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Original Article

Risk factors for para-aortic lymph node metastasis in endometrial cancer: a retrospective analysis of 217 patients

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Abstract: Objective: To investigate the risk factors for para-aortic lymph node (PALN) metastasis in patients with endometrial carcinoma who underwent comprehensive surgical staging. Methods: Two hundred and seventeen patients with pathological confirmation of endometrial cancer who underwent comprehensive surgical staging including pelvic and PALN dissection were retrospectively reviewed. Clinical data including baseline characteristics, laboratory findings and pathological results were collected. Univariate and multi-variate logistic regression analyses were performed to investigate the risk factors for PALN metastasis. Results: Sixteen patients (7.4%) were identified with PALN metastasis including 11 (5.1%) with pelvic and para-aortic and 5 (2.3%) with isolated para-aortic infiltration. Univariate analysis found patients with PALN metastasis were more at advanced International Federation of Gynecology and Obstetrics (FIGO) stage III or IV (P<0.001), more with type II endometrial carcinoma (P = 0.025), >50% myometrial invasion (P<0.001), cervical stromal invasion (P<0.001), lymphovascular space invasion (LVSI, P<0.001), microcystic, elongated and fragmented (MELF) pattern (P = 0.017) and pelvic node metastasis (P<0.001), and with higher serum CA125 levels (P<0.001), bigger tumor diameter (P = 0.012). Multi-variate logistic regression analysis found that positive pelvic nodes (adjusted odds ratio (OR) = 53.73; 95% confidence interval (CI = 13.78 to 209.5, P<0.001), LVSI (adjusted OR = 6.66; 95% CI = 1.01 to 44.01, P = 0.049) and type 2 endometrial cancer (adjusted OR = 7.60%, CI = 1.25 to 46.18, P = 0.028) were the independent risk factors for PALN metastasis. Conclusion: Pelvic lymph node metastasis, LVSI and type 2 endometrial cancers were associated with higher risk of PALN metastasis in patients with endometrial carcinoma.

Keywords: Para-aortic lymph node, endometrial carcinoma, retrospective analysis

Introduction

Endometrial carcinoma has become the most common gynecologic cancer in USA and other developed countries, and in developing countries, it is second to cervical carcinoma [1, 2]. Although most of the endometrial carcinoma grow slowly and is limited to the endometrium or the uterine cavity for several years, some pathological types of carcinoma may develop rapidly and spread within a short period of time with poor prognosis [3, 4].

Lymph node metastasis plays an important role in the spread of endometrial carcinoma [5]. It is found about one tenth of the endometrial carcinomas confined to the womb have lymph node metastases [6]. Comprehensive lymphadenectomy including pelvic lymph node and para-aortic lymph node (PALN) remains an essential part in the International Federation of Gynecology and Obstetrics (FIGO) surgical staging system which aims to improve the prognosis of endometrial carcinoma [7]. In fact, surgical staging including pelvic and para-aortic lymphadenectomy was found to be the most important prognostic factor for overall survival in endometrial cancer [8]. However, debate about lymphadenectomy, especially PALN resection for endometrial cancer is rising [9]. The recent meta-analysis of clinical trials supported that for patients with presumed stage I cancer, lymphadenectomy fails to decrease death or recurrence, but is associated with higher risk of

Table 1. Clinicopathological features of patients with endometrial carcinoma

Characteristics	n = 217
Age at surgery (years), mean ± SD	55.8
BMI (kg/m^2), mean ± SD	22.8±6.2
Preoperative CA125 (U/mL), median (interquartile)	17.4 (11.3-32.2)
Preoperative CA125 (U/mL), n (%)	
≤25	147 (67.7)
>25	70 (32.3)
Histopathology type, n (%)	
Type 1	160 (73.7)
Type 2	57 (26.3)
FIGO Stage, n (%)	
I	166 (76.5)
II	32 (14.7)
III	18 (8.3)
IV	1 (0.5)
Primary tumor diameter (cm), median (interquartile)	3 (1.9-4.0)
Primary tumor diameter, n (%)	
≤2 cm	75 (34.6)
>2 cm	142 (65.4)
Cervical stromal invasion, n (%)	38 (17.5)
Myometrial invasion ≥50%, n (%)	72 (33.2)
MELF pattern, n (%)	19 (8.8)
LVSI, n (%)	64 (29.5)
Lymph node metastasis, n (%)	31 (14.3)
Pelvic only	15 (6.9)
Para-aortic only	3 (1.4)
Pelvic and para-aortic	13 (6.0)

Note: SD, standard deviation; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; MELF, microcystic, elongated and fragmented; LVSI, lymphovascular space invasion.

surgery-related systemic morbidity or lymphedema/lymphocyst formation [10]. On the other hand, PALN metastasis of endometrial carcinoma is difficult to detect without surgical staging [11]. Considering that PALN metastasis is crucial for deciding surgical resection extension, adjuvant therapy as well as radiotherapy [12, 13], there is an urgent need to determine the patients who were at high risk for PALN metastasis. The aim of current study was to determine the risk factors for PALN metastasis in endometrial carcinoma.

Materials and methods

Patients

This retrospective study has gained ethical approval from Institutional Review Board of Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China. Due to its retrospective design, no informed consent from the patient was needed.

From January 1st 2010 to December 31st 2016, 265 patients who underwent comprehensive surgical staging including pelvic and PALN resection for endometrial cancer were retrospectively reviewed. Comprehensive surgical staging was defined as pelvic washing, peritoneal biopsy, bilateral pelvic and PALN dissection, double ovarian salpingectomy, and hysterectomy. The eligible patients should meet all the following criteria: 1) full records of baseline characteristics, preoperative serum CA125 levels, surgical procedures and intraoperative findings and pathological diagnosis; 2) comprehensive surgical staging with at least ten pelvic lymph nodes resected and five PALNs removed [14]; 3) no concomitant tumor diseases and no preoperative chemotherapy or radiation therapy. After screening, records from 217 patients were identified.

Data collection

The clinical, surgical and pathological data were all collected after review of medical records. They included demographics (age and body mass index (BMI)), preoperative serum CA125 levels, tumor size (the largest number measured in three dimensions for the largest lesion), number of excised and positive pelvic or PALNs, caner type (type 1 and type 2 based on pathological results), histological type, FIGO staging, myometrial invasion (≤50 or >50%), cervical stromal invasion, lymphovascular space invasion (LVSI) and microcystic, elongated and fragmented (MELF) pattern [15-18].

Outcome measures and statistical analysis

The main goal of this study was to determine the risk factors for PALN metastasis in patients

Table 2. Clinicopathological features of patients with or without para-aortic lymph node metastasis

Characteristics	No PALN metastasis (n = 201)	PALN metastasis (n = 16)	*P* value
Age (years), mean ± SD	55.4±8.7	57.4±10.5	0.385
BMI (kg/m^2), mean ± SD	22.7±6.2	24.2±5.9	0.345
Preoperative CA125 (U/mL), median (interquartile)	16.0 (11.0-27.2)	75.1 (37.6-111.1)	<0.001
Preoperative CA125 (U/mL), n (%)			
≤25	147 (73.1)	0	<0.001
>25	54 (26.9)	16 (100.0)	
Histopathology type, n (%)			
Type 1	152 (75.6)	8 (50.0)	0.025
Type 2	49 (24.4)	8 (50.0)	
FIGO Stage, n (%)			
I and II	192 (95.5)	6 (37.5)	<0.001
III and IV	9 (4.5)	10 (62.5)	
Primary tumor diameter (cm), median (interquartile)	3 (1.8-4.0)	3.5 (3.0-5.0)	0.012
Primary tumor diameter, n (%)			
≤2 cm	74 (36.8)	1 (6.2)	0.013
>2 cm	127 (63.2)	15 (93.8)	
Cervical stromal invasion, n (%)	30 (14.9)	8 (50.0)	0.001
Myometrial invasion ≥50%, n (%)	59 (29.4)	13 (81.3)	<0.001
MELF pattern, n (%)	15 (7.5)	4 (25.0)	0.017
LVSI, n (%)	51 (25.4)	13 (81.3)	<0.001
Pelvic lymph node metastasis, n (%)	15 (7.5)	13 (81.3)	<0.001

Note: SD, standard deviation; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; MELF, microcystic, elongated and fragmented; LVSI, lymphovascular space invasion; PALN, para-aortic lymph node.

with endometrial cancer. We divided the patients into PALN positive group and negative group according to the pathological results. Univariate analysis was first performed to identify different variables between groups. Then multiple logistic regression models with backward stepwise Wald method were utilized to investigate the independent risk factors for PALN metastasis ($\alpha_{included}$ = 0.05, $\alpha_{excluded}$ = 0.10). All statistical analyses were performed using the statistical Package for the Social Sciences (SPSS) software v. 23 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean and standard deviation (mean ± SD) if normal distribution and homogeneity of variance assumed and analyzed using one-way ANOVA. Otherwise, median (interquartile) was used and the Mann-Whitney U test was performed for statistical analysis. Categorical variables were expressed as number (percent) and chi-square test was used for inter-group comparison. A *P* value of smaller than 0.05 was considered statistically significant.

Results

Data from a total of 217 eligible patients were collected. **Table 1** shows the demographical, surgical and pathological features of these patients. The mean patient age was 55.6±8.9 years old with a BMI of 22.8±6.2 kg/m^2. All the patients underwent bilateral pelvic and para-aortic lymphadenectomy. The median number for the pelvic and para-aortic nodes resected were 19 (interquartile: 14-23, range 10-42) and 7 (interquartile: 6-8, range 5-21) respectively. There were 31 patients diagnosed with lymph node metastasis, including 15 with positive pelvic lymph nodes only, 3 with PALN metastasis only and 13 with both pelvic and PALNs found positive.

The patients were divided into 2 groups based on whether PALN metastasis was present. The baseline characteristics and pathological findings of the two groups were shown in **Table 2**. No significant difference was detected for age at surgery or BMI. Patients with PALN metasta-

sis were more at FIGO stage III or IV (P<0.001), more with type II endometrial carcinoma (P = 0.025), >50% myometrial invasion (P<0.001), cervical stromal invasion (P<0.001), lymphovascular space invasion (LVSI, P<0.001), microcystic, elongated and fragmented (MELF) pattern (P = 0.017) and pelvic node metastasis (P<0.001). Moreover, serum CA125 levels were higher (P<0.001) and tumor diameters were bigger (P = 0.012) in patients with PALN metastasis.

Multivariate logistic regression analysis confirmed that pelvic lymph node dissemination (adjusted OR = adjusted OR = 53.73; 95% CI = 13.78 to 209.5, P<0.001), LVSI (adjusted OR = 6.66; 95% CI = 1.01 to 44.01, P = 0.049) and type 2 endometrial cancer (adjusted OR = 7.60% CI = 1.25 to 46.18, P = 0.028) were the independent risk factors for the development of PALN metastasis in women with endometrial carcinoma. The combination of these variables yielded a correction rate of 0.954.

Discussion

Compared to pelvic lymph node infiltration, PALN involvement was much less seen in patients with early stage endometrial carcinoma [19]. Solmaz et al. reported an incidence of 1.1% in patients with FIGO stage I and 5.6% for stage II [14]. Similar to this, we found 6/198 patients with FIGO Stage I or II has positive PALNs. The low incidence suggested no need of para-aortic lymphadenectomy considering the fact that hysterectomy alone was associated with similar outcomes in patients with low or intermediate-risk endometrial cancer [20, 21].

Several factors have been reported to be associated with PALN metastasis in endometrial cancer. One of the most well-known risk factors is the involvement of pelvic lymph nodes [14, 22-24]. According to previous reports, about half of the patients with pelvic lymph node metastasis have PALN dissemination [14, 25]. Similar to these results, 46.4% of patients with positive pelvic lymph nodes had PALN metastasis in the current study. The logistic regression model also identified pelvic lymph node metastasis as the independent risk for PALN metastasis.

In the endometrial carcinoma, the route of isolated PALN involvement also existed. We found 3/16 of the patients had PALN metastasis and did not have pelvic lymph node metastasis. This incidence was also similar to reports from Solmaz et al., Numanoglu et al. and Todo et al. [11, 14, 23]. It was fund that the prognosis of PALN metastasis in patients with endometrial cancer patients and no pelvic lymph node involvement was poor [11]. This highlightened the importance of identifying specific risk factors for isolated PALN metastasis. Due to the small number of patients with isolated PALN metastasis, we did not perform the risk factor analysis here. Chang et al. reported LVSI was the only significant independent factor for isolated PALN metastasis [26]. However, their study only included 5 patients with isolated PALN metastasis. Larger sampled studies were still needed.

In this study, we found that the patients at high risk for PALN metastasis can be identified by a combined absence of positive pelvic lymph nodes, LVSI and type 2 endometrial cancer. This result was similar to findings by Solmaz et al. who found LVSI and positive pelvic lymph nodes were independent risk factors for para-aortic nodal metastasis in endometrioid endometrial cancer [14]. Different from these findings, the study by Numanoglu et al. identified positive pelvic lymph nodes as the only risk factor for PALN metastasis [23]. The small sample of the study might be the reason for difference.

Two limitations must be considered when interpreting the results. Firstly, the retrospective design was associated with the risk of information and selection bias and confounding variables which could not be known which might weaken the strength of our findings. Secondly, we did not separate type 1 and type 2 endometrial cancers. Due to the different histology, the risk factors for PALN metastasis might be different. Future prospective studies should be conducted to solve the uncertainty caused by the limitations.

In conclusion, LVSI, pelvic LN metastasis and type 2 endometrial cancer were independent risk factors for PALN metastasis in patients with endometrial cancer.

Disclosure of conflict of interest

None.

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