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# The prediction of para-aortic lymph node metastasis in endometrioid adenocarcinoma of endometrium

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**The aim of this study was to assess factors associated with para-aortic lymph node metastasis in endometrioid adenocarcinoma. The data of 157 patients with endometrioid adenocancer, who underwent staging surgery, was reviewed retrospectively. A total of 23 patients (14.6%) had pelvic and 19 patients (12.1%) had para-aortic lymph node metastasis; 21% (4/19) of the patients with para-aortic lymph node involvement did not have pelvic lymph node metastasis. Para-aortic lymph node involvement was significantly more common in the presence of LVSI and pelvic lymph node metastasis, and pelvic lymph node metastasis was the only independent risk factor for para-aortic lymph node involvement. The sensitivity and NPV of positive pelvic lymph node in the prediction of para-aortic lymph node metastasis were found to be 78.9% and 97%, respectively. The corresponding rates for obturator and/or external iliac lymph node were 63.1% and 95%, respectively. In conclusion, although pelvic lymph node metastasis is the only independent risk factor for para-aortic lymph node involvement, negative pelvic lymph node is not enough to omit para-aortic lymph node dissection. On the other hand, intraoperative frozen section examination of obturator and/or external iliac lymph node to omit para-aortic lymphadenectomy might be a good option for the patients who have high medical risks for surgery.**

**Keywords:** Endometrioid adenocarcinoma, endometrium cancer, lymph node metastasis, para-aortic lymph node, pelvic lymph node

## Introduction

Endometrial cancer is one of the most common gynaecological cancers in the world. Even though a complete surgical staging, including pelvic and para-aortic lymph node dissection, was recommended by the International Federation of Gynecology and Obstetrics (FIGO) (Shephert 1989), the extent of lymph node dissection continues to be a controversial issue. Since endometrial cancer patients have various complicating illnesses such as obesity, diabetes, hypertension, and complete lymphadenectomy carries the risk of ileus, massive bleeding, vascular injury and postoperative pulmonary embolism, some physicians limit the operation to hysterectomy and oophorectomy, while some perform only pelvic lymph node dissection (Tanaka et al. 2006). However, the detection of para-aortic lymph node involvement plays a critical role in planning the adjuvant therapy. The lack of adequate surgical staging leads to pelvic radiotherapy, which undertreats most of the patients with lymph node metastasis due to the high frequency of simultaneous para-aortic nodal involvement (Mariani et al. 2008).

Even though grade 1 tumours without myometrial invasion are not expected to metastasise to the para-aortic nodal region, there has been no standard method for selecting the patients who do not need para-aortic lymphadenectomy. Imaging tests such as computerised tomography (CT), magnetic resonance imaging (MRI), 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) and FDG-PET/CT, are inadequate to detect lymph node metastasis in endometrial cancer (Marnitz and Köhler 2012). There are only a few studies which have investigated the factors associated with para-aortic lymph node metastasis. In these studies, pelvic lymph node metastasis and lymphovascular space involvement (LVSI) were shown to be related to the existence of para-aortic lymph node metastasis (Mariani et al. 2004; Nomura et al. 2006; Turan et al. 2011).

Previous studies have estimated different routes of lymphatic spread to para-aortic lymph nodes in endometrial carcinoma. Mariani et al. (2001) reported that para-aortic dissemination occurred via common iliac lymph nodes when tumour involves the cervix, while spread via obturator lymph node was more common when the tumour site was the corpus only. Tanaka et al. (2006) reported that external and common iliac lymph nodes were the key lymph nodes associated with para-aortic lymph node metastasis, while Turan et al. (2011) showed an independent correlation between obturator and presacral lymph nodes, and para-aortic lymph node metastasis.

The objective of the present study was to assess the factors associated with para-aortic lymph node metastasis in endometrioid adenocarcinoma. We also aimed to investigate the most commonly involved pelvic lymph node group and to evaluate its performance in the prediction of para-aortic lymphatic metastasis.

## Material and material

The data of patients with endometrioid adenocancer who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy between January 2003 and December 2010 was reviewed retrospectively. Pelvic lymphadenectomy was carried out for

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Table I. Demographic characteristics of patients ($n = 157$).

| Characteristics | n | (%) |
|---|---|---|
| Age (mean ± SD) | 56.01 ± 8.5 | |
| Gravida (median, range) | 4 (0–14) | |
| Parity (median, range) | 3 (0–10) | |
| Menopause | 121 | 77.1 |
| BMI (mean ± SD) | 30.5 ± 4.9 | |
| Diabetes mellitus | 38 | 24.2 |
| Hypertension | 67 | 42.6 |
| Currently smoker | 19 | 12.1 |
| Stage | | |
| I | 113 | 72.3 |
| II | 14 | 9.0 |
| III | 28 | 14.7 |
| IV | 2 | 1.3 |
| Grade | | |
| 1 | 35 | 21.3 |
| 2 | 86 | 55.5 |
| 3 | 36 | 23.2 |
| MI | | |
| < 1/2 | 68 | 43.3 |
| ≥ 1/2 | 89 | 56.7 |
| LVSI | 59 | 37.6 |
| Cervical involvement | | |
| None | 119 | 75.8 |
| Glandular | 20 | 12.7 |
| Stromal | 18 | 11.5 |
| Lymph node involvement | | |
| Negative | 130 | 82.8 |
| Only pelvic metastasis | 8 | 5.1 |
| Only paraaortic metastasis | 4 | 2.5 |
| Pelvic + paraaortic metastasis | 15 | 9.6 |

BMI, body mass index; MI, myometrial invasion; LVSI, lymphovascular space involvement.



all patients except for those with no myometrial invasion. Para-aortic lymphadenectomy (PALND) was performed when pre- and intraoperative assessments suggested one of the following: (1) grade 3 tumour, (2) > 50% myometrial invasion, (3) cervical involvement, (4) adnexal involvement. Pelvic lymphadenectomy was defined as the bilateral removal of all lymphatic tissue of the common, external and iliac vessels and obturator fossa. The lymph nodes removed were submitted for analysis separately according to the site of origin (common iliac, external iliac, internal iliac and obturator). Para-aortic lymphadenectomy involved the nodes located from the bifurcation of the aorta to the level of renal vein above the inferior mesenteric artery (IMA). All

Table II. Intra- and postoperative characteristics of patients.

| Characteristics | n | (%) |
|---|---|---|
| Retrieved pelvic lymph node number (mean ± SD) | 17.48 ± 5.37 | |
| Retrieved para-aortic lymph node number (mean ± SD) | 6.10 ± 2.33 | |
| Operative time (min) | 152.42 ± 18.51 | |
| Estimated blood loss (ml) | 302.55 ± 89.47 | |
| Complications | | |
| Early complications | | |
| Wound infection | 2 | 1.7 |
| GIS injury | 0 | 0.0 |
| Vascular injury | 5 | 3.2 |
| Late complications | | |
| Wound separation (hernia) | 11 | 12.1 |
| Lymphocyst | 7 | 7.7 |
| Lymphoedema | 9 | 9.9 |

GIS, gastrointestinal system.

Table III. Clinicopathological features of patients with and without para-aortic nodal involvement.

| | With PALNM ($n = 19$) | | Without PALNM ($n = 138$) | | |
|---|---|---|---|---|---|
| | n | (%) | n | (%) | p value |
| Age (year) | | | | | 0.44 |
| < 60 | 12 | 62.3 | 99 | 71.7 | |
| > 60 | 7 | 36.7 | 39 | 28.3 | |
| BMI (kg/m$^2$) | | | | | 0.88 |
| < 30 | 10 | 52.6 | 75 | 54.3 | |
| > 30 | 9 | 47.4 | 63 | 45.7 | |
| Menopause | | | | | 0.77* |
| Yes | 14 | 73.7 | 107 | 77.5 | |
| No | 5 | 26.3 | 31 | 22.5 | |
| Grade | | | | | 0.20 |
| 1 | 2 | 10.5 | 33 | 23.9 | |
| 2 | 10 | 52.6 | 76 | 55.1 | |
| 3 | 7 | 36.8 | 29 | 21.0 | |
| LVSI | | | | | 0.003 |
| Yes | 13 | 68.4 | 46 | 33.3 | |
| No | 6 | 31.6 | 92 | 66.7 | |
| Myometrial invasion | | | | | 0.06 |
| < 50% | 7 | 36.8 | 82 | 59.4 | |
| ≥ 50% | 12 | 63.2 | 56 | 40.6 | |
| Cervical involvement | | | | | 0.07 |
| None | 13 | 68.4 | 106 | 76.8 | |
| Glandular involvement | 1 | 5.3 | 19 | 13.8 | |
| Stromal involvement | 5 | 26.3 | 13 | 9.4 | |
| Tumour diameter | | | | | 0.24* |
| < 20 mm | 2 | 10.5 | 35 | 25.4 | |
| ≥ 20 mm | 17 | 89.5 | 103 | 74.6 | |
| Positive peritoneal cytology | | | | | |
| Yes | 7 | 36.8 | 29 | 21.0 | 0.14* |
| No | 12 | 63.2 | 109 | 79.0 | |
| Positive pelvic lymph node (LN) | 15 | 78.9 | 8 | 5.8 | 0.0001* |
| Positive obturator LN | 9 | 47.4 | 4 | 2.9 | 0.0001* |
| Positive external iliac LN | 8 | 42.1 | 2 | 4.2 | 0.0001* |
| Positive internal iliac LN | 2 | 10.5 | 0 | 0.0 | 0.014* |
| Positive common iliac LN | 3 | 15.8 | 0 | 0.0 | 0.002* |

PALNM, para-aortic lymph node metastasis; BMI, body mass index; LVSI, lymphovascular space invasion.
*Fisher's exact test was used for analyses.

operations were performed by gynaecological oncologists and all pathological specimens were interpreted at the same institution. None of the patients received any neoadjuvant therapy. The data including age, parity, smoking status, menopausal status, body mass index, comorbid conditions, operative characteristics, postoperative complications and histopathological features were collected by reviewing the charts.

All statistical analyses were performed using SPSS for Windows version 15.0. Pearson $\chi^2$ and Fisher's exact tests were used for comparing the categorical data where appropriate. The variables associated with para-aortic lymph node metastasis were assessed by univariate and multivariate analysis. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of pelvic lymph node involvement in the prediction of the para-aortic lymph node metastasis were calculated. A $p$ value of $< 0.05$ was considered as significant.

## Results

A total of 157 patients who underwent pelvic and para-aortic lymphadenectomy were analysed for this study. The mean age of patients was 56.01 ± 8.5 and most of the patients

Table IV. Univariate and multivariate analysis of variables for the presence of para-aortic lymph node metastasis in patients with endometrial cancer.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variable | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| Age > 60 years | 0.67 | 0.24–1.84 | 0.44 | – | | |
| Grade | | | | | | |
| 1 | ref. | | | | | |
| 2 | 0.25 | 0.40–1.30 | 0.10 | – | | |
| 3 | 0.54 | 0.19–1.56 | 0.26 | – | | |
| Positive cytology | | 0.79–6.09 | 0.13 | – | | |
| ≥ 50% of MI | | 0.93–6.77 | 0.06 | – | | |
| LVSI | | 1.57–12.13 | 0.005 | 1.02 | 0.22–4.55 | 0.99 |
| Cervical involvement | | | | | | |
| None | ref. | | | – | | |
| Glandular | 2.08 | 0.25–16.98 | 0.49 | – | | |
| Stromal | 0.68 | 0.03–11.94 | 0.79 | – | | |
| Tumour diameter ≥ 20mm | | 0.63–13.13 | 0.17 | – | | |
| Pelvic LNI | | 16.37–226.71 | 0.0001 | 60.31 | 13.58–267.78 | 0.0001 |

MI, myometrial invasion; LVSI, lymphovascular space invasion; LNI, lymph node involvement.



were postmenopausal ($n = 121$, 77.1%) at the time of surgery. The majority of cases were diagnosed at FIGO stage I disease ($n = 113$, 72.3%). The clinical characteristics of the patients with endometrial carcinoma are summarised in Table I. Of all the patients, 14.6% (23/157) had pelvic lymph node involvement and 12.1% (19/157) had para-aortic lymph node involvement; 4/19 (21%) patients had isolated para-aortic lymph node metastasis. A total of 23 patients had pelvic nodal metastasis and 15 (65.2%) of them had simultaneous para-aortic lymph node involvement. Obturator lymph nodes were most commonly affected by metastasis ($n = 13$, 8.3% of the all cohort and 56.5% of the patients with pelvic lymph node metastasis). External iliac, internal iliac and common iliac lymph node metastases were detected in 6.4%, 1.3% and 1.9% of patients, respectively.

The mean number of total retrieved lymph nodes was 23.5 ± 6.04 (range 10.0–46.00). The mean number of pelvic lymph nodes was 17.48 ± 5.37 (range 6–35) and of para-aortic lymph nodes was 6.10 ± 2.33 (3–18). The mean operative time was 152.42 ± 18.51 min. Table II summarises treatment and outcome characteristics of the patients.

Table III shows the clinicopathological features of the patients with and without para-aortic lymph node involvement. Para-aortic lymph node involvement was significantly more common in the presence of LVSI and pelvic lymph node metastasis ($p = 0.003$ and $p = 0.0001$, respectively). A multivariate logistic regression analysis was performed introducing these significant variables into the model. The logistic regression analysis revealed that only pelvic lymph node metastasis (OR 60.31; 95% CI 13.58–267.78; $p = 0.0001$) remained to be the independent risk factor for para-aortic lymph node involvement (Table IV).

When the patients with positive pelvic lymph nodes for tumour were considered at high risk for para-aortic lymph node metastasis, sensitivity and NPV were found to be 78.9% and 97%, respectively. Para-aortic lymph node involvement was correctly estimated in 145 women (92.3%), overestimated in eight women (5.1%) and underestimated in four women (2.6%). The diagnostic indices for each pelvic lymph node group are shown in Table V. When obturator and/or external iliac lymph nodes were involved, sensitivity and NPV were found to be 63.1% and 95%, respectively.

In this study, 19 patients had para-aortic lymphatic involvement and four of them (21%) had no pelvic lymph node metastasis. Of these four patients, two had grade 2 tumours with ≥ 1/2 myometrial invasion, one had grade 2 tumour with < 1/2 myometrial invasion and one had grade 3 tumour with < 1/2 myometrial invasion. Cervical invasion and LVSI were detected in three and two patients, respectively. None of the patients had serosal and adnexal invasion or positive peritoneal cytology (Table VI).

## Discussion

Identifying positive para-aortic lymph nodes helps to define the patients who require more aggressive treatment such as extended field radiation therapy to cover the para-aortic nodes and/or systemic chemotherapy. The recent SEPAL study concluded that overall survival is significantly longer in the combined pelvic and para-aortic lymphadenectomy group compared with the pelvic lymphadenectomy group (Todo et al. 2010). On the other hand, the para-aortic lymph node dissection involves some perioperative risks such as longer surgical time, risk of vascular/nerve injury and lymphocyst formation. For this reason, we investigated the factors associated with the para-aortic lymph node involvement with the aim to define the patients in whom para-aortic lymph node dissection can be omitted. We found that LVSI and pelvic lymph node metastasis were significantly associated on the basis of univariate analysis. However, only pelvic nodal metastasis was found to be an independent factor for para-aortic nodal involvement. Previously, we reported that LVSI is an independent factor for pelvic lymph node involvement in endometrial cancer (Akbayir et al. 2012). In the present study, LVSI could not be demonstrated as an independent factor

Table V. Diagnostic indices of pelvic lymph node metastasis in the prediction of para-aortic lymph node involvement (%).

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| Pelvic LNI | 78.9 | 94.2 | 65.2 | 97 |
| Obturator LNI | 47.3 | 97.1 | 69.2 | 93.1 |
| External iliac LNI | 42.1 | 98.5 | 80 | 92.5 |
| Internal iliac LNI | 10.5 | 100 | 100 | 89.1 |
| Common iliac LNI | 15.7 | 100 | 100 | 87.3 |
| Obturator + External iliac LNI | 63.1 | 96.3 | 70.5 | 95.0 |

LNI, lymph node involvement; PPV, positive predictive value; NPV, negative predictive value.

Table VI. Clinicopathological features of patients with isolated para-aortic lymph node metastasis.

| Pt | Age (years) | Retrieved PLN | Retrieved PALN | LVSI | MI | Grade | Cervical involvement | Adnexal involvement | Serosal involvement | Peritoneal cytology |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 51 | 18 | 3 | − | < 1/2 | 2 | + | – | – | – |
| 2 | 65 | 15 | 4 | + | < 1/2 | 3 | − | – | – | – |
| 3 | 67 | 17 | 7 | + | ≥ 1/2 | 2 | + | – | – | – |
| 4 | 52 | 23 | 7 | − | ≥ 1/2 | 2 | + | – | – | – |

Pt, patient; PLN, pelvic lymph node; PALN, para-aortic lymph node; LVSI, lymphovascular space involvement; MI, myometrial invasion.



for para-aortic lymph node involvement and we speculate that LVSI affects the para-aortic involvement dependently to pelvic nodal metastasis. By contrast, Turan et al. (2011) and Mariani et al. (2004) reported that both LVSI and pelvic metastasis were independent factors for para-aortic lymphatic involvement.

Isolated para-aortic lymph node metastasis is reported to be 0–6% in the literature (Mariani et al. 2004). Mariani and colleagues (2008) reported that ipsilateral nodes below the IMA were not involved in 60% of patients and that the ipsilateral common iliac nodes were not involved in 71% patients with positive nodes above the IMA. For this reason, a para-aortic dissection up to the renal vessels is needed to exclude para-aortic metastasis. Metastasis via a direct route from corpus to the para-aortic node-bearing basins by the lymphatic channels adjacent to the infundibulopelvic ligament seems to be the reason for the isolated para-aortic involvement (Lecuru et al. 1997). In the present study, of the 19 patients with para-aortic lymph node metastasis, four had no pelvic lymph node involvement. Cervical invasion was detected in three patients with isolated para-aortic lymph node involvement and none of the patients had adnexal or serosal involvement. In addition to the aforementioned hypothesis, this might be explained by microscopic pelvic node metastasis identified by immunohistochemical staining but not by histological assessment (Erkanli et al. 2011).

In the present study, we aimed to find the accuracy of pelvic lymph node involvement in the prediction of para-aortic lymph node metastasis, and found the sensitivity and NPV of pelvic lymph node involvement to be 78.9% and 97%, respectively. Turan et al. (2011) also reported similar rates in their study of 204 patients who had pelvic and para-aortic lymphadenectomy. We investigated which pelvic lymph node group was most commonly associated with para-aortic lymph node involvement, and found that obturator lymph node was the most commonly involved lymph node group (47.4%), which was followed by external iliac lymph node (42.1%). The NPV of these lymph node groups for para-aortic lymph node involvement was 93.1% and 92.5%, respectively. When the combination of obturator and external iliac lymph node was evaluated, the NPV was as high as 95%. The intraoperative evaluation of these two lymph node groups seems to be a more practical approach than the evaluation of all pelvic lymph nodes. Similarly, Tanaka et al. (2006) reported that the most commonly involved lymph node was the obturator lymph node and suggested the combination of common and external lymph node involvement to be used with the aim to omit para-aortic lymphadenectomy in case of a negative frozen section result, since the sensitivity and specificity of this combination was 90.9% and 96.7%, respectively. On the other hand, in the literature, the data regarding frozen section histological examination of pelvic lymph nodes is controversial. Tanaka et al. (2006) stated that intraoperative frozen section was a reliable method with a false-negative rate of only 0.2%. By contrast, Pristauz et al. (2009) in their study of 131 patients, reported the false-negative rate as high as 59%. Furthermore, Fanfani et al. (2004) compared the findings of frozen section examination with the final histological diagnosis and found the accuracy of frozen section to be 92.4%. The authors emphasised the importance of the skill and the experience of pathologists, since the accuracy was 95% and 90%, when only the nodes evaluated by specialist pathologists and general pathologists were taken into account, respectively. From our point of view, frozen section examination of obturator and external lymph nodes before para-aortic dissection seems to be a good option for the patients with high risk of morbidity and mortality due to extensive staging procedures. However, prospective randomised studies with larger cohorts are needed for the prediction of para-aortic lymphatic involvement according to the intraoperative frozen examination of pelvic lymph nodes.

The strength of this study is that only the endometrioid adenocarcinomas were included. We excluded the other histological types, since they are different from endometrioid adenocarcinoma in terms of biological behaviour and lymphatic spread characteristics. Thus, our cohort was more homogeneous and specific than the previous studies, which included all histological types (Mariani et al. 2004; Tanaka et al. 2006; Turan et al. 2011).

In conclusion, pelvic lymph node metastasis is the only independent risk factor for para-aortic lymph node involvement. However, as para-aortic lymph node involvement is isolated in 21% (4/19) of patients, negative pelvic lymph node is not enough to omit para-aortic lymph node dissection. On the other hand, obturator and/or external iliac lymph node involvement has a high NPV in the prediction of para-aortic lymph node metastasis; intraoperative frozen section examination of these nodes to omit para-aortic lymphadenectomy might be a good option for the patients who have high medical risks for surgery, in particular morbid obesity.

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