Size of Abdominal Lymphadenopathy in ovarian cancer; does it Matter?

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Aims and objectives

Introduction

The diagnosis of lymphatic metastases from pelvic tumor represents an important challenge of modern imaging. Nodal metastasis is an important mechanism of tumor dissemination (in addition to other modes of distant metastasis). Lymphatic Metastasis has an important impact on the stage of pelvic tumor, and accordingly the mode of treatment and their prognosis[1 on page ]

Ovarian cancer may spread by direct extension to other pelvic organs and surrounding soft tissues where the uterus, fallopian tubes, and contralateral adnexa are most commonly involved and less likely the rectosigmoid colon, bladder, and pelvic lateral walls also can be directly invaded. Distant metastases may occur by intraperitoneal seeding, lymphatic transmission, or hematogenous dissemination of cancer cells.[2 on page ]

Where the 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 paraaortic and paracaval nodes at the level of the kidney; 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 on page ]

In lymph node metastases, in contrast to other organs metastases , the metastatic lesion itself is usually not visualized at cross sectional imaging where authors noted that preoperative lymph node staging rely on the fact that that malignant lymph nodes were larger than benign ones. The 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). As that the short axis diameter is considered the best predictor of the presence of metastatic disease [4-9 on page ]

The diagnostic accuracy of cross sectional imaging (CT and MRI) for nodal staging of cancers in the abdomen and pelvis varies widely in the literature. For pelvic malignancies, the accuracy of CT and MR imaging is quite similar where The reported sensitivities range from 40 to 87% and the specificities from 64 to 100% was achieved for nodal staging[8 on page , 10-13 on page ]. In addition to nodal enlargement other criteria as necrosis or clustering of nodes along the main pathway of lymphatic drainage may be indicative of metastatic involvement [14 on page ]
Lymph nodes measuring more than 1 cm in the short axis diameter were considered malignant. However, the size threshold varies with anatomic site and underlying tumor type; as in rectal cancer, lymph nodes more than 5mm are considered as pathological. [7 on page ]

The Potential pitfalls in nodal assessment on CT Using multi-planar reformats makes errors in interpretation less likely and understanding of the pathway of tumor spread allows better observation of the most likely sites of nodal involvement.[7 on page ]

The preoperative identification of abnormal lymph nodes is helpful for planning retroperitoneal lymph node dissection where the presences of enlarged suprarenal lymph nodes, especially at the level of the celiac axis and porta-hepatis, is frequently an indication for neoadjuvant chemotherapy, thus it has to be reported carefully.[1 on page ]

Different studies are contradictory. Regarding the correlation between nodal size and the likelihood of the metastasis in lymph node [15 on page ]

Newer imaging techniques such as positron emission tomography (PET) and PET-computed tomography (CT) are utilized with increasing frequency to diagnose nodal involvement.[7 on page ]

Where PET performed with fluoro-deoxy-D-glucose (FDG) has proved valuable in providing important tumor-related qualitative and quantitative metabolic information that is essential for diagnosis and follow-up. PET-CT is a unique combination of the cross-sectional anatomic information provided by CT and the metabolic information provided by PET, which are acquired during a single examination and fused. The uptake of FDG is used to discriminate between benign and malignant nodes. PETCT can detect malignancy in non-enlarged nodes, which can lead to a change in patient management. [16 on page ]

However, there are some potential pitfalls using PETCT for nodal staging. These include (a) nodes smaller than 1 cm may be beyond the ability of the PET camera to detect the tracer activity; (b) tumors with low FDG metabolism can lead to false-negative results; (c) inflammatory processes may cause false-positive findings.[7 on page ]

Some tumors are FDG negative and they can be examined by other tracers, such as [11C]acetate is utilized in prostatic cancer.[7 on page ]

Still 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 on page ]
Despite the multiple attempts to provide criteria depending upon morphologic and size to differentiate benign from malignant lymph nodes on cross-sectional imaging studies, none of these alone has demonstrated sufficient diagnostic accuracy because of the substantial overlap of the imaging findings [10 on page , 12 on page , 17 on page , 18 on page ]. Given the limited accuracy of any of these features considered alone, it seems essential to use a combination of morphology, shape, size, and internal architecture criteria together.

Our aim in this research was to reach a reliable cutoff point for lymphadenopathy size to determine it is significant to have a metastatic likelihood or not in patients with ovarian cancer.
Methods and materials

Normal 0 false false false EN-US X-NONE AR-SA

Patient population:

73 PET/CT scans of 52 female patients with pathologically proved ovarian carcinoma treated with cytoreductive surgery followed by chemotherapy, underwent PET/CT examination for diagnosis, post-treatment surveillance "detection of recurrent disease" or assessment of therapy response to residual/recurrent disease.

Serum tumor markers and other recent imaging results also included in the assessment when available.

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

**The inclusion criteria:** patients with pathologically proven ovarian carcinoma who were referred for post-treatment surveillance "detection of residual disease or recurrence" or assessment of therapy response.

**The exclusion criteria:** 1) Patients known to have another malignant disease 2) Uncontrolled diabetes 3) known allergy to contrast media or 4) severely ill patients. 5) patients with raised renal chemistry

The study was approved by the Institutional Review Board, and a written informed consent were obtained.

**PET/CT Imaging Protocol**

The patients were instructed to fast for at least 6 hours and their blood glucose level was measured at the time of the tracer injection and should be below 200 mg/dl.

A dose of 0.1-0.17 MBq/Kg of 18F-FDG was injected intravenously adjusted according to patient's weight. For the optimal delineation of bowel structures, 400-600 ml of diluted mannitol solution was administered 1 hour before CT imaging.

1 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 and was used for attenuation correction. Then 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 CE-CT (contrast enhanced CT) was acquired using 120 kV, 300 mAs, and a 512 x 512 matrix size using a non-ionic contrast media with concentration 300-350 mg of iodine equivalent.
The images were transferred to the viewing stations for reviewing in axial, coronal, and sagittal planes and in a maximum-intensity-projection (MIP) three-dimensional cine mode using the manufacturer's review station.

**Data interpretation:**

All studies were stripped of patient names.

The findings of CE-MDCT were interpreted by two experienced radiologist unaware of PET/CT findings with knowledge of aim of the study. At least 2 experienced nuclear medicine physicians who were unaware of CE-CT findings examined PET images, evaluating localization and characterization and compared them to co-registered PET/CT images.

Visualized lymph nodes are recorded by their anatomical sites and reviewed in axial, coronal and sagittal planes, measurements were performed in 2 perpendicular planes, the short axis diameter (is the perpendicular measure on the long axis diameter ) is recorded (fig1)

Any foci of FDG uptake that was increased relative to the back-ground and not located in areas of physiological uptake were considered to be positive on PET/CT. Maximum standardized uptake values (SUV max) of lesions were calculated on PET/CT fusion images.

Diagnostic accuracy was determined on a patient level and a region level.

- Statistical analysis:

The collected data were verified and coded by the researchers. Data entry file was designed by using Excel program. After this, the files were converted to the SPSS program version 16 and defining the variables was done. Analysis of data was done using SPSS program version 16. Statistical methods were applied including many descriptive statistics. A significant p value was considered when it less than 0.05.
**Fig. 1:** Fig (1) : measurements of lymphadenopathy, where 1(a) schematic diagram of lymph node measurements as the dotted line [in red] represents long axis diameter while the solid line [in black] represents short axis diameter, 1(b) shows para-aortic lymph node with short axis diameter 7 mm where 1(c) shows right inguinal lymph node with short axis diameter 11 mm

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Results

Of the 73 scans reviewed 47 scans (38 patients) showed significant lymph node metastases with percentage of 64% of total number of cases (fig. 2).

Regarding the high percentage of metastatic lymphadenopathy (more than 60% of scans) indicates the importance of lymph node as a route of metastasis in ovarian cancer patients and that radiologist had to clarify them in details, the employment of functional imaging is essential in their characterization.

The groups of metastatic lymphadenopathy were seen by MDCT as follows (table 1)

<table>
<thead>
<tr>
<th>Lymph node group</th>
<th>Number of cases with significant lymphadenopathy</th>
<th>Range of short axis diameter in mm</th>
<th>Mean short axis diameter</th>
<th>Cut-off value in mm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aortic</td>
<td>6</td>
<td>5-14</td>
<td>10</td>
<td>===</td>
<td>====</td>
</tr>
<tr>
<td>Right external iliac</td>
<td>8</td>
<td>5-25</td>
<td>10.29</td>
<td>5.5</td>
<td>0.113</td>
</tr>
<tr>
<td>Left External iliac</td>
<td>8</td>
<td>6-14</td>
<td>10.29</td>
<td>5.5</td>
<td>0.113</td>
</tr>
<tr>
<td>Right internal iliac</td>
<td>7</td>
<td>5-13</td>
<td>6.5</td>
<td>6</td>
<td>0.302</td>
</tr>
<tr>
<td>Left internal iliac</td>
<td>9</td>
<td>5-17</td>
<td>6.4</td>
<td>6</td>
<td>0.302</td>
</tr>
<tr>
<td>Right inguinal</td>
<td>15</td>
<td>6-18</td>
<td>11</td>
<td>6.5</td>
<td>0.214</td>
</tr>
<tr>
<td>Left inguinal</td>
<td>25</td>
<td>5-20</td>
<td>11</td>
<td>6.5</td>
<td>0.214</td>
</tr>
</tbody>
</table>

NB: more than one lymph node group may be detected in the same scan

*Table (1): clarification the abdominopelvic lymphadenopathy size criteria among the study population by MDCT.*

The groups of metastatic lymphadenopathy were characterized by PET as follows (table 2)
<table>
<thead>
<tr>
<th>Lymph node group</th>
<th>Number of cases with Metastatic lymphadenopathy detected by PET</th>
<th>Mean SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aortic</td>
<td>9</td>
<td>5.3-13.8</td>
</tr>
<tr>
<td>Right external iliac</td>
<td>4</td>
<td>3-11</td>
</tr>
<tr>
<td>Left external iliac</td>
<td>7</td>
<td>2.7-13.8</td>
</tr>
<tr>
<td>Right internal iliac</td>
<td>6</td>
<td>2.7-13</td>
</tr>
<tr>
<td>Left internal iliac</td>
<td>5</td>
<td>4.5-9.1</td>
</tr>
<tr>
<td>Right inguinal</td>
<td>7</td>
<td>5.3-13.1</td>
</tr>
<tr>
<td>Left inguinal</td>
<td>9</td>
<td>2.9-14</td>
</tr>
</tbody>
</table>

NB. More than one lymph node group may be detected in the same scan

*Table (2): characterization of the abdomino-pelvic metastatic lymphadenopathy size criteria among the study population by PET*

The column chart (fig 3) shows the high incidence of non-specific inguinal lymphadenopathy in comparison to other groups.

The cut-off value for para-aortic LNs could not be accurately calculated while the cutoff point of significant short axis diameter of external iliac LN is 5.5 mm were ranging from 5 to 25 mm (mean 10.29), while that of internal iliac lymph node is 6 mm were ranging from 5 to 17 mm (mean 11 mm) and that of inguinal lymph node is 6.5 mm were ranging from 5 to 21 mm (mean 11 mm) and these results show no significant statistical values where p value was 0.113, 0.302 and 0.214 respectively.

Regarding the cutoff value of the short axis diameter of metastatic lymphadenopathy, No significant statistical correlation between pelviabdominal lymph node size and likelihood of malignancy in patients with ovarian cancer. With no reliable cut off value could be employed.

Regarding the combined sensitivity was 70% with low specificity 36% on using a threshold of 7.5mm short axis diameter for metastasis.

Sample of cases in the attached case figures
Fig. 1: Fig (1) :measurements of lymphadenopathy ,where 1(a) schematic diagram of lymph node measurements as the dotted line [in red] represents long axis diameter while the solid line [in black] represents short axis diameter , 1(b) shows para-aortic lymph node with short axis diameter 7 mm where 1(c) shows right inguinal lymph node with short axis diameter 11 mm

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Fig. 2: Pie chart showing percentage of scans with metastatic lymphadenopathy among study population

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Fig. 3: chart showing different lymphadenopathy groups among study population

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**Fig. 4:** Case 1: 52-year-old female patient with chemotherapy treated cancer ovary metastatic to liver and bones, currently she is presenting for assessment of response to therapy. Last PET/CT was positive for multiple bone lesions and single hepatic focal lesion. CE-CT detected Rt internal iliac LN 11 mm and Lt inguinal LN 5mm, both showed no active FDG avid tumor tissue and were negative on PET images. Their non malignant nature was confirmed on follow up PET/ CT scan 7 months later

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**Fig. 5:** Case (2): 54 years old, pan-abdominal hystectomy+ bilateral salpingo-oophorectomy+ splenectomy about 1.5 years, CTH ended about 1 year, then presented with intestinal obstruction and ascitis, CA-125 = 7 . CE-CT detected Left internal iliac LN (7 mm), Left iliac LN (11mm), Right iliac LN (9 mm), Right internal iliac (8 mm) and Left inguinal LN (10mm), all with no significant FDG fixation indicating their benign nature

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Fig. 6: case(3): 51 years old, underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy followed by chemotherapy (6 cycles ended 4 months before PET/CT) CA-125 950, CT 33 days before the scan was normal. Pathology: papillary serous adenocarcinoma. CE-CT detected multiple abdominal, Rt and Lt internal iliac, Lt external iliac and Lt inguinal (size ranges from 11-14 mm), most of these nodes showed active FDG uptake on PET images (SUVmax range 4.2 to 10.9).

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Fig. 7: follow up of case3

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Conclusion

Lymph nodes measuring more than 1 cm in the short axis diameter are used to be considered malignant. However, the size threshold varies with anatomic site and underlying tumor type; e.g. in rectal cancer, lymph nodes larger than 5mm are regarded as pathological. In addition, size criteria may be different for different cancers. The 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.

Conventional CT and MR imaging are limited by their ability to detect metastases in normal or minimally enlarged lymph nodes. Relying on size as a sole criterion for the diagnosis of nodal metastases represent a fundamental problem.

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

In our study we tried to calculate a cut-off point for each lymph node group as we agree with the fact that depending on size criteria is difficult as there is wide variation in size of non-metastatic lymph nodes, which can substantially overlap with the size of metastatic nodes.

Koh et al recommend 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 is considered "suspicious." In our study we employed a size threshold of 7.5 mm in short-axis diameter; we had 70% sensitivity.

While Dorfman, et al and Magnusson reported, the upper limit of the short axis diameter of normal nodes in the abdomen varies from 6 to 10mm. While other authors pointed that the upper limit of a normal retrocrural node is 6 mm, a retroperitoneal node is 10mm and 8 to 10mm for nodes in the pelvis.

Fukuda et al demonstrated a sensitivity and specificity, respectively, of 85.7% and 77.8% on a per-patient basis.

Moreover, other authors used a threshold of 5-mm short-axis diameter for metastasis (from a variety of pelvic tumors) receiving 78% and 97%, respectively.
On the other hand, smaller range of diameters is employed in rectal cancer where almost 60% of the involved lymph nodes are smaller than 5 mm in diameter [17 on page ] while in another study it was reported that there were 8 involved lymph nodes from 1.5mm to 2.9mm in diameter. And 4 metastatic nodes had diameter from 3.0mm to 5 mm. The mean size of involved lymph nodes was 2.9mm[15 on page ]

On the other hand, lymph nodes measuring larger than or equal to 4 mm, especially those located anterior to the midpoint of the aorta, should raise a suspicion of metastases in patients with testicular non-seminomatous germ cell cancer[18 on page ]

In our study; we had a high non-specific incidence of inguinal lymphadenopathy this is in agreement that a great normal size of benign inguinal lymph nodes is also remarkably variable, measuring up to 15 mm in short axis diameter [19 on page , 22 on page ] . In patients with tumors that do not usually drain to inguinal nodes, this normal size range is an important consideration. However, in evaluation of inguinal lymph nodes in patients with tumors for which these nodes are an expected regional site of disease, many metastatic lymph nodes will be smaller than this "normal" size range. For example, in a study assessing inguinal nodal metastasis from vulvar cancer with MR imaging,[27], Bipat et al [4 on page ] also reported using a size cut-off of 8-mm (short-axis diameter) and found a per-groin sensitivity of only 52% for metastatic nodal involvement with a mean short-axis diameter of metastatic inguinal nodes of approximately 10 mm.

All these studies highlights both the limitations of using size criteria alone for nodal staging and the importance of knowledge of regional nodal drainage pathways. [1 on page ] even that Macdonald et al. explored the 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 a preoperative size .[6 on page ]

Also the debate is still going regarding the other tumoral locations in the body, no clear correlation of lymph node size and metastatic involvement is seen. For example, Vogel et al. 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 their infiltration by cancer cells[23 on page ] In addition, size criteria may be different for different cancers [19 on page ] even that para-aortic lymph nodes are often involved at initial presentation than pelvic lymph nodes [22 on page ]. Radiologists should be particularly alert for lymphadenopathy in suprarenal sites such as porta hepatitis, portacaval, celiac axis, and cardiophrenic lymph nodes.

Several advantages of the study were noted as we performed correlation of both morphological data from MDCT with its multiplanar capabilities in combination with the functional metabolic data from PET in characterization of the lymphadenopathy seen in our cases
The disadvantages our study included lack of histopathological confirmation of positive studies, tumor markers were not available in some cases, the cost effectiveness of PET CT versus MDCT is another economic disadvantage and thus the limited number of cases.

Our study showed few limitations among them small number of cases (inspite that we have more than 60% of the studies with LN metastases), dependence only on size in terms of short axis diameter with no recording of ratio of long to short axis or other morphological data.

We recommend that: Understanding the pathway of tumor spread is essential allowing close observation of the most likely sites of nodal involvement. To overcome the limited ability of conventional CT and MR imaging to detect metastases in normal or minimally enlarged lymph nodes, combination with metabolic data like FDG PETCT or functional data of MRI diffusion will guide the process of characterization.
Personal information

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