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Original Research

Prediction of lymph node involvement in epithelial ovarian cancer by PET/CT, CT and MRI imaging

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Objective: The aim of this study is to detect retroperitoneal metastatic lymph nodes in epithelial ovarian cancer with preoperative imaging methods (MRI, CT, 18F-FDG PET/CT). *Material and method*: Patients with epithelial ovarian cancer followed by the Akdeniz University Faculty of Medicine Gynecologic Oncology Surgery Department registered in the hospital's electronic file system, who had undergone pelvic and/or paraaortic lymphadenectomy, and having undergone at least one imaging method (MRI, CT, PET/CT), were included in the study. Based on the data available, 89 patients were included in the study. Lymph node metastasis in the histopathology reports of these patients was accepted as the gold standard. The presence of lymph nodes on the imaging modalities (MRI, CT, PET/CT) was regarded as positive and was compared with the gold standard pathological lymph node metastasis. By doing so, the accuracy, specificity, sensitivity, PPV and the NPV of the imaging methods in predicting lymph node metastasis were calculated. *Findings*: Thirty-eight (42.7%) of 89 patients included in our study were at stage 3C. Based on the data, while 85 of the 89 patients included in the study obtained had undergone pelvic and paraaortic lymphadenectomy, four patients had undergone only pelvic lymphadenectomy. Of the patients, 73 had undergone a CT, 20 had undergone a PET/CT and 12 had undergone an MRI. The sensitivity, specificity, PPV, NPV and the accuracy of CT regarding all nodal involvement was 62%, 52%, 57%, 57%, and 57%, respectively. The PET/CT's values were 63%, 66%, 70%, 60% and 65%, respectively. The sensitivity, specificity, PPV, NPV and the accuracy of PET regarding paraaortic nodal involvement alone were 50%, 91%, 80%, 73% and 75%, respectively. *Conclusion*: According to the data we obtained, it is challenging to decide whether to perform systemic pelvic and paraaortic lymphadenectomy based on imaging modalities (MRI, CT, PET/CT), and hence, further investigation is needed for more accurate imaging techniques.

Keywords

PET/CT; MRI; CT; Lymphadenectomy; Ovarian cancer; Preoperative imaging

1. Introduction

While epithelial ovarian cancer is the 9th most common cancer among all cancers in western countries, it is also the 5th most common cause of death among women [1]. Nearly 70% of the patients are diagnosed at advanced stages, and the 5-year overall survival (OS) is 35–50%. Only 30% of the cases are diagnosed at early stages and have a good prognosis and an OS of 85–95% [2, 3].

The optimal treatment of early-stage ovarian cancer is based on surgery. Conventionally, the surgery includes hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal biopsies, systematic pelvic-paraaortic lymphadenectomy (SAPL), and platinum-based chemotherapy according to the risk factors [2–4].

Lymphatic spread is significant in ovarian cancer, even if the tumor is limited to the ovaries or the pelvis [5–9]. According to the meta-analysis published by Kleppe *et al.*, the rate of lymph node metastasis is 14.2% (only pelvic: 3.3%, only paraaortic: 6.7%, and both pelvic and paraaortic: 4.3%). While the risk of lymph node metastasis is relatively low in grade 1 tumors and mucinous histological types, the risk is 15–30% in undifferentiated or grade 2–3 serous histological types [10]. While SAPL is a part of the optimal debulking in advanced stage ovarian cancer with bulky pelvic and paraaortic lymph nodes [11], it gains importance in early-stage ovarian cancer as it primarily enables cancer staging and the selection of patients who are candidates for adjuvant chemotherapy [12–16].

The sensitivity of CT and MRI in detecting lymph node metastasis is similar and low for lesions with a short axis no longer than 1 cm. Tempany *et al.* [17] identified the sensitivity of CT for detecting lymph node metastasis in ovarian cancer as 40% and its specificity as 85–90%. Ricke *et al.* [18] prospectively evaluated the performance of MRI in detecting pelvic and paraaortic lymph nodes. They identified the sensitivity, specificity, positive predictive value, and negative predictive values as 64.3%, 75%, 85.7%, and 47.4%, respectively.

As for ovarian cancers, there is limited data about the role of PET/CT in showing the presence of lymph node metastasis. According to a meta-analysis of 882 patients and 18 studies obtained from the MEDLINE and EMBASE data between 1990 and 2010 published by Yuan Y. *et al.* [19, 20] in 2012, no difference was found between CT and MRI in demonstrating lymph node metastasis in ovarian cancer in the paired comparison. PET or PET/CT has a significantly higher sensitivity and OR (odds ratio) than CT and MRI imaging ($p < 0.05$). It is evident that the presence of metastatic lymph nodes is an important prognostic factor for patients with ovarian cancer and that identifying the location of the lymph node is essential for treatment selection and predicting optimal resection [19]. According to this meta-analysis, PET or PET/CT seem to be the most accurate imaging methods for detecting metastatic lymph nodes. CT and MRI performed similarly [19].

Some retrospective analyses advocate the potential survival benefit of performing systematic pelvic and paraaortic lymphadenectomy together with the tumor being removed completely macroscopically in advanced ovarian cancer. However, this has not been demonstrated in a randomized prospective study [14]. In the Lymphadenectomy in Ovarian Neoplasms (LION) study, although there was no difference in terms of overall and progression-free survival in the group with normal lymph nodes before or during the operation, in which the tumor was removed entirely macroscopically and systemic lymphadenectomy was performed, there was a higher incidence of postoperative complications [11].

Therefore, the use of non-invasive modalities for cancer staging at early and advanced stages and to identify patients with lymph node metastasis for direct lymphadenectomy is crucial to avoid the potential complications of pelvic and paraaortic lymphadenectomy. Our aim in this study was to determine the effectiveness of preoperative imaging methods (MRI, CT, 18F-FDG PET/CT) in detecting lymph node metastasis, to guide surgery, and to reduce the incidence of postoperative complications.

2. Material and methods

Patients with epithelial ovarian cancer, followed-up by the Department of Oncological Surgery at the Akdeniz University Faculty of Medicine, who were registered in the hospital's electronic file system were included in the study. Patients over 18 years of age who were diagnosed with epithelial ovarian cancer and underwent pelvic and/or paraaortic lymph node dissection at all stages and who were used at least one imaging method (MRI, CT, PET/CT) were included in the study. Patients with ovarian cancer who were not epithelial, had a second primary tumor, lymphoma, received neoadjuvant chemotherapy, and were diagnosed with biopsy by interventional radiology were excluded in the study. A total of 89 patients were included. Some of the histopathological results and radiological imaging methods of these 89 patients were evaluated in centers other than the Akdeniz University Faculty of Medicine, and the histopathological and radiological imaging reports of these patients were registered in the hospital's electronic file system. The study was evaluated by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee and was approved under the decision number 1107 dated 27 November 2019. Based on the histopathology reports in the hospital's electronic file system and the radiology reports of the imaging methods used, lymph node involvement was evaluated. The information obtained retrospectively was analyzed and interpreted. Pelvic and/or paraaortic lymph node metastasis in the histopathological evaluation report was accepted as the gold standard. Detection of lymph nodes on MRI, CT, PET/CT was regarded as a positive finding, and these lymph nodes were grouped as 1 cm and smaller, 1–2 cm, and 2 cm and larger. Positive or negative lymph nodes in imaging methods were compared with histopathological lymph node metastasis, which is the gold standard. Based on this, the accuracy, specificity, sensitivity, PPV, and the NPV of MRI, CT, PET/CT in predicting lymph node metastasis was calculated.

2.1 Statistical analysis

The statistical analysis of the data obtained from the electronic file system (MEDI-HASTA and MIA-MED) of the Akdeniz University Faculty of Medicine was carried out using the SPSS version 20 software. The findings in the histopathology reports were accepted as the gold standard. The descriptive findings for the numerical variables were presented as average, standard deviation, minimum, and maximum, and for the categorical variables, as frequency and percentage. Four-fold cross tables were used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and the accuracy percentages. For all patients, the specificity analyses specific to the pelvic and paraaortic areas were also presented. The size variable, which is the categorical data obtained from imaging methods, and the pathology result were compared using the Chi-square test. Conditions where the type-1 error margin was under 5% were interpreted as the diagnostic value of the test being significant.

3. Findings

The average age of the patients was 57.02 $\pm$ 11.9, and 10% were smokers. There was a family history of cancer in 15 (16.8%) of the patients. Thirty-eight (42.7%) of 89 patients included in our study were at stage 3C. In the histopathological evaluation of the patients, serous cancer (62%) was the most common, followed by endometrial (10%) as the second and clear cell (10%) as the third (Table 1).

Of the 89 patients, 85 had undergone pelvic and paraaortic lymphadenectomy, and four patients had undergone pelvic lymphadenectomy alone. In the surgeries of the patients, 4182 lymph nodes were excised and evaluated histopathologically. The average number of lymph nodes excised was 51 (minimum 10, maximum 118 lymph nodes).

Metastatic lymph nodes were detected in the histopathology of 50% of the group with lymph node sizes reported as 1 cm and smaller, 70% in the group reported as 1–2 cm, and 80% in the group reported as 2 cm and larger on CT. But this relationship was not statistically significant (p = 0.330) (Table 2).

In our retrospective study, we identified the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CT in detecting lymph node metastasis as 62%, 52%, 57%, 57%, and 57%, respectively. The values for detecting pelvic lymph node metastases alone were 40%,

Table 1. The clinical and demographic characteristics of the patients.

		n	Total
Age		57.02 ± 11.9 (Min = 28, Max = 85)	
Smoking		10 (11.2%)	
Family Ca history		15 (16.8%)	
Stage	I	14 (15.7%)	89 (100%)
	II	9 (10.1%)	
	III	57 (64.3%)	
	IV	9 (10.1%)	
Histology	Serous	55 (62%)	89 (100%)
	Endometrioid	9 (10%)	
	Clear	9 (10%)	
	Mucinous	5 (5.6%)	
	Mixed type	11 (12.3)	

79%, 50%, 71%, and 65%, respectively, and that for detection of paraaortic lymph nodes alone, the values were identified as 48%, 69%, 50%, 67%, and 60%, respectively. We identified the sensitivity, specificity, positive predictive value, negative predictive value and the accuracy of MRI in detecting lymph node metastasis as 75%, 37.5%, 37.5%, 75%, and 50%, respectively. The values of MRI in detecting pelvic lymph node metastases alone were 33%, 77%, 33%, 77%, and 66%, respectively and 25%, 87%, 50%, 70%, and 66%, respectively for detecting paraaortic lymph nodes alone. We identified the sensitivity, specificity, positive predictive value, negative predictive value and the accuracy of PET/CT in detecting lymph node metastases as 63%, 66%, 70%, 60%, and 65%, respectively (Table 3).

4. Discussion

Lymphatic spread is important in ovarian cancer, even if the tumor is limited to the ovaries or the pelvis [5–9]. While SAPL is a part of the optimal debulking in advanced stage ovarian cancer with bulky pelvic and paraaortic lymph nodes [11], it is important in early-stage ovarian cancer, mainly because it helps the staging of cancer and the selection of patients who are candidates for adjuvant chemotherapy [12–16]. However, SAPL is a serious procedure that is associated with serious morbidities such as lymphedema, lymphocyst, ileus, blood loss, nerve and vascular injury, blood transfusion, longer operation time and longer hospital stay [13–16]. While systemic pelvic and paraaortic lymphadenectomy (SAPL) is commonly used in the surgical treatment of advanced epithelial ovarian cancer, the evidence from randomized clinical studies supporting this procedure is limited [11]. In the Lymphadenectomy in Ovarian Neoplasms (LION) study, although there was no difference in terms of overall and progression-free survival in the group with normal lymph nodes before or during the operation, in which the tumor was removed entirely macroscopically and systemic lymphadenectomy was performed, postoperative complications were found to have a higher incidence [11]. Therefore, it is very important to use non-invasive modalities for direct lymphadenectomy, especially in advanced stage ovarian cancer, to identify patients with bulky lymph node metastasis in order to avoid potential complications of systematic pelvic and paraaortic lymphadenectomy.

Although the short axis of the lymph node being greater than 8–10 mm is generally accepted as the criterion for a positive lymph node, more than 21% of lymph nodes that are 10 mm or shorter are malignant, and more than 40% of lymph nodes larger than 10 mm are benign [21, 22]. In our study, lymph node metastasis was also observed in 50% of the lymph nodes that were 1 cm or shorter on CT. As the size of the lymph node detected by CT increased, the metastasis rate also increased. While the metastasis rate was 70% in lymph nodes between 1–2 cm, the rate was determined as 80% in lymph nodes that were 2 cm or greater. Although there was no statistical significance ($p = 0.330$), we think that there may be a direct correlation between lymph node size on CT and lymph node metastasis in histopathology. It was considered that the same association could not be established for MRI and PET due to the low number of patients (n = 5 and n = 10, respectively).

In a prospective study published by Nam EJ *et al.* [23] in 2010, histopathological values were taken as the reference standard and the sensitivity, specificity, positive and negative predictive values of MRI or CT in detecting lymph node metastases were 62.5%, 83.6%, 60%, and 85%, respectively (p values of 0.074, 0.113, 0.083, and 0.097, respectively). In our retrospective study, we identified the sensitivity, specificity, positive predictive value, negative predictive value and the accuracy of CT in detecting lymph node metastasis as 62%, 52%, 57%, 57%, and 57%, respectively. The values for detecting pelvic lymph node metastases alone were 40%, 79%, 50%, 71%, and 65%, respectively. And for the detection of paraaortic lymph nodes alone, the values were identified as 48%, 69%, 50%, 67%, and 60%, respectively. The sensitivity value of CT was found to be similar to the literature (for example: when compared to the study by Nam EJ and colleagues, 62.5% to 62%), but the specificity was lower than the other studies in the literature. The study by Nam EJ and col-

Table 2. Comparison of CT, MRI and PET/CT results with pathology results.

			Pathology			
Imaging			Positive	Negative	Total	*p* value
CT	Diameter	**≤1 cm**	12 (30.7%)	12 (30.7%)	24 (61.4%)	0.330
		1–2 cm	7 (17.9%)	3 (7.7%)	10 (25.6%)	
		≥2 cm	4 (10.2%)	1 (2.5%)	5 (12.7%)	
	Pelvic	Positive	10 (13.7%)	10 (13.7%)	20 (27.4%)	
		Negative	15 (20.5%)	38 (52.05%)	53 (62.55%)	
	Paraaortic	Positive	13 (18.8%)	13 (18.8%)	26 (37.6%)	
		Negative	14 (20.2%)	29 (42.02%)	43 (62.22%)	
	Overall	Positive	23 (31.5%)	17 (23.2%)	40 (54.7%)	
		Negative	14 (19.1%)	19 (26%)	33 (45.1%)	
PET/CT	Diameter	**≤1 cm**	1 (10%)	1 (10%)	2 (20%)	0.386
		1–2 cm	3 (30%)	0 (0.0%)	3 (30%)	
		≥2 cm	3 (30%)	2 (20%)	5 (50%)	
	Pelvic	Positive	1 (8.3%)	2 (16.6%)	3 (24.9%)	
		Negative	2 (16.6%)	7 (58.3%)	9 (75.1%)	
	Paraaortic	Positive	4 (20%)	1 (5%)	5 (25%)	
		Negative	4 (20%)	11 (55%)	15 (75%)	
	Overall	Positive	7 (35%)	3 (15%)	10 (50%)	
		Negative	4 (20%)	6 (30%)	10 (50%)	
MR	Diameter	**≤1 cm**	2 (40%)	2 (40%)	4 (80%)	0.600
		1–2 cm	1 (20%)	0 (0.0%)	1 (20%)	
	Pelvic	Positive	3 (15%)	2 (10%)	5 (25%)	
		Negative	6 (30%)	9 (45%)	15 (75%)	
	Paraaortic	Positive	1 (8.3%)	1 (8.3%)	2 (16.6%)	
		Negative	3 (25%)	7 (58.3%)	10 (100.0%)	
	Overall	Positive	3 (25%)	5 (41.6%)	8 (66.6%)	
		Negative	1 (8.3%)	3 (25%)	4 (33.3%)	

CT, Computerized Tomography; MRI, Magnetic Resonance Imaging; PET/CT, Positron Emission Tomography.

leagues was a prospective study in which CT or MR imaging was performed on 85 patients. Our study was conducted retrospectively, and some of the radiological imaging methods of the patients were evaluated in centers other than the Akdeniz University Faculty of Medicine. We believe that the fact that the evaluations were not performed in a single center by experienced individuals and that different individuals carried out the assessments in the Akdeniz University Faculty of Medicine, lowered the specificity. The low specificity made us think that the presence of lymph nodes was reported upon the slightest suspicion on the CTs evaluated in our hospital.

MR is used less than other radiological methods in ovarian cancer. Although the number of patients undergoing MRI was lower than the number of patients undergoing CT (n = 20 and n = 73), when we evaluated the MRI data, the specificity value of MRI in detecting lymph node metastases in the paraaortic area is remarkable (87%). In our study, MRI was more successful in detecting negative lymph nodes in the paraaortic area compared to CT (69%).

Kitajima *et al.* [24] took surgical and histopathological findings as the reference standard, evaluated the accuracy of 18F-FDG PET/CT in preoperative ovarian cancer staging, and compared it with CT. The results of CT and PET/CT were consistent with the pathological staging 22 of 40 (55%) and 30 of 40 (75%) patients, respectively. The authors concluded that FDG-PET/contrast-enhanced CT was a more accurate imaging modality for ovarian cancer staging and was more useful than contrast-enhanced CT in selecting patients who are candidates for treatment (although it is insufficient in demonstrating lesions smaller than 0.5 cm). The sensitivity of contrast-enhanced CT and PET/CT in detecting lymph node metastases in the pelvic and paraaortic region was 38% and 75%, 38% and 88%, respectively (p = 0.023) [23]. The study conducted by Signorelli M and colleagues in 2013 [25] was the first to evaluate the capacity of 18F-FDG PET/CT in detecting lymph node metastases in early-stage ovarian cancer. The reason for inclusion of only early-stage ovarian cancer in the study is that SAPL is considered a part of tumor debulking in advanced-stage ovarian cancer and as a mandatory subset of the staging procedure in early stages. In this prospectively planned study, the high performance of 18-FDG PET/CT was observed. Its sensitivity was determined as 83.3%, specificity as 98.2%, the positive predictive value as 91% and the negative predictive value as 96.5%. All false-negative results were associated with lesions in which metastatic deposits were smaller than 5 mm.

Table 3. Sensitivity analysis of CT, MRI and PET/CT results.

Imaging method		Sensitivity	Specificity	PPV	NPV	Accuracy
	Pelvic	40%	79%	50%	71%	65%
CT	Paraaortic	48%	69%	50%	67%	60%
	Overall	62%	52%	57%	57%	57%
	Pelvic	33%	81%	60%	60%	60%
PET/CT	Paraaortic	50%	91%	80%	73%	75%
	Overall	63%	66%	70%	60%	65%
	Pelvic	33%	77%	33%	77%	66%
MR	Paraaortic	25%	87%	50%	70%	66%
	Overall	75%	37%	37%	75%	50%

CT, Computerized Tomography; MRI, Magnetic Resonance Imaging; PET/CT, Positron Emission Tomography.

In our study, we identified the sensitivity, specificity, positive predictive value, negative predictive value and the accuracy of PET/CT as 63%, 66%, 70%, 60%, and 65%, respectively. When compared to CT (62%, 52%, 57%, 57%, and 57%), PET/CT had a higher sensitivity and specificity. However, these values are low compared to the study by Signorelli and colleagues. Although PET/CT appears to be the most important instrument in identifying patients that will benefit from systemic lymphadenectomy and in accurately detecting lymph node metastases in the study by Signorelli and colleagues, we cannot make this statement according to the data of our study. The study by Signorelli and colleagues enrolled 68 patients; all patients had undergone PET/CT before surgery, followed by systemic pelvic and paraaortic lymphadenectomy, and the PET/CT was compared to histopathology. In our study, the number of patients with PET/CT was low compared to the study in question (n = 20), and our study was conducted retrospectively by reading the reports registered in the hospital's electronic file system. The limitations we have mentioned previously for CT are also valid for PET/CT. It also includes reports evaluated by individuals with different experiences in different centers.

Furthermore, in our study, we identified the sensitivity of PET/CT in detecting pelvic lymph node metastases as 33%, and as 50% in evaluating paraaortic lymph node metastases. We think that sensitivity is higher in the paraaortic area because masses in the pelvic area make it difficult to visualize the pelvic lymph nodes, as mentioned before. Compared to the data of Kitajima *et al.* (38% pelvic and 88% paraaortic), the sensitivity of PET/CT in evaluating pelvic lymph nodes is similar. Still, the sensitivity in evaluating paraaortic lymph nodes was low (33% pelvic and 50% paraaortic) in our study. In our study, the specificity of PET/CT in identifying pelvic lymph node metastasis was 81% and 91% for paraaortic lymph node metastasis. In the study by Signorelli and colleagues, these values were determined as 99.1% and 100%, respectively. Compared to intraoperative surgical palpation, PET/CT improves the accurate detection of lymph node metastases [25]. The sensitivity and specificity of intraoperative surgical palpation are 41.6% and 85.7%, respectively.

The sensitivity and specificity of CT interestingly falling short in the assessment of retroperitoneal lymph nodes may be due to the presence of a microscopic tumor metastasis without a bulky lymph node visible on imaging of advanced ovarian cancer with positive lymph nodes in 50% of cases [26]. In the LION study [11], even when patients without lymph mode involvement were included in the preoperative radiological study, 55.7% of the patients who underwent lymphadenectomy had pathologically lymph node involvement. This clearly demonstrated the difficulty of radiological modalities in detecting lymph node involvement.

Considering the limitations of our study, it is naturally a bias in patient selection due to its retrospective nature. Small number of patients, difficulty in detecting lymphatic metastases or micrometastases smaller than 1 cm with radiological techniques, inability to definitively distinguish inflammatory and necrotic tissues from metastatic lymph nodes, and especially the presence of intra-abdominal and bladder movements for PET/CT, prevent imaging and making interpretation difficult, show other limitations of our study.

5. Conclusions

In conclusion, the sensitivities of the other two imaging methods (CT and PET/CT) except MRI, are higher in the paraaortic area. It does not appear appropriate to decide whether or not to perform systemic pelvic and paraaortic lymphadenectomy according to the statistical values of the imaging methods. More studies and perhaps a method other than imaging are required.

Author contributions

NEU, MSB and ÖB conceived and designed the study; MSB, ÖB performed the study; CK and TS analyzed the data; TS and CK contributed materials and evaluation; NEU, MSB and ÖB wrote the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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