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ORIGINAL RESEARCH

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Risk factors of lymph node metastasis in patients with type II endometrial carcinoma: a retrospective signle-center study

Nan Wang[1], Zhi-feng Yan[1], Ming-xia Ye[1], Ming-xia Li[1], Ming-yang Wang[1], Yuan-guang Meng[1,*]

[1]Department of Gynecology and Obstetrics, The First Medical Center of Chinese PLA General Hospital, 100853 Beijing, China

***Correspondence**
meng6512@vip.sina.com
(Yuan-guang Meng)

Abstract

In this study, we explored the risk factors for lymph node metastasis in patients with type II endometrial carcinoma (EC). Patients diagnosed with type II EC who underwent staged surgery and lymph node dissection were included. Univariate analysis was performed using a chi-square test for factors such as age, body mass index (BMI), menopausal status, histologic type, histologic grade, myometrial invasion, lymphatic vascular invasion (LVSI), tumor volume index, and para-aortic lymph node (PALN) or pelvic lymph node (PLN) metastasis. An analysis of multivariate factors was performed on the factors that were statistically significant in the univariate analysis. Pelvic lymph node metastasis was identified in 38 of the 184 patients with type II EC. Univariate analyses revealed that age $\geq$55 years, menopause, more than one-half myometrial invasion, and LVSI were risk factors for pelvic lymph node metastasis. Multivariate analysis indicated that myometrial invasion of more than one-half (hazard ratio (HR): 4.259) and LVSI (HR: 3.317) were independent risk factors for pelvic lymph node metastasis. Para-aortic lymph node metastasis was identified in 13 of the 184 patients with type II EC. Univariate analysis indicated that para-aortic lymph node metastasis was significantly associated with LVSI and pelvic lymph node metastases. Multivariate analysis suggested that pelvic lymph node metastasis (HR: 5.887) was an independent risk factor for para-aortic lymph node metastasis. LVSI and myometrial invasion depth $>$1/2 were significant predictors of pelvic lymph node metastasis in patients with type II EC. Patients with type II EC who have pelvic lymph node metastasis may be at risk of para-aortic lymph node metastasis.

Keywords

Risk factors; Lymph node metastasis; Type II endometrial carcinoma

1. Background

Endometrial carcinoma (EC) is one of the most commonly diagnosed malignancies in women [1]. Statistics from the China Cancer Center (2015) showed that the incidence of EC is approximately 63.4/100,000 [2]. The current World Health Organization (WHO) classification divides EC into two types: type I EC includes G1 and G2 endometrioid carcinomas, which are estrogen-dependent; and type II EC includes G3 endometrioid carcinomas, uterine serous carcinomas, clear cell carcinomas, carcinosarcomas, mixed epithelial and mesenchymal tumors, and undifferentiated carcinomas, which arise in the absence of endocrine and metabolic disturbances. Type II EC is also associated with atrophic endometria, which are poorly differentiated and have less favorable outcomes [3]. According to the International Federation of Gynecology and Obstetrics (FIGO), surgery to remove the uterus via total hysterectomy with pelvic and para-aortic lymph node dissection (LND) is the standard therapy strategy for EC (mandated through the staging system) [4, 5]. In recent years, the utility of LND in the pelvic and para-aortic areas has been disputed [6]. However, lymph node metastasis is a critical prognostic factor for EC [7] and LND also identifies patients who require adjuvant radiation therapy (RT) or systemic therapy [8].

Some well-known risk factors for pelvic lymph node metastasis in EC are the histologic type, volume index, and histologic grade. Of these, the volume index was found to be an independent risk factor for para-aortic lymph node metastasis [9, 10]. Type II ECs account for approximately 20% of all ECs but are responsible for approximately 40% of EC deaths [11]. However, there is considerable debate about the risk factors for type II EC para-aortic lymph node (PALN) or pelvic lymph node (PLN) metastasis.

In this study, we analyzed the risk factors of PALN and PLN metastases in patients with type II EC. Our study aimed to guide future therapeutic decisions.

2. Methods

2.1 Study design and participants

We retrospectively collected and reviewed data from 01 June 2010 to 01 June 2020 from the Obstetrics and Gynecology Department of the First Medical Center of the PLA General Hospital, which is a comprehensive EC institution in Beijing, China. The Declaration of Helsinki was followed during the conduct of this study (revised in 2013). Subgroup analysis was performed to compare clinical data. Patients who had undergone systematic lymphadenectomy but had negative lymph node metastasis were compared withpatients who had positive lymph node metastasis. Medical history, surgical details, histology, and tumor stage were reviewed.

2.2 Cohort selection and study variables

The inclusion criteria were as follows: participants diagnosed with type II EC and who underwent an EC staging operation (total double adnexectomy with pelvic and para-aortic lymph node resection) were taken into consideration. The exclusion criteria were as follows: pathological results of type I EC, those who had not undergone systemic LND or those who only underwent pelvic lymphadenectomy or lymph node biopsy, and those who underwent preoperative radiotherapy, chemotherapy, or hormone therapy.

The following patient demographic and clinical characteristics were collected at the baseline: age [12], menstrual status, tumor diameter, clinical TNM (cTNM) staging [13], pathological biopsy reports, and lymphovascular space invasion (LVSI) [14]. The histologic type and grade of preoperative endometrial biopsy specimens were evaluated. The histologic type and grade of postoperative pathologic specimens were evaluated [15], histologic grade [16], and myometrial invasion (no invasion, invasion of less than half of the myometrium, or invasion of half or more of the myometrium). All postoperative specimens were examined by a gynecology pathologist and reviewed by another pathologist. Definitive histological analysis by surgical biopsy was performed for the inclusion of patients.

2.3 Statistical analysis

Statistics on the case data of patients with type II EC included age, body mass index (BMI), menopausal status, histologic type, histologic grade, myometrial invasion, LVSI, and PLN and PALN metastasis. Logistic regression analysis was used to screen for risk factors for PLN and PALN metastases. We included in the multivariate analysis variables that demonstrated statistical significance in the univariate analysis. Statistical significance was set at $p < 0.05$. Data were analyzed using the SPSS software suite (version 22.0, SPSS Inc., Chicago, IL, USA).

3. Results

Our retrospective cohort included 184 patients with type II EC (Fig. 1). PLN metastasis was identified in 38 (20.7%) of the 184 patients with type II EC. The results of the logistic regression analysis are presented in Tables 1 and 2. Age, BMI, menopausal status, myometrial invasion, LVSI, tumor diameter, histologic type, and histologic grade in the preoperative settings were used as independent variables. PLN metastasis was the dependent variable.

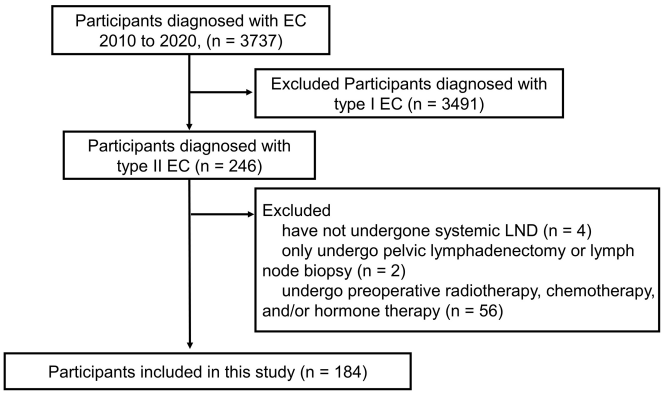

FIGURE 1. Flow chart of study population. EC: endometrial carcinoma; LND: lymph node dissection.

Univariate analyses revealed that age ≥55 years, menopause, myometrial invasion of more than half, and LVSI were risk factors (Table 1). Multivariate analysis indicated that myometrial invasion of more than half (HR = 4.259, 95% CI 1.907–9.514) and LVSI (HR = 3.317, 95% CI 1.396–7.882) were independent risk factors for PLN metastasis (Table 2).

PALN metastasis was identified in 13 (7.1%) of the 184 patients with type II EC. Univariate analysis indicated that PALN metastasis was significantly associated with LVSI and PLN metastasis (all $p < 0.05$), but was not significantly associated with age, BMI, menopause, myometrial invasion, tumor diameter, histologic type, or histologic grade (all $p > 0.05$) (Table 3).

Statistically significant factors indicated by the univariate analysis above were subjected to multivariate analysis by logistic regression. Multivariate analysis suggested that PLN metastasis was an independent risk factor for PALN metastasis ($p < 0.05$) (Table 4).

4. Discussion

Lymph node metastasis is a key prognostic factor for EC [7]. EC is a highly heterogeneous disease from an epidemiological, clinical manifestation, pathological, and molecular perspective [17]. The prognosis of type I EC patients is mostly good, while patients with type II EC are susceptible to distant metastasis, recurrence, and poor prognosis [18, 19]. Risk factors for lymph node metastasis in EC have been previously reported [9, 10]. However, few studies have investigated the risk factors for lymph node metastasis in type II EC. Our study showed that the independent risk factors for PLN metastasis in patients with type II EC include LVSI and a myometrial invasion depth >1/2, while the independent risk factor for PALN metastasis in patients with type II EC is PLN metastasis. Deep myometrial invasion and LVSI have been listed as potential risk factors according to the NCCN guidelines [20], which is consistent with the present study. A multivariate analysis study by

TABLE 1. Univariate analysis of the factors associated with pelvic lymph node metastasis.

Risk factor	Pelvic lymph node metastasis (n/N)	*p*
Age		
≥55	28/109 (25.69%)	0.042
<55	10/75 (13.33%)	
BMI		
≥28	6/38 (15.79%)	0.406
<28	32/146 (21.92%)	
Menopause		
Yes	33/130 (25.38%)	0.014
No	5/54 (9.26%)	
Histologic type		
G3 Endometrioid adenocarcinoma	15/96 (15.63%)	0.185
Mucinous carcinoma	1/13 (7.69%)	
Serous carcinoma	14/47 (29.79%)	
Clear cell carcinoma	3/16 (18.75%)	
Undifferentiated carcinoma	1/3 (33.33%)	
Neuroendocrine tumors	4/9 (44.44%)	
Myometrial invasion		
no invasion	0	0.000
>1/2	22/51 (43.14%)	
≤1/2	16/133 (12.03%)	
LVSI		
Yes	16/36 (44.44%)	0.000
No	22/148 (14.86%)	
Histopathologic grades		
G1	1/8 (12.5%)	0.783
G2	2/12 (16.67%)	
G3	35/164 (21.34%)	
Tumor diameter		
>2 cm	24/116 (20.69%)	0.987
≤2 cm	14/68 (20.59%)	

BMI: body mass index; LVSI: lymphatic vascular invasion.

TABLE 2. Multivariate analysis of independent risk factors of pelvic lymph node metastasis.

Risk factor	*p*	Hazard ratio	95% Confidence interval
Age, years (<55 *vs.* ≥55)	0.672	1.250	0.445–3.511
Menopause (no *vs.* yes)	0.278	2.020	0.567–7.200
LVSI (no *vs.* yes)	0.007	3.317	1.396–7.882
Myometrial invasion (≤1/2 *vs.* >1/2)	0.000	4.259	1.907–9.514

LVSI: lymphatic vascular invasion.

TABLE 3. Univariate analysis of the factors associated with para-aortic lymph node metastasis.

Risk factor	Para-aortic lymph node metastasis (n/N)	*p*
Age		
≥55	9/109 (8.26%)	0.447
<55	4/75 (5.33%)	
BMI		
≥28	4/38 (10.53%)	0.350
<28	9/146 (6.16%)	
Menopause		
Yes	10/130 (7.69%)	0.607
No	3/54 (5.56%)	
Histologic type		
G3 Endometrioid adenocarcinoma	4/96 (4.17%)	
Mucinous carcinoma	0/13 (0.00%)	
Serous carcinoma	6/47 (12.77%)	0.241
Clear cell carcinoma	1/16 (6.25%)	
Undifferentiated carcinoma	1/3 (33.33%)	
Neuroendocrine tumors	1/9 (11.11%)	
Myometrial invasion		
no invasion	0	
>1/2	5/51 (9.80%)	0.369
≤1/2	8/133 (6.02%)	
LVSI		
Yes	6/36 (16.67%)	0.012
No	7/148 (4.73%)	
Histopathologic grades		
G1	0/8 (0.00%)	
G2	0/12 (0.00%)	0.426
G3	13/164 (7.93%)	
Tumor diameter		
>2 cm	8/116 (6.90%)	0.907
≤2 cm	5/68 (7.35%)	
Pelvic lymph node metastasis		
Yes	8/38 (21.05%)	0.000
No	5/146 (3.42%)	

BMI: body mass index; LVSI: lymphatic vascular invasion.

TABLE 4. Multivariate analysis of independent risk factors of para-aortic lymph node metastasis.

Risk factor	*p*	Hazard ratio	95% Confidence interval
Pelvic lymph node metastasis (no *vs.* yes)	0.005	5.887	1.692–20.480
LVSI (no *vs.* yes)	0.186	2.335	0.665–8.195

LVSI: lymphatic vascular invasion.

Nomura *et al*. [21] also reported that PLN metastasis was an independent risk factor for PALN involvement, which supports the conclusion of this study.

Lymphatic metastasis is three times more likely in type II EC than in type I EC (27.8% in type II versus 9.4% in type I) [18]. This study showed that the rate of PLN metastasis in 184 patients with type II EC was 20.65% and the rate of PALN metastasis was 7.07%. As patients with type II EC have a higher rate of lymph node metastasis, LND should be performed in type II EC patients, especially in those with LVSI and myometrial invasion depth >1/2 [22, 23]. Regarding the level of LND, Kumar *et al*. [23] found that the positive rate of PALN was only 0.6% in EC patients without risk factors. Type II EC was considered an important independent risk factor for PALN metastasis [24, 25]. The NCCN guidelines also recommend resection of PALN to the level of the inferior mesenteric artery or subrenal vessels in patients with type II EC [20]. Approximately 51% of EC patients with PLN metastases are diagnosed with PALN metastases [24]. This study also suggested that type II EC PLN metastasis is an independent risk factor for PALN metastasis. Therefore, lymph nodes should be dissected to the para-aortic level for patients with type II EC with risk factors.

Whether patients with EC need routine LND is currently inconclusive [26]. The FIGO guidelines [4] propose that lymphadenectomy be used primarily for staging and should be considered in women with high-risk factors. However, several studies have suggested that LND does not improve the prognosis of related patients, including those with type II EC [27, 28]. The use of sentinel lymph node biopsy as an alternative to lymphadenectomy to stage women with EC is on the rise [29, 30]. It is undeniable that lymphadenectomy of the pelvic and para-aortic lymph nodes increases operative time, large vessel or nerve injury (1.4%), ureteral or bowel injury (0.6%), and intestinal obstruction (13%), among other risks [27, 28]. Based on the results of our study, lymph node dissection might be necessary for high-risk patients with type II EC. Further studies with larger samples are imperative.

The current study was limited by its single-center retrospective design, which is prone to non-response bias. This study included adults from a small population. The present study also had limitations related to PALN and PLN metastases risk factors. History of pregnancy and childbirth, immunohistochemical markers of uterine cancer lesions, and serum cancer antigen 125 (CA125) before surgery were not assessed in this study.

5. Conclusions

LVSI and a myometrial invasion depth >1/2 were significant predictors of pelvic lymph node metastasis in patients with type II EC. Patients with type II EC with pelvic lymph node metastasis may be at risk of PALN metastasis.

ABBREVIATIONS

EC, endometrial carcinoma; LVSI, lymphatic vascular invasion; PALN, para-aortic lymph node; PLN, pelvic lymph node; FIGO, Federation of Obstetrics and Gynecology; LND, lymph node dissection.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

NW—conceptualized and designed the study and collected data. ZFY, MXY, and MXL—substantially contributed to data analysis and interpretation. NM, MYW, and YGM—drafted the manuscript, analyzed, cross-checked, and interpreted all the results, and made substantial revisions to produce the final manuscript. All authors reviewed the final manuscript and approved it for submission.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for the study was obtained from the Research Ethics Committee of the PLA General Hospital (Ethical Application Ref: No. GH301-21058). All the subjects enrolled in the study provided written informed consent to participate.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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