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Real-time ultrasound virtual navigation in 3D PET/CT volumes for superficial lymph-node evaluation: innovative fusion examination

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KEYWORDS: breast cancer; fusion imaging; gynecological cancer; lymph node; PET/CT; ultrasonography

CONTRIBUTION

What are the novel findings of this work?
Fusion imaging with virtual navigation, combining positron emission tomography/computed tomography (PET/CT) with real-time ultrasound imaging, is technically feasible and able to detect target lymph nodes even when PET/CT and ultrasound findings are inconsistent.

What are the clinical implications of this work?
The possibility of avoiding or restricting diagnostic surgical procedures with the aid of fusion imaging during the management of oncological patients would be of considerable value in clinical practice. For example, a patient with vulvar cancer, presenting with comorbidities and at an advanced age, who is unable to undergo surgical diagnostic procedures, could benefit from fusion-imaging-guided biopsy. The technique could also be used to guide the injection of radiotracer for selective surgical nodal excision, enabling more sparing, selective surgery. This innovative technique could open up multiple diagnostic and therapeutic opportunities in breast and gynecological oncology.

ABSTRACT

Objective *To evaluate the feasibility and clinical application of fusion imaging with virtual navigation, combining ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) with real-time ultrasound imaging, in assessing superficial lymph nodes in breast-cancer and gynecological-cancer patients.*

Methods *This was a pilot study of breast- and gynecological-cancer patients with abnormal uptake of ^{18}F-FDG by axillary or groin lymph nodes on PET/CT scan, examined at our institution between January 2017 and May 2019. Fusion imaging was performed, uploading preacquired PET/CT DICOM images onto the ultrasound machine and synchronizing them with real-time ultrasound scanning performed at the lymph-node site. In the first phase, we assessed the feasibility and reliability of fusion imaging in a series of 10 patients with suspicious lymph nodes on both PET/CT and ultrasound, and with full correspondence between both techniques in terms of size, shape and morphology of the lymph nodes (Group A). In the second phase, we included 20 patients with non-corresponding findings between PET/CT and ultrasound: 10 patients with lymph nodes that were suspicious or pathological on PET/CT scan but not suspicious on ultrasound assessment (Group B), and 10 patients with suspicious or pathological lymph nodes on both PET/CT and ultrasound but with no correspondence between the two techniques in terms of number of affected lymph nodes (Group C).*

Results *In the 30 selected patients, fusion imaging was assessed at 30 lymph-node sites (22 inguinal and eight axillary nodes). In the first phase (Group A), the fusion technique was shown to be feasible in all 10 lymph-node sites evaluated. In the second phase, fusion imaging was*

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completed successfully in nine of 10 cases in Group B and in all 10 cases in Group C. In all groups, fusion imaging was able to identify the target lymph node, guiding the examiner to perform a core-needle aspiration biopsy or to inject radiotracer for selective surgical nodal excision, according to the radio-guided occult lesion localization technique.

Conclusion *Fusion imaging with virtual navigation, combining PET/CT and real-time ultrasound imaging, is technically feasible and able to detect target lymph nodes even when PET/CT and ultrasound findings are inconsistent. Fusion imaging can also be used to guide the performance of core-needle aspiration biopsy, avoiding further surgical diagnostic procedures, or the injection of radiotracer for selective surgical nodal excision, enabling more sparing, selective surgery. This innovative technique could open up multiple diagnostic and therapeutic opportunities in breast and gynecological oncology.*
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INTRODUCTION

Lymph-node status is a major prognostic indicator in early breast cancer[1,2] and the main factor affecting choice of surgical procedure (sentinel lymph-node biopsy *vs* lymphadenectomy) in both breast[3,4] and vulvar[5,6] cancer. Accurate preoperative lymph-node assessment is therefore crucial to individualize management and plan the most appropriate treatment, guiding the choice of surgical procedure, if necessary, and avoiding unnecessary procedures and possible complications[7–11]. Currently, several imaging methods are available for this purpose, including ultrasound examination[12], ultrasound-guided core-needle aspiration biopsy[13] and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT)[14].

Ultrasound is widely available, low-cost and risk-free. It has been demonstrated to have high specificity in detecting metastatic superficial lymph nodes[12] when performed by an experienced examiner[15]. PET/CT can provide additional information about tumor metabolic activity and tumor-draining lymph nodes. However, its specificity and positive predictive value are suboptimal[14,16].

The best diagnostic tool with which to assess superficial lymph nodes thus remains undefined, and the work-up of patients with suspicion of lymph-node involvement is challenging. In our institution, patients with lymph nodes not suspicious on ultrasound but showing abnormal ^{18}F-FDG uptake on PET/CT scan may be managed, according to the patient's characteristics and the clinician's decision, by: (1) diagnostic surgery (e.g. partial or radical nodal excision), which is reliable, but may result in overtreatment, with the additional risk of postoperative complications[4,9,11,17]; (2) conventional ultrasound-guided core-needle aspiration biopsy, which is conservative but may give false-negative results; or (3) conservative management and careful follow-up, with the risk of underestimating or delaying the diagnosis[15,18].

The novel fusion technique is advanced 'precision imaging' technology that integrates real-time ultrasound imaging with images acquired previously using other advanced complementary techniques, such as single-photon emission computed tomography (SPECT)/CT. It is being used increasingly for lymph-node assessment and was recently applied to the detection of sentinel lymph nodes[19–24]. It was also used recently for the first time in our institution to evaluate the feasibility of fusion imaging with virtual navigation in SPECT/CT three-dimensional (3D) volumes from vulvar cancer patients, providing further evidence of its possible role in detecting sentinel lymph node(s)[25].

In this study, we applied fusion imaging, combining real-time ultrasound with 3D volumes acquired using PET/CT, to examine superficial lymph nodes in breast- and gynecological-cancer patients, aiming to evaluate its feasibility and clinical application in these patients.

METHODS

Study design

This was a single-center pilot study, approved by the institutional review board of our institution (study code: 31-10-18157). All patients gave written informed consent, agreeing to undergo all the procedures and to data collection.

Between January 2017 and May 2019, we evaluated consecutive patients affected by gynecological or breast cancer, including those with a new diagnosis, those with residual disease after neoadjuvant treatment and those with suspicion of recurrence. Inclusion criteria for fusion imaging analysis were: increased ^{18}F-FDG uptake in at least one inguinal or axillary lymph node on PET/CT scan; and availability of an ultrasound scan examining the same lymph nodes.

Our study included two phases. In the first phase, we included 10 patients (Group A) with superficial lymph nodes showing clearly abnormal ^{18}F-FDG uptake on PET/CT (see below for the criteria used to define lymph-node status on PET/CT) and pathological features on ultrasound (according to subjective assessment)[15], with full correspondence between both techniques in terms of size, shape and morphology of the lymph nodes. In this group of patients, fusion imaging was performed to verify the feasibility and reliability of the image coregistration and navigation. In the second phase, we included patients with non-corresponding findings between PET/CT and ultrasound, divided into two groups: Group B included patients with lymph nodes that were suspicious or pathological on PET/CT but not suspicious on ultrasound examination, and Group C included patients with suspicious or pathological lymph nodes on both PET/CT and ultrasound examination, but with no correspondence between the two techniques in terms of number of affected lymph nodes. In all cases, fusion imaging analysis

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aimed to identify on real-time ultrasound the most suspicious lymph node identified on PET/CT, referred to herein as the 'target lymph node'. The time required to perform the fusion imaging examination was recorded.

^{18}F-FDG-PET/CT

Before the PET/CT examination, patients fasted for 6 h, in order to achieve the necessary blood glucose level of < 200 mg/dL, and were hydrated with a 500-mL intravenous infusion of saline. ^{18}F-FDG tracer (3–3.7 MBq/kg body weight) was administered by intravenous injection 60 min (± 10 min) prior to the scan. This was a low-dose CT scan (120 KeV, 80 mA), for anatomical localization and attenuation correction, performed using a hybrid scanner (Gemini GXL Philips, Philips Medical Systems, Cleveland, OH, USA; or Biograph mCT, Siemens Medical Solutions USA, Inc., Malvern, PA, USA). PET/CT images were reconstructed, using the line-of-response row-action maximum likelihood algorithm (three iterations and 33 subsets; voxel size, $4 \times 4 \times 4$ mm^3), and reviewed independently by two physicians experienced in nuclear medicine (A.C., V.R.), using Siemens Healthineers (Erlangen, Germany) *syngo*.via workstations. The physicians were blinded to clinical information and, if they disagreed regarding lymph-node status, they discussed until reaching a consensus[26–29]. Their evaluation was limited to visual analysis of ^{18}F-FDG uptake by the superficial lymph nodes. Lymph nodes were considered clearly normal on PET/CT scan if they presented no ^{18}F-FDG uptake, had short-axis diameter < 5 mm and were elliptical in shape, with an identifiable fatty hilum on coregistered low-dose CT. They were considered inflammatory if they showed ^{18}F-FDG uptake higher than background level and lower than liver activity, with any short-axis diameter, elliptical shape and presence of the fatty hilum on coregistered low-dose CT. They were considered suspicious for malignancy if they presented ^{18}F-FDG uptake higher than background level and lower or higher than liver activity, had a short-axis diameter < 8 mm, a round shape and absence of the fatty hilum on coregistered low-dose CT. Lymph nodes were considered clearly abnormal if they presented ^{18}F-FDG uptake higher than liver activity, had a short-axis diameter ≥ 8 mm, a round shape and absence of the fatty hilum at coregistered low-dose CT. The PET/CT scan was performed at least 3 weeks after any invasive diagnostic procedure or at least 3 weeks after the end of treatment with radio- and/or chemotherapy.

Ultrasound examination

Ultrasound examination was performed using a MyLab Twice (Esaote, Genova, Italy) ultrasound system, equipped with a linear probe and 7–12-MHz transducer. All examinations were performed by a skilled gynecological oncologist with more than 10 years of experience in both gynecological-cancer and breast-cancer diagnosis. Morphological, dimensional and color Doppler parameters were assessed as reported previously[15]. Lymph nodes were considered suspicious for malignancy on the basis of the final subjective assessment of the ultrasound examiner.

Fusion imaging with virtual navigation

The fusion imaging system comprises a commercial ultrasound machine (MyLab™ Eight eXP, Esaote Spa), built-in Virtual Navigator software (Esaote, Spa) and an integrated electromagnetic tracking system, which records the probe position and orientation in a 3D environment. The procedure had three steps, as described previously[25] (Videoclip S1). In Step 1, 3D volumes (Digital Imaging and Communications in Medicine (DICOM) images) were acquired and suspicious superficial lymph nodes identified on PET/CT, as described above. The standard DICOM images from PET and CT 3D volumes were uploaded onto the ultrasound machine, and the cross-sectional images of each were compared on the screen, synchronized and scrolled jointly, showing the multimodal images on the same scan. After identification of the suspicious superficial lymph node(s), a colored marker ('virtual marker') was added. Step 2 involved coregistration and synchronization of PET/CT and ultrasound images. In this step, any or more precise anatomical structures that could be recognized in both examinations were frozen and taken as primary landmarks (e.g. pubic symphysis or sternum) (Table 1). This step allowed the alignment of PET/CT and ultrasound examination images. Once primary landmarks were taken in both images (ultrasound and PET/CT), the dynamic navigation was generated. Step 3 involved fine-tuning and fusion imaging virtual navigation. During virtual navigation, small misalignments could be corrected by freezing the PET/CT image and realigning it to the ultrasound scan. This process could be accomplished by minute fine-tuning movements using additional anatomical reference points (secondary landmarks) (Table 1).

Presurgical, surgical and histopathological procedures

Except for six cases in Group A, which already had histological findings of the primary tumor and

Table 1 Anatomical landmarks for coregistration of PET/CT and ultrasound images in women with breast or gynecological cancer undergoing fusion imaging to investigate suspicious lymph nodes

Primary landmarks	*Secondary landmarks*
Groin and pelvic region	Small vascular ramifications
Pubic symphysis	Lymph nodes
Saphenous–femoral junction	Muscular structures
Femoral artery bifurcation	Bone structures
Common iliac artery and vein bifurcation	
Axillary region	
Xiphoid process	
Sternal manubrium	
Sternocostal junction	

PET/CT, positron emission tomography/computed tomography.

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pathognomonic signs on both PET/CT and ultrasound, which showed gross involvement of the lymph nodes, all cases (24/30) underwent either ultrasound-guided core-needle aspiration biopsy or diagnostic surgery for pathological assessment of the suspicious lymph node(s). This decision was made on a case-by-case basis by a multidisciplinary team, according to international guidelines on breast and gynecological cancers[3,5,30]. In case of selective excisional diagnostic surgery, at the end of the fusion imaging examination, a metal clip (a 'tissue marker') was placed on the target lymph node, and/or a preoperative radio-guided occult lesion localization (ROLL) procedure was carried out[31–34]. All diagnostic and surgical procedures were performed by a specialized oncological surgeon (G.G., S.F., S.B.).

Options for further management, including surgery, chemotherapy, radiotherapy and follow-up, were discussed by the appropriate dedicated hospital tumor boards, supported by the vulvar cancer multidisciplinary team, the breast unit tumor board and the multidisciplinary team in gynecological oncology, according to international guidelines.

Statistical analysis

All data were collected in an electronic Excel database (Microsoft Corp., Redmond, WA, USA) and managed according to international privacy regulations. Data are expressed as median (range) or number (percentage), as appropriate.

RESULTS

Between January 2017 and May 2019, we evaluated 33 patients affected by gynecological or breast cancer who had an increased ^{18}F-FDG uptake in at least one superficial lymph node. Of these, 30 were included in this analysis (three patients did not consent to undergo fusion imaging). There were 19 (63%) cases with a diagnosis of vulvar cancer (15 primary tumors and four recurrences), six (20%) with breast cancer (four primary tumors and two recurrences), three (10%) with cervical cancer (two primary tumors and one recurrence) and two (7%) with recurrence from other gynecological tumors. Table 2 shows the clinical characteristics of all patients. Their median age was 68 (range, 33–90) years and most patients ($n = 26$, 87%) were postmenopausal. Eighteen (60%) patients were overweight (body mass index ≥ 25 kg/m^2) and 18 (60%) had a high perioperative risk due to multiple comorbidities.

Fusion imaging was performed on 30 lymph-node sites: 22 (73%) inguinal nodes and eight (27%) axillary nodes. The median time interval between PET/CT examination and fusion imaging was 3 (range, 1–5) days.

In Group A (patients with clearly abnormal lymph nodes on both PET/CT and ultrasound examination and with full correspondence between both techniques in terms of size, shape and morphology of the lymph nodes), the fusion imaging technique was found to be feasible in all 10 cases: both synchronization of PET/CT with real-time ultrasound and virtual navigation were performed successfully at all lymph-node sites, confirming the correspondence of the two techniques in terms of number, morphology and localization of the lymph nodes. Six of these patients already had histological findings of

Table 2 Clinical characteristics of study population of 30 women with breast or gynecological cancer and with abnormal uptake of axillary or groin lymph nodes on PET/CT scan, undergoing fusion imaging

Characteristic	*Value*
Age (years)	68 (33–90)
Body mass index	
< 25 kg/m^2	12 (40)
25–29.9 kg/m^2	10 (33)
≥ 30 kg/m^2	8 (27)
Menopausal status	
Premenopausal	4 (13)
Postmenopausal	26 (87)
Comorbidities*	18 (60)
Previous oncological surgical treatment	
Gynecological surgery	11 (37)
Breast surgery	6 (20)
No previous surgery	13 (43)
Other previous oncological treatment	
Chemotherapy	7 (23)
Radiotherapy	3 (10)
Radiotherapy and chemotherapy	4 (13)
None	16 (53)
Primary tumor†	
Vulvar cancer	19 (63)
Breast cancer	6 (20)
Cervical cancer	3 (10)
Other gynecological cancer	2 (7)
Site of suspicious lymph node(s) on PET/CT	
Groin	22 (73)
Axilla	8 (27)
Histological assessment of target lymph nodes	
Core-needle biopsy (fusion-guided)	20 (67)
Selective excisional diagnostic surgery (fusion-guided)	3 (10)
Diagnostic radical lymphadenectomy (not fusion-guided)	1 (3)
None‡	6 (20)
Management after diagnosis	
Surgery	11 (37)
Groin	
Sentinel lymph-node biopsy	6
Inguinofemoral lymphadenectomy	4
Axillary	
Sentinel lymph-node biopsy	0
Axillary dissection	1
Medical treatment§	13 (43)¶
Conservative management and follow-up	6 (20)

Data are given as median (range), *n* (%) or *n*. *Including endocrine, metabolic and cardiovascular comorbidities. †Recurrence of vulvar cancer in four patients, breast cancer in four patients and cervical cancer in one patient, and recurrence in two patients with other gynecological malignancies. ‡Biopsy was not performed in six cases from Group A (feasibility study), which already had imaging findings of gross involvement of the lymph nodes, and who were referred directly for treatment based on the histology of the primary tumor site. §Chemotherapy and/or radiotherapy. ¶A further three cases referred for medical treatment later also underwent surgery. PET/CT, positron emission tomography/computed tomography.

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the primary tumor; the other four underwent core-needle aspiration biopsy. Each patient was then referred for surgical treatment ($n = 4$) or medical treatment (chemo- and/or radiotherapy ($n = 6$), as appropriate.

In the second phase of the study, in Group B (patients with lymph nodes that were suspicious on PET/CT but not suspicious on ultrasound examination), fusion imaging was completed successfully in nine of the 10 cases. In one case, the examination was stopped at Step 1 (coregistration of data) due to discordance in the patient's position in the axillary region during the PET/CT scan and the real-time ultrasound examination for the fusion imaging: her arms were lowered during PET/CT acquisition but raised during ultrasound evaluation. In all nine remaining cases, fusion imaging was able to identify the target lymph node, i.e. the node that was suspicious on PET/CT and not on ultrasound. After identification of the target lymph node, a fusion-imaging-guided core-needle aspiration biopsy was performed in seven cases. In the remaining two cases, the suspected lymph node was targeted under the guidance of fusion imaging first by inserting a metal clip ('tissue marker') and then, just before surgery, by injecting radiotracer for the ROLL technique. All nine biopsies were informative, being negative for malignancy. All nine patients were then referred as appropriate to surgical treatment ($n = 5$) or to conservative management with follow-up ($n = 4$). None had local recurrence of disease after follow-up of almost 14 months. In the single case of breast cancer in which fusion imaging failed, a histology sample was obtained conventionally by radical lymphadenectomy. The histology was positive, and the patient was referred for chemotherapy.

In Group C (patients with suspicious or pathological lymph nodes on both PET/CT and ultrasound examination, but not corresponding in terms of number of affected lymph nodes), fusion imaging was completed successfully, identifying the target lymph node in all 10 cases. After identification of the target lymph node, fusion imaging was applied to the performance of ultrasound-guided core-needle aspiration biopsy in nine cases and to target the lymph node for radiotracer injection directly before surgery in one case. All biopsies were informative: the histological findings were negative for malignancy in four lymph-node sites and positive in six. The patients with negative results on histology were referred as appropriate for surgical treatment ($n = 2$) or conservative management and follow-up ($n = 2$). All six patients with positive histological findings were referred for medical treatment, followed, in three cases, by surgery.

The overall median time for the fusion imaging examination was 27 (range, 12–45) min; for Step 1 it was 8 (range, 4–12) min, for Step 2 it was 6 (range, 4–12) min and for Step 3 it was 11 (range, 5–20) min.

DISCUSSION

This study demonstrated that it is feasible to use fusion imaging combining real-time ultrasound with PET/CT to study superficial lymph nodes in patients with breast or gynecological malignancy, this being performed successfully in almost all cases. Using fusion imaging, we were able to detect the target superficial lymph node in almost all patients with results that were inconsistent between initial PET/CT and ultrasound examinations. It could be used successfully to guide the examiner performing a core-needle aspiration biopsy, thereby avoiding further diagnostic surgical procedures, or to target the lymph node by inserting a metal clip and/or injecting a radiotracer for selective surgical nodal excision, thereby limiting the extent of surgery at the target lymph node(s).

To our knowledge, this is the first study exploring the use of fusion imaging to combine real-time ultrasound with PET/CT for the study of superficial lymph nodes in patients with breast and gynecological malignancies. We explored the fusion technique using two of the imaging methods included in the routine preoperative work-up for the assessment of lymph-node status in these patients. The main limitation of the study is the heterogeneity of the series, including different types of tumors, which made it difficult to classify patients and procedures into homogeneous categories. However, the sample size is consistent with that of other published studies on fusion imaging, and the inclusion of patients with different malignancies offered the advantage of allowing us to explore the role of fusion imaging in several different pathologies. Indeed, the vast majority of studies exploring the feasibility of fusion imaging in breast and gynecological diseases included few cases, studied by magnetic resonance imaging[35–38], SPECT/CT[10,25,39] or freehand SPECT[20–22], and the fusion technique using real-time ultrasound and PET/CT to localize pathological axillary lymph nodes has been reported in only one other study[24], which included two patients (one with breast cancer and one with B-cell lymphoma). In both of these cases, fusion imaging allowed the operators to identify easily the target lymph nodes, which were dissected successfully under local anesthesia, and they concluded that this technique was able to target the lymph nodes, resulting in shorter surgical time and reducing the risk of unsatisfactory axillary complications.

The possibility to avoid or restrict diagnostic surgical procedures during the management of oncological patients is of considerable value in clinical practice. This is even more relevant today, in light of the recent international recommendations related to the risk of infection with severe acute respiratory syndrome coronavirus-2, which indicate that diagnostic and therapeutic procedures should be limited to the bare minimum, especially in the most fragile categories of patient[40–46]. For instance, patients with vulvar cancer presenting with comorbidities and at an advanced age who are unable to undergo surgical diagnostic procedures could benefit from fusion-imaging-guided biopsy. Fusion imaging can also help to limit the impact of a surgical diagnostic procedure at the target lymph node, by labeling it through the insertion of a tissue marker and/or a radiotracer

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injection before surgery, and thereby potentially reducing the likelihood of surgical side effects.

Fusion imaging could also play a crucial role in patients with multiple suspicious lymph nodes in whom there is inconsistency between PET/CT and ultrasound results in terms of the number of lymph nodes involved. For example, in two patients belonging to Group C, an initial conventional core-needle biopsy was performed choosing arbitrarily one lymph node among multiple suspicious nodes (both axillary and inguinofemoral nodes) under the guidance of conventional ultrasound, which showed negative histology. Given the persistence of a strong suspicion of lymph-node metastasis, in order to choose another lymph node for a second biopsy, the patient underwent fusion imaging. The fusion-imaging-guided biopsy of the target lymph node showed positive histology. In both of these cases, the diagnosis was thus reversed by repeating the biopsy with the application of the fusion imaging technique, allowing accurate staging of the disease and development of the best management plan for each patient.

Finally, this study found that the median overall time for the fusion imaging examination was 27 (range, 12–45) min. Step 1 showed least variation in terms of duration, as this depends mainly on the time taken to load the DICOM data onto the ultrasound machine. Step 3 showed the greatest variation in timing, a likely consequence of the progressive learning of the examiners. Furthermore, this third phase is the most difficult to carry out technically, mainly due to the requirement to recognize the different anatomical structures and to align them precisely on the 3D scans, for which the operator needs to be trained.

In conclusion, our study has demonstrated that fusion imaging with virtual navigation, combining PET/CT with real-time ultrasound imaging, is technically feasible and able to detect target superficial lymph nodes even when PET/CT and ultrasound findings are inconsistent. This fusion imaging technique is safe, precise, conservative and reliable. It can be used to guide the examiner to perform a core-needle biopsy of the target lymph node, thereby avoiding further surgical diagnostic procedures, or to inject radiotracer for selective surgical nodal excision, enabling more sparing, selective surgery. This innovative technique could open up multiple diagnostic and therapeutic opportunities in breast and gynecological oncology.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Videoclip S1 Fusion imaging: video summarizing basic principles and clinical applications of real-time ultrasound virtual navigation in three-dimensional positron emission tomography/computed tomography volumes for superficial lymph-node evaluation.

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