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Lymphovascular space invasion and positive pelvic lymph nodes are independent risk factors for para-aortic nodal metastasis in endometrioid endometrial cancer

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ABSTRACT

Objective: Para-aortic lymph node dissemination in endometrioid endometrial cancer is uncommon, and systematic para-aortic lymph node dissection increases morbidity. The purpose of this study was to identify a subgroup of endometrioid endometrial cancer patients who did not require para-aortic lymphadenectomy.

Study design: All patients who had undergone surgery for endometrioid endometrial cancer between 1 January 1995 and 31 December 2012 were retrospectively reviewed. Patients with higher risk factors for nodal metastasis and inadequate lymphadenectomy were excluded. Para-aortic lymph node dissemination was defined as nodal metastasis when pelvic and para-aortic lymph node dissection was performed, when para-aortic lymph node recurrence occurred after negative para-aortic lymph node dissection or when para-aortic lymph node dissection was not performed. Multivariate logistic regression models were used to identify the pathological features as predictors for para-aortic lymphatic dissemination.

Results: A total of 827 patients were assessed, 516 (62.4%) of whom underwent pelvic and para-aortic lymph node dissection. Sixty-seven (13%) patients (37 with only pelvic, 26 with pelvic and para-aortic, and 4 with only para-aortic metastasis) had positive lymph nodes in the pelvic and para-aortic lymph node dissection group. Multivariate analysis confirmed positive pelvic nodes (odds ratio 20.58; $p < 0.001$) and lymphovascular space invasion (odds ratio 8.10; $p = 0.022$) as independent predictors of para-aortic lymphatic dissemination. When these two factors were absent (in 83% of patients), the predicted probability of para-aortic lymph node metastasis was 0.1%.

Conclusion: Positive pelvic nodes and lymphovascular space invasion are highly associated with para-aortic lymph node metastasis. These markers may be useful for identifying those patients who require para-aortic lymph node dissection.

Introduction

Endometrial cancer (EC) is the most common malignancy of the female reproductive system [1]. Most women are diagnosed at an early stage because of irregular vaginal bleeding. A total hysterectomy plus bilateral salpingo-oophorectomy is the primary operation used to treat EC. The practice of systematic lymphadenectomy, especially para-aortic (PA) lymph node dissection (LND), in patients with EC is controversial [2]. There are no existing randomized data suggesting a survival benefit of lymphadenectomy in patients with EC. Therefore, lymphadenectomy is performed in most centers on therapeutic and prognostic grounds and to individualize adjuvant treatment. Within the gynecologic oncologic community, there is no consensus regarding the indications and extent of lymphadenectomy in managing EC.

Currently, uterine histopathologic features have become increasingly important and may be used as surrogate risk markers for lymph node spread. It is essential to clarify the indications for

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PA LND because of concerns regarding the potential morbidity and cost of this procedure [3].

The objective of this study was to identify a subgroup of endometrioid EC patients in whom PA LND was not required.

Materials and methods

All patients who underwent surgery for EC at the Tepecik Training and Research Hospital, Izmir, Turkey between 1 January 1995 and 31 December 2012 were retrospectively reviewed. This study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee at our institution. Patients with strong risk factors for nodal metastasis were excluded. These risk factors included the following: non-endometrioid histology, International Federation of Gynecology and Obstetrics (FIGO) stage IV disease, gross uterine serosal and/or gross adnexal involvement, and the presence of synchronous cancers. Patients who underwent prior neoadjuvant chemotherapy or radiotherapy and inadequate lymphadenectomy were also excluded. An adequate pelvic (P) lymphadenectomy was defined as the removal of at least 10 P lymph nodes, and an adequate PA lymphadenectomy was defined as the removal of 5 or more PA lymph nodes [4,5]. The final study population consisted of 827 patients with endometrioid EC.

Demographic data, such as age at surgery, body mass index (BMI), and parity, as well as laboratory findings, including preoperative CA125 levels, were obtained from the medical records. As a routine surgical procedure, peritoneal washing cytology, hysterectomy plus bilateral salpingo-oophorectomy, and frozen section analysis were performed in all cases. During the study period, the management of EC varied among the practitioners, particularly with respect to the role of lymphadenectomy; no lymph nodes were sampled in some patients, only the P or PA nodes were sampled in some patients, complete staging with bilateral P LND was applied in some patients, and some patients underwent complete staging with bilateral P and PA LND. The individual practitioners were responsible for these variations over the study period.

Pathological data, including the FIGO grade, primary tumor diameter (PTD), myometrial invasion (MI), cervical stromal invasion, lymphovascular space invasion (LVSI), and tumor-free distance (TFD) from the uterine serosa, were obtained from the pathology reports. An experienced gynecologic pathologist reviewed all pathology slides. The PTD was defined as the largest area in each of the three dimensions of the tumor. If more than one tumor was present, the tumor with the largest diameter was considered. LVSI was defined as the presence of tumor cells in a vascular space lined by endothelium and/or the attachment of tumor cells to the vascular wall irrespective of the number of LVSI foci. The presence of P/PA lymphatic dissemination was defined in the following circumstances: (1) nodal metastasis when P/PA LND was performed, (2) P/PA lymph node recurrence within 2 years of a negative LND, or (3) P/PA LND was not performed. The latter criterion was based on an assumption that unrecognized positive PA lymph nodes would be clinically detectable within the median time to nodal recurrence, which has been reported to be less than 2 years [6,7]. Among the patients who underwent surgery without PA LND or those with negative nodes in the context of an inadequate PA LND, the following exclusion criteria were applied to ensure the complete recognition of PA lymph node metastasis (PAM): (1) patients who died within the first 2 years whose date of last follow-up was more than 3 months prior to death, and (2) patients who were last known to be alive but lacked 2 years of follow-up.

The follow-up evaluations were scheduled every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Computed tomography or magnetic resonance imaging was performed annually. Lymph node recurrence was considered as any P/PA lymphatic recurrence identified after the primary cancer surgery, in which a new mass was detected in the P/PA regions either by clinical examination or by imaging techniques. Diagnostic confirmation of the recurrence was performed by diagnostic biopsy or at the time of secondary debulking surgery.

Statistical analysis was performed using IBM SPSS Statistics 21.0 (SPSS Inc., Chicago, IL). The variables were assessed using visual (histograms, probability plots) and analytical (Shapiro–Wilk test) methods to determine whether they were normally distributed. Continuous data [presented as the mean ± SD or median (Q1–Q3)] were analyzed using the Mann–Whitney *U* test for non-normal data. The chi-square test (Pearson chi-square and Pearson exact chi-square tests) was used to compare the proportions between groups. Univariate and multiple logistic regression models were used to identify the risk factors. A p-value <0.05 was defined as statistically significant.

Results

A total of 827 patients with endometrioid EC who were treated surgically and fulfilled the inclusion criteria were considered in this study. Table 1 shows the baseline characteristics and pathological features of all of these patients. Among the 827 patients, 205 (24.8%) underwent P LND, and 516 (62.4%) underwent P/PA LND. Sixty-seven (13%) patients (37 had only P, 26 had P and PA, and 4 had only PA metastases) had positive lymph nodes in the P/PA LND group, whereas 5 (2.4%) patients had positive lymph nodes in the P LND group. The median numbers of removed P and PA lymph nodes were 22 (range, 15–28) and 8.5 (range, 5–16),

Table 1
Baseline characteristics and pathologic variables of patients with endometrioid endometrial cancer.

Characteristics	$n=827$
Age at surgery (years)	56.5 ± 9.5
BMI (kg/m^2)	33.2 ± 4.9
Parity	3.0 ± 1.8
FIGO grade	
1	693 (83.8)
2	58 (7.0)
3	76 (9.2)
Primary tumor diameter	
≤2 cm	309 (60.7)
>2 cm	518 (62.6)
Myometrial invasion	
≤50%	502 (60.7)
>50%	325 (39.3)
Cervical stromal invasion	
No	727 (87.9)
Yes	100 (12.1)
Lymphovascular space invasion	
No	690 (83.4)
Yes	137 (16.6)
TFD from serosa (cm)	1.1 ± 0.9
Pelvic lymphadenectomy	
No lymphadenectomy	106 (12.8)
Pelvic lymphadenectomy, no positive nodes	653 (79)
Pelvic lymphadenectomy, positive nodes	68 (8.2)
Lymph node status	
No lymph node dissemination	755 (91.3)
Lymph node dissemination	72 (8.7)
Only pelvic dissemination	42 (5.1)
Only para-aortic dissemination	4 (0.5)
Pelvic and para-aortic dissemination	26 (3.1)

BMI, body mass index; LVSI, lymphovascular space invasion; TFD, tumor-free distance; and FIGO, International Federation of Gynecology and Obstetrics. Values for continuous variables are presented as the mean ± standard deviation. Values for categorical variables are presented as the number/total number of cases (%).