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Research Article

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# Diagnostic Value of Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and Positron Emission Tomography (PET) in the Detection of Lymph Node Metastases in Gynaecologic Cancers

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## Abstract

***Background:*** *A factor that affects the staging of gynaecological cancers is the status of adenopathy's and imaging tests are a fundamental part of staging.*

***Primary Objective:*** *To assess the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in the detection of pathological lymphadenopathies in gynaecological cancers of magnetic resonance imaging (MRI), computerized axial tomography (CAT) and positrons emission tomography (PET).*

***Study Hypothesis:*** *Imaging tests are not as valid as lymphadenectomy for the diagnosis of pathological lymphadenopathies.*

***Trial Design:*** *Retrospective study performed in the gynaecological oncology unit of a tertiary hospital.*

***Major Inclusion/Exclusion Criteria:*** *Patients diagnosed with genital cancer (endometrium, ovary or cervix) in the period between January 1, 2014 and December 31, 2018, who meet the following inclusion criteria: (i) have requested a diagnostic test of image (RNM, CT or PET-CT) prior to undergoing surgery; (ii) have undergone surgery for the treatment of cancer and (iii) have undergone lymphadenectomy, pelvic and / or para-aortic, during surgery.*

***Primary Endpoint:*** *Correlation between the imaging tests and the anatomopathological result of the lymph node biopsies.*

***Sample Size:*** *219 patients who underwent pelvic, para-aortic lymphadenectomy or both due to cancer of the endometrium, ovary or cervix, and at least one imaging test prior to surgery.*

***Results:*** *In our study, PET presents the highest sensitivity (42%) of the diagnostic tests evaluated, the TAC the highest specificity (95%) and the highest PPV (77%) and the MRI the highest NPV (76%).*

***Conclusions:*** *The diagnostic value of imaging tests in the detection of lymph node metastases in gynaecological cancers is limited.*

**Keywords:** Gynaecological cancer; MRI; CT scan; PET; Accuracy; Sensibility; Specificity; Positive Predictive Value; Negative Predictive Value

## Introduction

Gynaecological tumours (cancer of the endometrium, cancer of the cervix and ovarian cancer) are the third most frequent neoplasm

in women behind breast cancer and colorectal carcinoma [1]. The treatment of these tumours generally includes surgery with lymphadenectomy, pelvic and / or para-aortic and its associated morbidity [2].

The role of lymphadenectomy has been one of the major controversies of oncological gynaecology for many years and the current trend is to limit the number of lymphadenectomies in patients with gynaecological cancers. Thus, in ovarian cancer the results of the LION study support to avoid lymphadenectomy in some cases of ovarian cancer; in endometrial cancer, selective sentinel lymph node biopsy is advocated and in cervical cancer, the para-aortic lymphadenectomy has been limited to the territory of the inferior mesenteric artery [3-5].

The decrease in the rate of lymphadenectomies must be accompanied by an adequate rate of detection of pathological nodes by complementary imaging tests performed during the study of a gynaecological neoplasm to avoid undertreated patients due to imaging tests are not sufficiently precise.

Unfortunately, conventional imaging methods such as magnetic resonance imaging (MRI) and computed tomography (CT) are not accurate enough to detect pelvic and / or para-aortic nodes in endometrial, ovarian, and cervical cancers since it is a large group of neoplasms, histology, degree of malignancy and variable age of presentation in which adenopathies act in a difficult way to foresee [6,7].

For these reasons, the introduction into the clinical practice of a non-invasive test to determine lymph node involvement is essential to make surgical decisions. Positron emission tomography using the radiolabelled glucose analogue 2- [18F] -fluoro-2-deoxy-D-glucose combined with the CT (18-F-FDG-PET / CT) combines the functional diagnosis based on the increase in glucose metabolism of malignant cells, with the precise anatomic location provided by the CT [8].

Some clinical practice guidelines consider the possibility of omitting lymphadenectomy when no pathological adenopathies are detected in the imaging tests [9].

The aim of our study was to evaluate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) in the detection of pathological lymph nodes in gynaecological cancers of the MRI, CT and PET-CT, to assess whether Imaging tests can replace lymphadenectomy in the staging of gynaecologic cancers.

## Methods

This is a retrospective study carried out in the gynaecological oncology unit of a tertiary hospital. All patients diagnosed with genital cancer (endometrium, ovary or cervix) in the period between January 1, 2014 and December 31, 2018, who met the following inclusion criteria were included in the study: (i) having a diagnostic imaging test (RNM, TAC or PET-CT) prior to undergoing surgery; (ii) have undergone surgery for the treatment of cancer; and (iii) have undergone pelvic and / or para-aortic lymphadenectomy, during surgery. The results of the surgical staging were compared with the findings of the preoperative imaging tests.

In our hospital, we generally perform pelvic MRI in patients with endometrial cancer, thoraco-abdominopelvic CT in patients with ovarian cancer and pelvic MRI and PET-CT in patients with cervical cancer. In 2016 we started a clinical trial (Esperanto Study) to validate the selective biopsy of the sentinel lymph node in cases of endometrial cancer and, from that moment and according to the trial protocol, we performed, in patients with intermediate or high-risk endometrial cancer, a PET-CT, in addition to the pelvic MRI.

The MRI is performed using a 1.5 T equipment with TSE T2, T1, DWI-ADC sequences (b values: 50, 400 and 800) and dynamic gadolinium study, the CT with a Siemens Somatom Definition AS instrument and the PET- CT with a PET-TC Gemini TF 16 from Philips. The radiological criteria used to classify lymph nodes in pathological or non-pathological were: adenopathies with a diameter greater than 10 mm in its short axis, in the case of para-aortic lymph nodes and greater than 8 mm in the case of pelvic nodes.

The main criterion of adenopathy positivity in PET is by visual analysis of the images, comparing vascular activity with that of the aorta and / or adjacent vessels and with liver activity. We consider the value of SUV (standardised uptake value) greater than 2.5 as pathological.

Patients underwent lymphadenectomy following the recommendations of the guidelines of the Spanish Society of Gynaecology and Obstetrics (SEGO) [9] and the European Society of Ginaecologycal Oncology (ESGO) [10]. In general, in cases of endometrial cancer and cancer of the cervix, lymphadenectomies are performed laparoscopically, either to the level of the left renal vein in cases where we perform para-aortic lymphadenectomy, or of the pelvic spaces of the iliac vessels and obturator fossa in the case of pelvic lymphadenectomy. In cases of ovarian cancer, except in the initial stages in which we perform a laparoscopic approach, lymphadenectomy is performed in the course of cytoreductive surgery by laparotomy.

The anatomopathological study of lymph nodes in all gynaecological tumours is carried out by dissecting all identified lymph nodes and their subsequent microscopic examination following the usual histological protocol. In the case of the sentinel lymph nodes of patients with endometrial cancer included in the Esperanto clinical trial previously mentioned, a specific protocol is carried out that includes the conventional study, with fixation in formaldehyde and inclusion in paraffin of a central section of 1 mm. of thickness of the ganglion, for subsequent serial study (3 levels at 0.2 mm intervals with haematoxylin-eosin staining (H & E) and cytokeratin 19), as molecular with the One Step Nucleic Acid Amplification (OSNA) method of the rest of the tissue ganglion. In the case of the sentinel lymph nodes of patients with cervical cancer, a conventional sentinel lymph node study was performed by serial study (3 levels at 0.2 mm intervals with H & E staining and wide-spectrum cytokeratin.

The lymph node metastases were classified according to their size following the established nomenclature for lymph node metastases in breast cancer. Thus, lymph node metastases in which the tumour cells occupy a size greater than 2 mm are classified as “macrometastasis”; “micrometastases” are defined as those in which the tumour size is between 0.2 and 2 mm; and metastases in which the size is less than 0.2 mm are defined as “isolated tumour cells”. In the ultrastaging study, the result is established based on the number of

copies of CK19 mRNA / µL obtained after processing each of the ganglia by OSNA method. The cut-off levels used for results are: macrometastasis (OSNA ++) is defined as > 5 x 103 mRNA copies CK19 / µl; micrometastasis (OSNA +) as 2.5 x 102 to 5 x 103 copies / µl; and isolated tumour cells (OSNA-ITC) as 1.6 x 102 to 2.5 x 102 copies / µl. When reporting each case, the number of copies / µl is specified in addition to the category. For our study, we considered as positive those ganglia with macro and micrometastases, and those with isolated tumour cells were not included.

The objective of the study was to evaluate the sensitivity (S), specificity (E), positive predictive value (PPV) and negative predictive value (NPV)[11] of the different diagnostic techniques per image usually used in different gynaecological tumours. For this, the results of the diagnostic imaging tests were compared with the final results of the anatomopathological analysis of the lymph node samples.

For the collection of data, a specific Excel sheet was designed in which information was collected on the type of tumour, age of the patient, histological type of tumour, pre- and postsurgical stage (in cases of endometrial cancer and cancer of the cervix), number of total lymph nodes excised and number of lymph nodes affected by metastasis after the anatomo-pathological study of them. Patient data was handled anonymously.

According with Spanish rules for investigation, as it is a retrospective, anonymous study, it is not necessary to collect the signed consent of the included patients and an approbation by an Ethic Committee is not necessary.

For the calculation of the S, E, VPP and VPN, tables 2 x2 proposed by Altman and Bland have been used [12].

## Results

During the study period, data were collected from 219 patients who underwent pelvic, para-aortic lymphadenectomy or both due to endometrial, ovarian or cervical cancer and at least one imaging test prior to surgery. Of the patients included, 115 (52.5%) were operated for endometrial cancer, 81 (37%) for having an ovarian cancer and 23 (10.5%) for having cervical cancer. Table 1 shows the characteristics of the patients included in the study. These 219 patients underwent 317 diagnostic imaging tests prior to surgery. 143 MRI (65.3% of patients), 98 CT (44.7% of patients) and 76 PET-CT (34.7% of patients) were performed. In 57 of the 219 patients, only MRI (26%) was performed, at 66 only one CT (30.1%) and at 4 (1.8%), only one PET-CT scan. Twenty patients (9.1%) had an MRI and a CT scan, 60 (27.4%) had an MRI and one PET-CT scan, 6 patients (2.7%) had a CT scan and a PET-CT scan. and another 6 patients (2.7%) underwent MRI, CT and PET-CT. Table 2 shows the imaging tests performed on each type of tumour. In 68 of the 219 cases (31%) the final anatomopathological diagnosis reported nodal metastases: 33 in the 115 endometrial cancers (28.7%); 26 in the 81 cases of ovarian cancer (32%) and 9 in the 23 cases of cervical cancer (39.1%). A total of 3644 lymph nodes were extracted and analysed, of which 193 (5.3%) were positive.

**Table 1: Characteristics of patients included in the study**

| Mean age | Range | |
|---|---|---|
| 60,03 years | 31-83 years | |
| Type of tumour | N | Patients with positive nodes (N & %) |
| Endometrial | | 33 (28,7) |
| Ovarian | | 26 (32,1) |
| Cervical | | 2 (8,7) |
| FIGO stage | N & % | N & % |
| Endometrial cancer* | | |
| I | 93 (80,9) | 21 (22,6) |
| II | 5 (4,3) | 2 (40) |
| III | 13 (11,3) | 7 (53,9) |
| IV | 4 (3,5) | 3(75) |
| Ovarian cancer** | | |
| I | 20 (24,7) | 0 (0) |
| II | 3 (3,7) | 0 (0) |
| III | 52 (64,2) | 25 (40,1) |
| IV | 6 (7,4) | 1 (16,7) |
| Cervical cancer* | | |
| I | 11 (47,8) | 0 (0) |
| II | 12 (52,2) | 2 (16,7) |

* Pre-surgical stage; ** Post-surgical stage

**Table 2: Type of imaging test performed based on the gynecological tumor**

| Imaging test / Tumour | MRI | CT | PET |
|---|---|---|---|
| Endometrial | 103/115 (89,5%) | 20/115 (17,4%) | 55/115 (47,8%) |
| Ovarian | 18/81 (22,2% | 77/81 (95%) | 3/81 (3,7%) |
| Cervical | 22/23 (95,6%) | 1/23 (4,3%) | 18/23 (78,2%) |
| Total | 143 | 98 | 76 |

**Table 3. Sensitivity, specificity, positive predictive value and negative predictive value for each of the diagnostic tests and the total of gynaecological tumours**

| Imaging test | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| **MRI** | | | | |
| All cancers | 31 | 91 | 59 | 76 |
| Endometrial cancer | 38 | 89 | 58 | 79 |
| Ovarian cancer | 20 | 92 | 50 | 75 |
| Cervical cancer | 13 | 100 | 100 | 67 |
| **CT** | | | | |
| All cancers | 29 | 95 | 77 | 71 |
| Endometrial cancer | 33 | 91 | 75 | 63 |
| Ovarian cancer | 24 | 96 | 75 | 72 |
| Cervical cancer | NA | NA | NA | NA |
| **PET-CT** | | | | |

| | | | | |
|---|---|---|---|---|
| All cancers | 42 | 90 | 69 | 75 |
| Endometrial cancer | 47 | 89 | 67 | 79 |
| Ovarian cancer | NA | NA | NA | NA |
| Cervical cancer | 25 | 100 | 100 | 63 |

MRI: Magnetic Resonance Imaging; CT: Computerized Tomography; PET: Positrons Emission Tomography; PPV: Positive Predictive value; NPV: Negative Predictive Value

## Discussion

In our study, PET presents the highest sensitivity (42%) of the diagnostic tests evaluated, the CT the highest specificity (95%) and the highest PPV (77%) and the MRI the highest NPV (76%). If we analyse the imaging tests depending on the type of gynaecological tumour, our results indicate that in cases of endometrial cancer the test that shows a greater sensitivity for the diagnosis of lymph node metastases is PET-CT (47%). In ovarian cancer the most sensitive test is the CT scan (24%) and in cervical cancer the PET-CT scan (25%). Taking into account that, in our centre, the interpretation of the images of the different diagnostic tests is performed by a team of radiologists and nuclear physicians trained in the interpretation of images related to gynaecological neoplasms, which to some extent eliminates the bias of the observer, our results probably reveal the inherent limitations of each image test.

Overall, our results indicate that imaging tests have low sensitivity and acceptable specificity in the diagnosis of pathological lymph nodes, but we must not forget that they are highly sensitive to determine the degree of myometrial infiltration, in endometrial cancers, the presence of peritoneal carcinomatosis or peritoneal implants, in ovarian cancer, or for the detection of distant metastasis and parametrial infiltration in cervical cancer. Therefore, the different imaging tests provide us with fundamental information for making decisions in the field of oncological gynaecology. However, it should be noted that false negative rates may compromise the survival of patients with gynaecological neoplasms, and one of the greatest limitations of these diagnostic imaging tests is their inability to detect metastatic lymph nodes smaller than 5 mm [13].

In general, it has been considered that, in endometrial cancer, MRI is useful in preoperative staging and, therefore, in treatment planning [14]. However, data from studies that have analysed the accuracy of MRI in the detection of lymph node metastases determine that MRI is less sensitive and specific than PET-CT. In the ENDOMET study, conducted in Denmark, which included 318 patients with endometrial cancer in which the results of three imaging tests were compared: PET-CT, MRI and two-dimensional ultrasound with the final anatomopathological results, the sensitivity for the detection of lymph node metastases of the PET-CT was 74% versus 59% for the RNM, the specificity of 93% v / s 93%, the PPV of 59% v / s 40% and the NPV of 91% v / s 90% [15]. In our study, the sensitivity of the MRI in endometrial cancer was 38% and the specificity was 89%.

The diagnostic value of PET-CT in patients with high or intermediate risk of endometrial cancer was evaluated in a prospective study that included 76 patients. The sensitivity of the PET-CT in the detection of lymph node metastases was 78.6%, the specificity of 98.4%, the PPV of 91.7% and the NPV of 95.3%, which places the PET-CT as the most accurate test for the presurgical determination of pathological adenopathies [16]. A systematic review and meta-analysis on the sensitivity and specificity of PET-CT in the detection of lymph node metastases in patients with endometrial cancer, which included 243 patients and 7 studies, determined that the sensitivity is 63% and the specificity 94.7% [17]. The data confirm that the absence of lymph node pathological uptake by the PET-CT in endometrial cancer does not allow us to avoid carrying out an anatomopathological study of the lymph nodes.

In a study of 159 patients diagnosed with cervical cancer in stage IB1-IIA with tumours <4 cm, the sensitivity of PET-CT in the detection of lymph node metastases was 32.1%, the specificity of 96.9%, the PPV of 69.2% and the NPV of 87% [18]. In another study with 21 patients diagnosed with cervical cancer, the rate of detection of lymph node metastases for PET was 86%, while that of the TAC was 57% [19]. Discrepancies regarding sensitivity can be interpreted in relation to the stage of the disease. The greater the spread of the neoplasm, the greater the likelihood of positive lymph nodes and the greater the ability to detect imaging tests. However, in the diagnosis of lymph node metastases in cervical cancer, PET-CT was more sensitive than MRI in a meta-analysis of 53 articles and 15,479 patients [20].

In a meta-analysis designed to determine the validity of PET-CT in the detection of peritoneal carcinomatosis in different types of gynaecological tumours, the authors found a sensitivity of 72.4% and a specificity of 96.7% [21]. If peritoneal carcinomatosis is secondary to an ovarian carcinoma, CT is more accurate than PET-CT in the detection of peritoneal implants [22]. A recent prospective study in which 93 patients diagnosed with ovarian epithelial cancer were included and in which the accuracy of vaginal and abdominal ultrasound compared to CT was evaluated, concluded that the detailed ultrasound examination of the abdominal cavity is so valid for the diagnosis of tumour extension as CT [23].

## Conclusion

According to our data and data from other similar studies, the diagnostic value of imaging tests in detecting positive lymph nodes in gynaecologic cancer is limited. Until the radiological techniques that allow reconstructions of the obtained images are incorporated into our daily clinical practice, it seems sense that in those cases in which the imaging tests do not detect pathological nodes, we perform a pathological study of the specific nodal areas of each type of tumour [24]. To avoid extensive lymphadenectomy, detection of the sentinel node can be an appropriate strategy in cases of endometrial cancer and cervical cancer [25].

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