Original Article
Middle East Journal of Cancer; April 2016; 7(2): 85-91

The Debate on Pelvic Lymphadenopathy Size Significance in Ovarian Cancer Patients

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Abstract

Background: This study attempts to ascertain a reliable cutoff size to determine whether pelvic lymph nodes are metastatic or not in ovarian cancer patients.

Methods: We retrospectively reviewed 73 PET/CT scans of 52 female patients with ovarian carcinoma who underwent surgery followed by chemotherapy. The findings of contrast enhanced MDCT were interpreted by two experienced radiologists unaware of the PET/CT findings. At least two experienced nuclear medicine physicians unaware of the contrast enhanced-MDCT findings examined the PET scans in order to localize, characterize and compare these scans to co-registered PET/CT images. A comparative study was done. Lymph node sizes were recorded in short axis diameter with a significant cut off estimated at 7.5 mm. Metabolic activities of different lymph node groups were assessed and the semi-quantitative SUV was calculated. The level of SUV significance was 2.5. Significant metastatic lymph nodes were judged by the assessment of integrated PET/CT results.

Results: Of the 73 scans, 47 showed significant lymph node metastases, with the following sensitivities: 75% (external iliac), 77.8% (internal iliac), and 75% (inguinal). The specificities were 84% (external iliac), 86% (internal iliac), and 54% (inguinal) with a *P*-value of 0.000 for the external an internal iliac groups and 0.079 for the inguinal group.

Conclusion: To improve detection of malignant pelvic lymph nodes, the size threshold should be decreased to 7.5 mm.

Keywords: Malignant, Pelvic lymph nodes, CT, PET/CT

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MEJC Middle East Journal of Cancer

Received: September 22, 2015; Accepted: December 5, 2015

Introduction

The diagnosis of lymphatic metastases from pelvic tumors represents an important challenge for modern imaging. Nodal metastasis is an important mechanism of tumor dissemination. Lymphatic metastasis has an important impact on the stage of the pelvic tumor, the mode of treatment and prognosis.[1]

Ovarian cancer may spread directly to surrounding pelvic organs and soft tissues affecting the contralateral adnexa through the uterus and fallopian tubes, and less likely the rectosigmoid colon, bladder, and pelvic lateral walls which can be directly invaded. Distant metastases may occur by intraperitoneal seeding, lymphatic transmission, or hematogenous dissemination of cancer cells.[2]

Lymphatic metastasis can occur through different pathways of lymphatic drainage. The first consists of the main lymphatic ducts, which follow the ovarian veins to the para-aortic and paracaval nodes at the level of the kidneys; this area is the most common site of metastatic adenopathy. Another pathway consists of lymph vessels that pass through the broad ligament to the pelvic nodes - the external iliac, hypogastric, and obturator nodal chains. The third pathway is constituted by lymph vessels to the inguinal nodes coursing along the round ligament.[3]

In contrast to other organs metastases, the lymph node metastatic lesion itself is usually not visualized during conventional cross-sectional imaging. However, it is observed that the malignant lymph nodes are larger than benign nodes. Lymph node enlargement is used as an important indicator of metastasis. When size is used as an indicator of metastasis, the short axis should be considered. The short axis diameter is measured perpendicular to the longest diameter of the lymph node and is considered the best predictor of the presence of metastatic disease.[4-9]

The diagnostic accuracy of conventional cross-sectional imaging (CT and MRI) for nodal staging of cancers of the abdomen and pelvis varies widely in the literature.[8,10-13] Lymph nodes that measure more than 1 cm in the short axis diameter are considered malignant. However, the size threshold varies with anatomic site and underlying tumor type.[7] Different studies are contradictory regarding the correlation between nodal size and the likelihood of lymph node metastasis.[14] There is a fundamental problem when relying on size as a main criterion for the diagnosis of nodal metastases. The difficulty is the wide variation in size of non-metastatic lymph nodes, which can substantially overlap with the size of metastatic nodes.[1]

Hybrid imaging techniques such as positron emission tomography (PET) and PET-computed tomography (CT) are utilized with increasing frequency to diagnose nodal involvement.[7] PET, performed with fluoro-deoxy-D-glucose (FDG), has proven valuable in providing important tumor-related qualitative and quantitative metabolic information essential for diagnosis and follow-up. PET-CT is a unique combination of the cross-sectional anatomic information provided by the CT and the metabolic information provided by the PET, both of which are acquired during a single examination and fused. The uptake of FDG is used to discriminate between benign and malignant nodes. PET-CT can detect malignancy in non-enlarged nodes, which can lead to a change in patient management.[15]

Our aim in this research was to reach a reliable value to determine whether pelvic lymph nodes

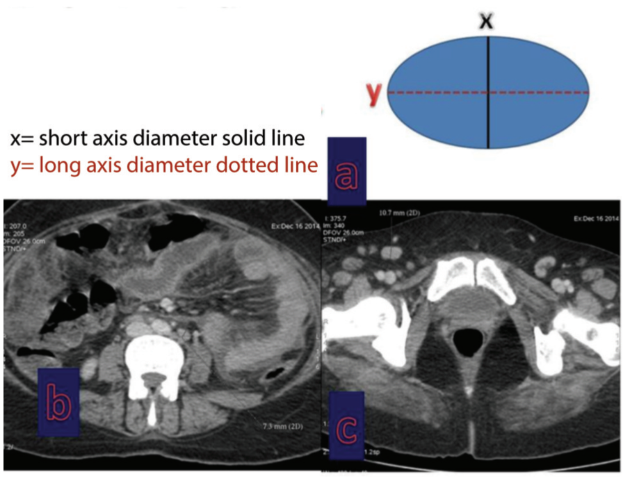

Figure 1. Lymphadenopathy measurements. (a) Schematic diagram of lymph node measurements. The dotted line (red) represents the long axis diameter. The solid line (black) represents the short axis diameter. (b) Para-aortic lymph node with a short axis diameter of 7 mm. (c) Right inguinal lymph node with a short axis diameter of 11 mm.

were metastatic in ovarian cancer patients by choosing a cutoff diameter of 7.5 mm.

Patients and Methods

This study was approved by the Institutional Review Board of the Faculty of Medicine, Assiut University. Written informed consent was obtained from each patient.

Patient population

We assessed 73 PET/CT scans from 52 female patients with pathologically proven ovarian carcinoma treated with cytoreductive surgery followed by chemotherapy. Patients underwent PET/CT examinations for diagnosis, post-treatment surveillance for detection of recurrent disease, or assessment of therapy response to residual/recurrent disease. Serum tumor markers and other recent imaging results were also included in the assessment.

Diagnosis of recurrence was based on clinical symptoms, suspicion of relapse at physical examination, or increase in blood tumor markers (CA-125) above the normal range (>35 U/ml) after achieving normal levels or a doubling of the lowest marker level after primary therapy.

Patients with pathologically proven ovarian carcinoma and those referred for post-treatment surveillance for detection of residual disease or recurrence, or assessment of therapy response were included. The exclusion criteria were: 1) patients known to have another malignant disease, 2) uncontrolled diabetes, 3) known allergy to contrast media, 4) severely ill patients, or 5) those with raised renal chemistry values.

PET/CT imaging protocol

The machine used was a Biograph 40 PET/CT Siemens processing system. Patients were instructed to fast for at least 6 hours and their blood glucose levels were measured at the time of the tracer injection. Blood glucose levels should be <200 mg/dl.

A dose of 0.1-0.17 MBq/kg of 18F-FDG was injected intravenously, adjusted according to the patient's weight. For the optimal delineation of bowel structures, 400-600 ml of diluted mannitol solution was administered one hour before CT imaging.

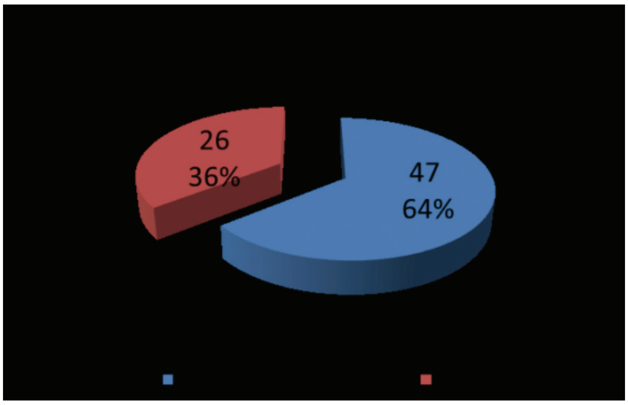

Figure 2. Percentage of scans with metastatic lymphadenopathy.

At one hour after tracer administration, a low-dose CT scan was obtained in a 64 multi-detector CT machine, from the skull base to the mid-thigh. This scan was used for attenuation correction. Next, an emission PET scan was acquired in a three-dimensional mode over the same anatomical regions. The acquisition time was 2 minutes per bed position, in 9 bed positions. Finally, a diagnostic contrast enhanced (CE)-CT was acquired using 120 kV, 300 mAs, and a 512×512 matrix size using a non-ionic contrast media with a concentration of 300-350 mg of iodine equivalent.

The images were transferred to the viewing stations for review in the axial, coronal, and sagittal planes and in a maximum-intensity-projection (MIP) three-dimensional cine mode using the manufacturer's review station.

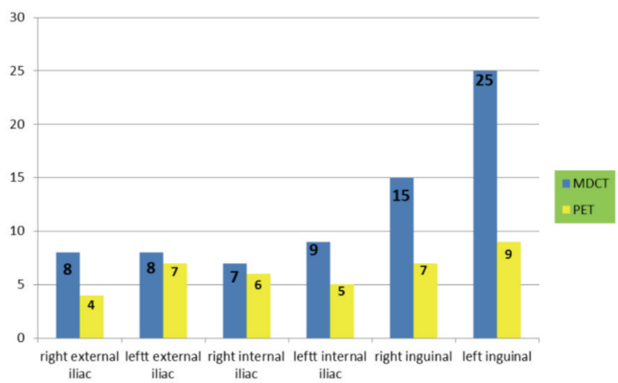

Figure 3. Different lymphadenopathy groups among the study population.

Table 1. Data for each pelvic lymphadenopathy group on lowering the cutoff to 7.5 mm.

Lymph node group	Sensitivity (%)	Specificity (%)	*P*-value
Para-aortic	37.5	94.9	0.07
External iliac	75	84.6	0.000
Internal iliac	77.8	86.8	0.000
Inguinal	75	54.3	0.079

Data interpretation

All imaging studies had the patients' names removed. The contrast enhanced multidetector CT (CE-MDCT) findings were interpreted by two experienced radiologists who were unaware of the PET/CT findings. The radiologists had knowledge of the study's aim. At least two experienced nuclear medicine physicians who were unaware of the CE-CT findings examined the PET images, evaluating localization and characterization and compared them to co-registered PET/CT images.

Visualized lymph nodes were recorded by their anatomical sites and reviewed in the axial, coronal and sagittal planes. Measurements were performed in two perpendicular planes, the short axis diameter (the perpendicular measure on the long axis diameter) was recorded (Figure 1). We chose 7.5 mm as the cutoff level of significance.

Any foci of FDG uptake that increased relative to the background and not located in the areas of physiological uptake was considered to be positive on PET/CT. Maximum standardized uptake values (SUV max) of the lesions were calculated on PET/CT fusion images. Diagnostic accuracy was determined on a patient level and a region level, An SUV cutoff of 2.5 or greater has been used to differentiate between benign and malignant lymph nodes.

Statistical analysis

The collected data were verified and coded by the researchers. A data entry file was designed by using an Excel program. The files were subsequently converted to SPSS version 16 where the variables were defined. Data analysis was done using SPSS program version 16. Statistical methods were applied that included numerous descriptive statistics and cross-tabulation. A *P*-value of <0.05 was considered significant.

Results

Of the 73 scans reviewed, 47 scans (38 patients) showed significant lymph node metastases. This finding comprised 64% of the total number of cases (Figure 2).

Figure 3 shows the high incidence of non-specific inguinal lymphadenopathy in comparison to the other groups.

The sensitivity, specificity and Pearson chi-square *P*-value are listed in Table 1.

Table 1 shows the groups with metastatic lymph adenopathy as seen by MDCT.

The differentiation of malignant from benign nature of pelvic lymph node groups had improved on lowering the cut off value to 7.5 mm. Where the least specificity were recorded with the inguinal nodes (Figure 4), while the iliac lymph node groups showed specificity 85% to 87%

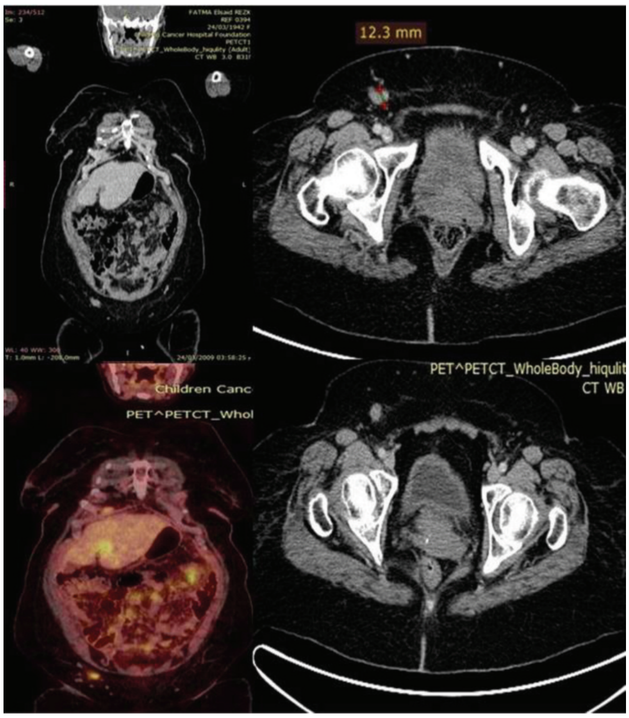

Figure 4. Right inguinal lymphadenopathy with short axis diameter 12 mm that has avid uptake in PET.

(Figure 5). On the other hand, the para-aortic group recorded reduced sensitivity 37.5% with specificity 94.9% (Figure 6), while multiple groups are seen in the same case (Figures 7 and 8).

Discussion

Lymph nodes that measure more than 1 cm in the short axis diameter are considered malignant. However, the size threshold varies with anatomic site and underlying tumor type. In rectal cancer, lymph nodes larger than 5 mm are regarded as pathological.[7] In addition, size criteria may differ for different cancers.[16] Preoperative identification of abnormal lymph nodes is helpful for planning retroperitoneal lymph node dissection. The enlargement of suprarenal lymph nodes, especially at the level of the celiac axis and porta hepatis, is frequently an indication for modification of the treatment plan and should therefore be included in the radiologist's report.[17]

Conventional CT and MR imaging are limited by their ability to detect metastases in normal or minimally enlarged lymph nodes. Relying on size as the sole criteria for diagnosis of nodal metastases represents a fundamental problem.[1] Our results show that it is deficient to depend on size alone for characterization with variable sensitivity ranging from 37.5% to 77.8% and specificity ranging from 54.3% to 94.9%

Prenzel et al.[9] relied on the premise that malignant lymph nodes were larger than benign ones.

In the current study we have attempted to reach a reliable value to determine whether the pelvic lymph nodes were metastatic in ovarian cancer patients by reducing the cutoff value from 10 mm to 7.5 mm and to calculate sensitivity and specificity for each lymph node group. We agree that reliance on size is difficult as there is a wide variation in non-metastatic lymph node sizes which can substantially overlap with the size of metastatic nodes.[1]

Chan et al.[16] recommended the use of a size threshold of 8 mm (short-axis diameter) for pelvic nodes and 10 mm for abdominal retroperitoneal nodes. In the case of testicular cancer, however, an 8-mm retroperitoneal abdominal node would be considered "suspicious." In the current study, we chose a size threshold of 7.5 mm in short-axis diameter. Therefore, the results had a sensitivity of 75% (external iliac), 77.8% (internal iliac), and 75% (inguinal).

Dorfman et al.[5] and Magnusson[19] reported that the upper limit of the short axis diameter of normal

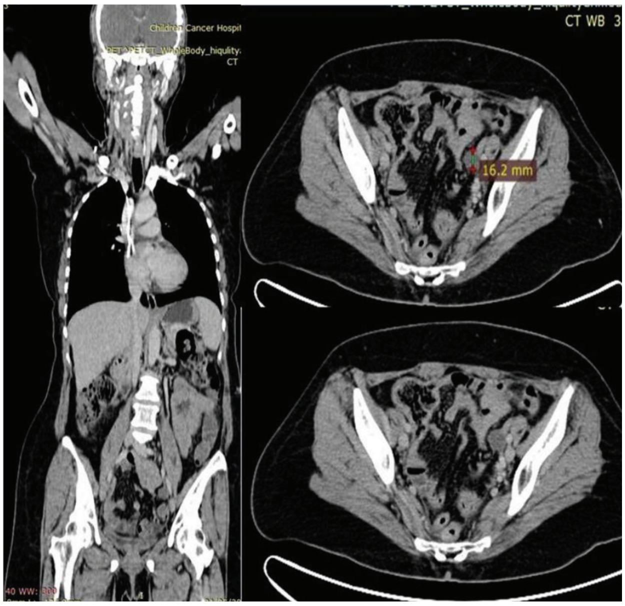

Figure 5. Left iliac lymphadenopathy with short axis diameter of 16 mm.

Figure 6. Para-aortic lymphadenopathy with short axis diameter of 9 mm.

nodes in the abdomen ranged from 6 to 10 mm.[5,19] Other authors reported that the upper limits for a normal retrocrural node was 6 mm, a retroperitoneal node was 10 mm[6] and pelvic nodes were 8 to 10 mm.[6,20] Fukuda et al.[10] reported a sensitivity of 85.7% and a specificity of 77.8% on a per patient basis.

Moreover, other authors used a threshold of 5 mm as the short-axis diameter for metastasis (from a variety of pelvic tumors) recording 78% sensitivity and 97% specificity, respectively.[1]

On the other hand, a smaller range of diameters was employed in rectal cancer where almost 60% of the involved lymph nodes were smaller than 5 mm in diameter.[21] In another study, Urievetal et al.[14] reported 8 involved lymph nodes that ranged from 1.5 mm to 2.9 mm in diameter, with 4 metastatic nodes that had diameters from 3.0 mm to 5 mm. The mean size of the involved lymph nodes was 2.9 mm.[14]

On the other hand, Hilton et al.[22] reported that lymph nodes larger than or equal to 4 mm, especially those located anterior to the mid portion of the aorta, should raise a suspicion of metastases in patients with testicular nonseminomatous germ cell cancer.[22]

These studies highlight both the limitations of using size criteria alone for nodal staging and the importance of knowledge of regional nodal drainage pathways.[1] Macdonald et al. explored level VI node size as a predictor of malignancy in papillary thyroid cancer. They concluded that the decision to perform a level VI neck dissection could not be based on preoperative size.[23]

The debate remains regarding other tumor locations in the body. No clear correlation between lymph node size and metastatic involvement is seen. Vogel et al.[24] measured the diameter of hilar and mediastinal lymph nodes in bronchial cancer. They found no sufficient correlation between the diameter of the lymph node and infiltration by cancer cells.[24] In addition, size criteria might be different for different cancers[16] even that para-aortic lymph nodes were often involved at initial presentation rather than pelvic lymph nodes.[25]

Several advantages of the study were noted. We performed correlation of both morphological data from MDCT with its multiplanar capabilities combined with the functional metabolic data from PET to characterize the lymphadenopathy seen in our cases.

Disadvantages of our study included lack of histopathological confirmation of positive studies, the cost effectiveness of PET/CT versus MDCT, as an economic disadvantage, and thus, the limited number of cases.

The current study had a few limitations, such as the small number of cases that depended only on size in terms of short axis diameter with no recording of the ratio of long to short axis or other morphological data.

The high percentage of metastatic lymphadenopathy indicates the importance of lymph nodes as a route for metastasis in ovarian cancer patients. Radiologists have to clarify them in detail, therefore the employment of functional imaging is essential for their characterization.

It is essential to understand the pathway of tumor spread which allows close observation of the most likely sites of nodal involvement. To overcome the limited ability of conventional CT and MR imaging in the detection of metastases in normal or minimally enlarged lymph nodes, the combination with metabolic data such as FDG PET/CT or functional data of MRI diffusion can guide the process of characterization.

Conflict of Interest

No conflict of interest is declared.

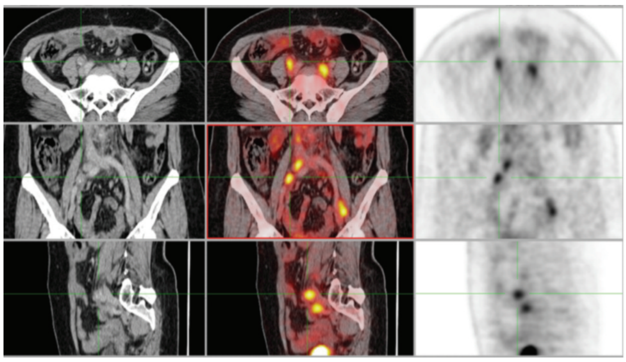

Figure 8. 51-year-old patient. Contrast enhanced (CE)-CT detected multiple abdominal, right and left internal iliac nodes, left external iliac and left inguinal nodes (range: 11-14 mm). Most of these nodes showed active FDG uptake on PET images (SUV_{max} range: 4.2-10.9).

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