SNB were considered as negative HPs. The sensitivity and specificity were 84.2% and 82.1%, respectively (Fig. 2).

4. Discussion

In the present study, SNB was more useful for detecting lymph node metastasis than FDG PET/CT, especially in patients with small metastatic lymph nodes. In contrast, FDG PET/CT could detect large metastatic lymph nodes. The combined diagnosis of FDG PET/CT and SNB improves the sensitivity; PET-positive nodes should be dissected regardless of SNB status and HPs in which SNB was not detected should be dissected systematically regardless of FDG PET/CT status.

A meta-analysis showed that the SLN detection rate in endometrial cancer was 81% (95% confidence interval,

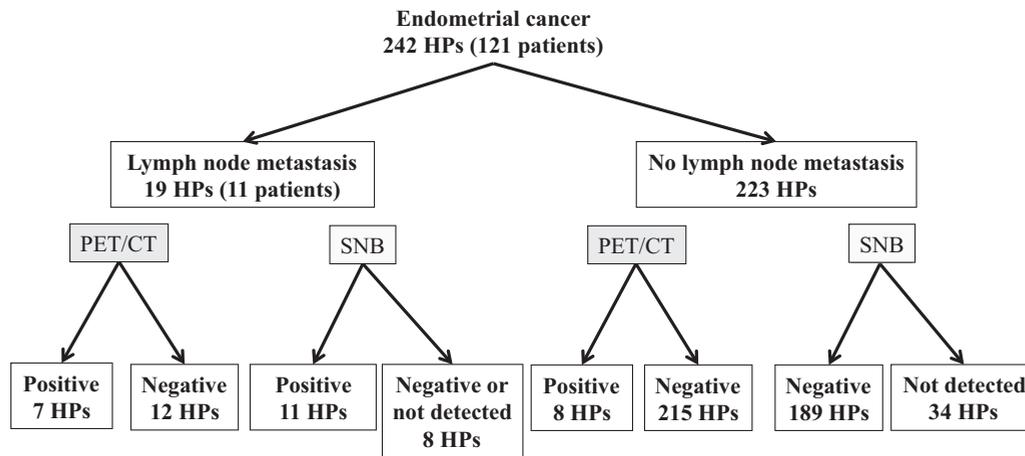


Figure 1. The results of SNB and FDG PET/CT in the prediction of lymph node metastasis. Among the 121 patients with cervical cancer, lymph node metastasis was detected in 19 HPs of 11 patients. In these cases, FDG PET/CT predicted 7 HPs (sensitivity 36.8%, [7/19]). In contrast, SNB predicted 11 HPs (sensitivity, 57.9% [11/19]). There was no metastasis in the remaining 223 HPs. FDG PET/CT predicted metastasis in 8 HPs and did not predict metastasis in 215 HPs; the specificity, false-positive rate, false-negative rate, positive predictive value and negative predictive value were 96.4% (215/223), 3.6% (8/223), 63.2% (12/19), 46.7% (7/15), and 94.7% (215/227), respectively. SNB detected no metastasis in 189 of the 223 HPs without metastasis (specificity, 84.8% [189/223]; negative predictive value, 97.9% [189/193]). FDG PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography, HPs = hemipelvises, SNB = sentinel node biopsy.

77–84%) with a bilateral pelvic node detection rate of 50% (95% confidence interval, 44–56%) and a para-aortic detection rate of 17% (95% confidence interval, 11–23%).^[25] The BMI, and tumor histology and grade did not affect the detection rate to a statistically significant extent. The sensitivity of sentinel node mapping in the detection of metastasis was 96% (95% CI, 91–98%). Ultra-staging did not improve sensitivity.^[25] We previously reported on SNB for endometrial cancer patients.^[21] Briefly, when the hemipelvis was considered as the unit of the analysis, the detection rate and sensitivity were 81% and 80%, respectively. Before the above-described meta-analysis, there were only 2 prospective multi-institution studies of SLN in patients with endometrial cancer.^[26,27] SENTI-ENDO was the first prospective multicenter study of SLB in patients with endometrial cancer. At least 1 SLN was detected in 111 of the 125 patients. Nineteen of these 111 (17%) patients had pelvic node metastasis. When the hemipelvis was considered as the unit of the analysis, the sensitivity was 100% and the NPV was 100%. When the patient was considered as the unit of the analysis, 3 patients (2.7%) with type 2 endometrial cancer had false-negative results.^[26] The FIRES trial was the other multicenter prospective cohort study of SNB. At least 1 SLN was successfully mapped in 293 (86%) of 385 patients. Forty-one patients (12%) had positive nodes, and the sensitivity and NPV were 97.2% and

99.6%, respectively.^[27] The sensitivity of SNBs in the present study was lower than in previously published studies. This difference is due to the method for calculating the sensitivity; the patients or lymph nodes that could not be detected were excluded in most previous studies. The sensitivity of the detected SLNs was 73.3% in our study.

On the other hand, there have been several studies on the detection of pelvic lymph node metastasis by FDG PET/CT.^[28,29] The meta-analysis showed that the overall pooled estimated sensitivity and specificity of FDG PET or PET/CT scans in the detection of pelvic and/or para-aortic metastasis were 63.0% and 94.7%, respectively.^[28] The sensitivity in our study was extremely low in comparison to that reported in the above-described meta-analysis. In our study, 67.8% patients had stage of IA disease and 77.7% patients had a grade of 1 or 2 histological type. The rate of pelvic lymph node metastasis was 9.1%; most participants had low-risk disease. The mean diameter of the short axis of the largest metastatic lymph node was 5.4 ± 2.6 mm. When the short axis diameter of the largest metastatic node was < 5 mm, the sensitivity of FDG PET/CT and SNB were 18.2% and 72.7%, respectively. In contrast, when the short axis diameter of the largest metastatic node was ≥ 5 mm, the sensitivity of FDG PET/CT and SNB were 62.5% and 37.5%, respectively. Furthermore, another study showed that preoperative FDG PET/CT has low value in predicting lymph node metastasis in patients with node-negative endometrial cancer on preoperative MRI. In this study, a lymph node with a short axis diameter of < 1 cm was considered to be MRI-defined node-negative. The sensitivity of FDG PET/CT in predicting lymph node metastasis was 18.5%.^[29] These findings suggested that it is difficult to identify metastasis when no swollen lymph nodes are detected on FDG PET/CT. In contrast, SNB could be useful for detecting small metastatic lymph nodes.

In the NCCN guideline, SNB algorithm is suggested, as SLN mapping requires the performance of side-specific nodal dissection in cases of failed mapping and the removal of any suspicious or grossly enlarged nodes regardless of mapping. We considered that FDG PET/CT might be useful in cases of failed mapping.^[20] Among the 38 failed mapping cases, 4 had positive nodes in the

Table 2

The accuracy of SNB versus FDG PET/CT in the prediction of pelvic lymph node metastasis.

	FDG PET/CT	SNB	P value
Sensitivity	36.8% (7/19)	57.9% (11/19)	.1
Short axis < 5 mm	18.2% (2/11)	72.7% (8/11)	.01
Short axis ≥ 5 mm	62.5% (5/8)	37.5% (3/8)	.2
Specificity	95.5% (213/223)	84.8% (189/223)	$< .01$
Negative predict value	94.7% (223/225)	97.9% (189/193)	.08
Kappa statistic	0.37 (0.15–0.59)	0.72 (0.53–0.90)	

FDG PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography, SNB = sentinel node biopsy.

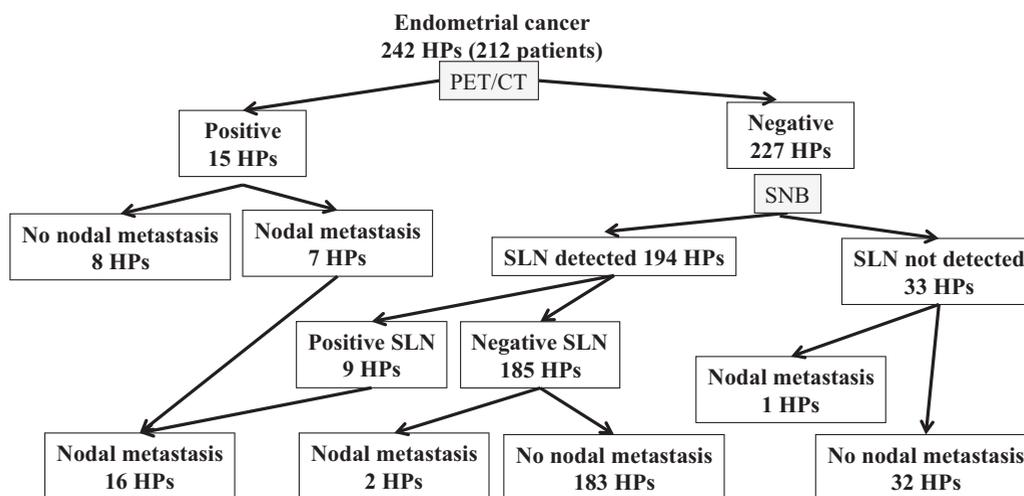


Figure 2. The combination of FDG PET/CT and SNB. Among the 12 HPs with positive-PET/CT, lymph node metastasis was identified in 8 on final pathology. In the remaining 227 HPs with negative PET/CT, SLN was detected in 194 HPs. SLN was positive in 9 HPs, however, among remaining 185 HPs with negative SLN, lymph node metastasis was identified in 2 HPs on final pathology. Among 33 HPs in which SLN was not detected, nodal metastasis was identified in 1 HPs on final pathology. The sensitivity and specificity of the combination of FDG PET/CT and SNB were 84.2% and 82.1%, respectively. FDG PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography, HPs = hemi-pelvises, SLN = sentinel lymph node.

present study. Among these 4 cases, FDG PET/CT succeeded to suggest metastasis in 3 cases, resulting the sensitivity of the combined diagnosis of FDG PET/CT and SNB was 84.2%. Although the combination of FDG PET/CT and an SNB was useful in our study, it is too low to omit the PLND; HPs in which SNB was not detected should be dissected systematically regardless of FDG PET/CT status.

The present study was associated with 2 major limitations that may reduce its value. First, the study included bias—for instance, the surgeons knew the PET/CT results before surgery. Second, ultra-staging <2 mm in diameter and immunohistochemistry was not performed. As such, our results must be confirmed in further studies.

In conclusion, SNB was more useful for detecting lymph node metastasis than FDG PET/CT, especially in patients with small metastatic lymph nodes. In contrast, FDG PET/CT could detect large metastatic lymph nodes. The combined diagnosis of FDG PET/CT and SNB improves the sensitivity; PET-positive nodes should be dissected regardless of SNB status and HPs in which SNB was not detected should be dissected systematically regardless of FDG PET/CT status.

Author contributions

Conceptualization: Tomohito Tanaka, Masahide Ohmichi.

Data curation: Tomohito Tanaka.

Investigation: Tomohito Tanaka, Yoshito Terai, Kazuhiro Yamamoto, Takashi Yamada.

Methodology: Yoshito Terai, Kazuhiro Yamamoto, Takashi Yamada.

Writing – original draft: Tomohito Tanaka.

Writing – review & editing: Masahide Ohmichi.

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