Clinical features related to lymphatic metastasis in grade 3 endometroid endometrial cancer: a retrospective cross-sectional study

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Abstract

Background Endometrial cancer (EC) has been one of the most general cancers with respect to gynecological malignancies; however, there are debates on clinical strategies concerning treatments especially for patients with grade 3 (G3) endometroid endometrial cancer (EEC). Present study aimed to evaluate the lymphatic metastasis (LM) related factors and figure out the necessity of lymphadenectomy for G3 EEC patients.

Methods From January 2009 to April 2019, 3751 EC patients were admitted to Obstetrics and Gynecology Hospital of Fudan University. Clinical characteristics include age, grade, stage, and clinical pathological features. A total of 1235 EEC patients were involved in the multivariable analysis. Three hundred and eighty-one patients were involved in the survival analysis and the data attributed to sufficient follow-up information. Kaplan-Meier curve and log-rank test were utilized to analyze the survival rate.

Results Among the 1235 EEC patients, 181 (14.7%) were categorized as G3 and 1054 (85.3%) were grade 1 to grade 2 (G1-2). Multivariate analysis demonstrated that lymphovascular space invasion, adnexal involvement, and cervical stroma involvement were independent risk factors of LM in G3 cohort with odds ratio 3.4, 5.8, and 8.9; 95% confidence interval 1.1–10.6, 1.5–22.4, and 2.8–28.0, respectively. LM rates increased from 3.3% (3/92) to 75% (9/12) for G3 EEC cohort as related factor numbers increased from one to three. There were no differences between G3 and G1-2 EEC in overall survival and progression free survival. Additionally, no survival advantage was observed for G3 EEC patients at early stage with different plans of adjuvant treatment.

Conclusions For G3 EEC patients without other pathological positive factor, the LM rate is lower than those with other pathological positive factor. Survival analysis showed no difference between G3 cohort and G1-2 cohort. Also, different adjuvant treatments had no impact on the overall survival for G3 EEC patients.

Keywords: Endometrial cancer; Lymphatic metastasis; Multivariate analysis; Survival

Introduction

Endometrial cancer (EC) is one of the most common gynecological malignancies and the prevalence is increasing.[1] In the United States of America (USA), the number of EC patients would reach 42.13 per 100,000 persons in 2030 according to the prediction.[2] In China, the incidence of EC had an upward trend for decades.[3] Around 75% EC patients were diagnosed at an early stage, which was stage I or II defined by the Federation of Gynecology and Obstetrics (FIGO).[4] Those patients could be treated timely; therefore, EC had a relatively good 5-year overall survival (OS) ranging from 74% to 91%.[3,5] The main treatment method of EC is standard surgery including hysterectomy, bilateral salpingo-oophorectomy, and lymph node metastasis evaluation. EC risk factors are often taken into considerations for decisions of operation scope.

Grade 3 (G3) had been classified as one of the high-risk factors for comprehensive surgery such as pelvic or para-aortic lymphadenectomy (LND) according to Mayo Clinic standards.[6,7] Whether the systemic LND could be performed for every G3 endometrioid endometrial cancer (EEC) patient is a very important issue.

Some researchers suggested that exclusive LND is unnecessary. Two randomized trials evaluated systematic pelvic LND comparing with no-LND. Neither trial showed survival benefit for the LND arm among early EC patients.[8,9] To avoid excessive side effects of LND, the biopsy of sentinel lymph node (SLN) has been utilized in

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the high-risk EC recently.[10,11] Yet this technique is not widely employed especially in the regions with poor medical resources. In addition, there is an awkward situation of pathological upgrading to G3 right after the operations. Therefore, it is challenging to make a decision of surgical spectrum before operations so as to achieve the goal of maximal resection of lesions with minimum injury.

This retrospective analysis was performed to study relevant risk factors for LM in G3 EEC patients so that better clinical decisions could be made to avoid overtreatment, especially for hospitals without sentinel biopsy techniques.

Methods

Ethical approval

This investigation had informed consents from all individual participants as well as ethical approval granted by the Ethics Committee in Obstetrics and Gynecology Hospital Affiliated to Fudan University (approval No. 2020-190).

Study population

The retrospective study was performed on 3751 patients with EC diagnosed in Obstetrics and Gynecology Hospital of Fudan University, who were enrolled from January 2009 to April 2019. The inclusion criteria were as follows: (1) patients that were diagnosed as EEC based on pathological diagnosis in Obstetrics and Gynecology Hospital of Fudan University; (2) patients that underwent total hysterectomy and comprehensive staging surgery; (3) patients that were willing and able to be followed up. The exclusion criteria were as follows: (1) patients who failed to receive comprehensive staging surgery; (2) patients that had no-endometroid histology type; (3) patients with incomplete or unknown baseline information. 2105 patients who did not receive comprehensive staging surgeries were excluded. Three hundred and thirty-one patients were excluded for non-endometrioid histology type and 80 patients were excluded for unknown/inconsistent pathologic staging [Figure 1].

The sample size was estimated to be 247 in each cohort and the total sample size was 494 after correction for

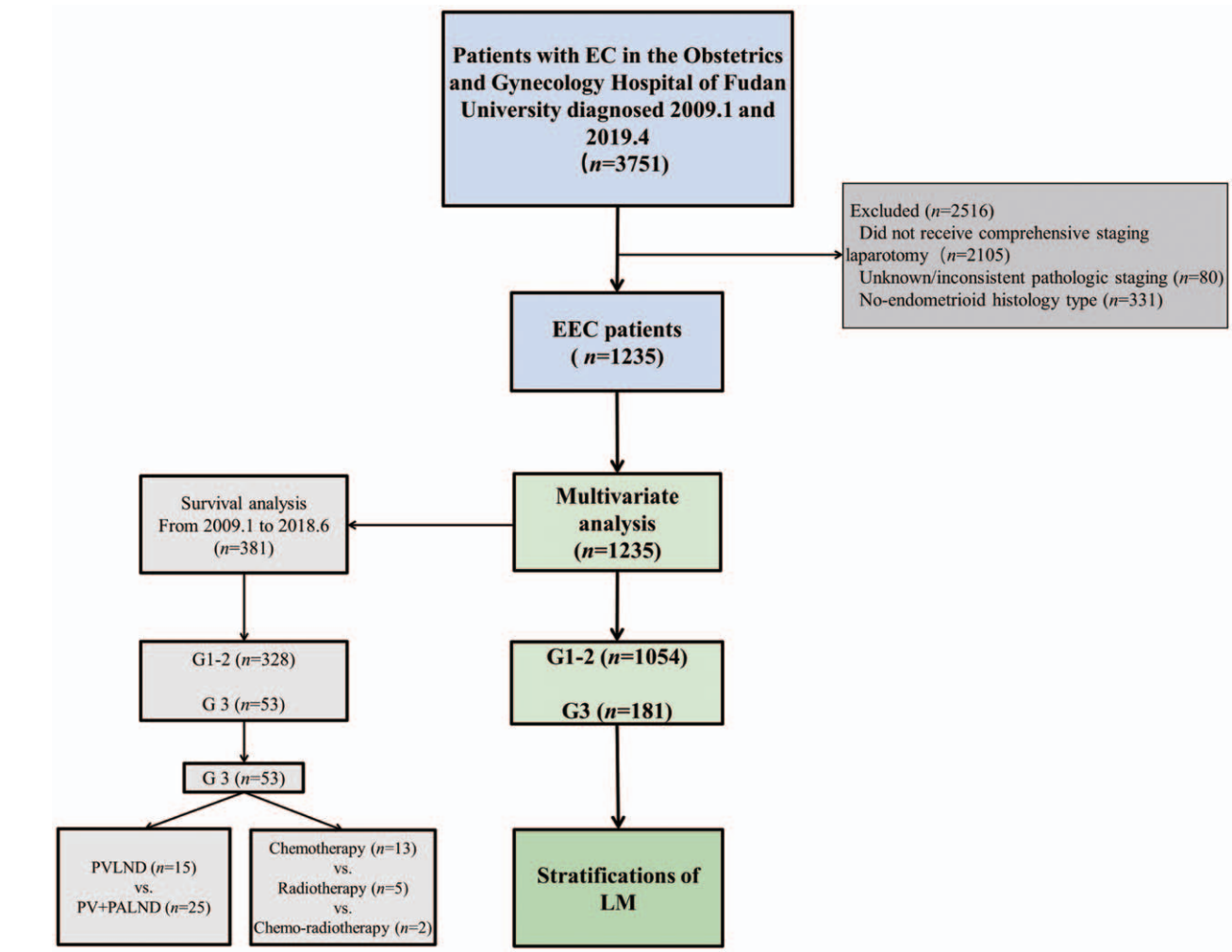

Figure 1: Cross-sectional clinical trial profile of endometrial cancer patients. Data are shown as numbers. Bold font indicates the main context of this research. EC: Endometrial cancer; EEC: Endometrioid endometrial cancer; G1-2: Grade1-2; G3: Grade 3; LM: Lymphatic metastasis; PA + PVLND: Pelvic and para-aortic lymphadenectomy; PVLND: Pelvic lymphadenectomy.

continuity according to principles of retrospective cross-sectional analysis[12,13] as well as estimated LM rates of G1-2 and G3 in Gynecologic Oncology Group pilot study ($\alpha = 0.05$, $1\text{-}\beta = 0.8$, $P1 = 0.18$, $P2 = 0.09$. $P1$ is the estimated possibility of LM in G3 EEC patients and $P2$ stands for the estimated possibility of LM in G1-2 EEC patients).[14]

Since a number of EEC patients refused to respond to follow-up calls, we lost some information during this period of 10 years. The follow-up loss rate is 69.1% (854/1235).

Clinical data collection

Clinical data were collected from EEC patients including age, grade, and FIGO stage. Pathological features such as Microcystic, Elongated, and Fragmented (MELF) pattern of invasion, lymphvascular space invasion, cervical stroma involvement (CSI), adnexal involvement (AI), parametrium involvement (PI), tumor size (TS), and myometrium invasion (MI) were collected after hysterectomy treatments. In FIGO definition, lesions without solid areas were grade 1. Tumors with less than 50% solid area were grade 2, and those with solid area greater than 50% were G3. MELF is a type of invasive pathologic pattern in EC.[15] LVSI was defined as the presence of tumor cells in a space lined by endothelial cells, which means cancer invading into lymph-vascular space.[16] CSI means EC invading the cervical stroma and AI is cancer involvement of ovary and fallopian tube diagnosed by pathology or imaging measurements.[17,18] PI stands for tumor metastasis of fibrous tissue adjacent to uterus.[19] According to TSs, patients were divided into two groups depending on the volume (small $\leq$2 cm; large $>$2 cm). MI includes: shallow invasion (tumor cells invading less than or equal to 50% of uterus myometrium) and deep invasion (tumor cells that involved over 50% of uterus myometrium).[20]

Statistical analysis

Statistical analysis was performed employing SPSS Statistics (v22.0; IBM Corporation, Armonk, NY, USA); STATA (v15.0; Stata Corp, College Station, TX, USA) and GraphPad Prism (v8; GraphPad Software, San Diego, CA, USA). Continuous variables including age were grouped into categorical variables, which were expressed as numbers of cases (%) and analyzed with Pearson Chi^2 test as well as Yates' adjusted Chi^2 test. The correlations between LM rates and clinical features were calculated by multivariate linear regression analysis.

The primary endpoint was defined as the timing of death. OS was defined as the time from the date of diagnosis until death or the last follow-up in June 2018. The secondary endpoint was EC recurrence and progression free survival (PFS) estimates were assessed. Medical records were reviewed to determine OS and PFS according to the status of lymphatic metastasis. Survival rates were estimated using Kaplan-Meier method and log-rank test was utilized to draw survival curve. A $P < 0.05$ was defined as statistically significant.

Results

Characteristics of study cohort

A total of 1235 cases were analyzed according to the inclusion criteria. There were 181 cases of G3 (14.7%) and 1054 cases of G1-2 (85.3%). For survival analysis, 53 G3 patients (13.9%) and 328 G1-2 patients (86.1%) were included, respectively [Figure 1]. The characteristics of the 1235 patients were as follows: (i) patients aged from 21 to 79 years old; (ii) patients at early stage (FIGO stage I or II) accounted for 85.5% (1056/1235); (iii) the OS ranged from 6 to 128 months and PFS ranged from 0 to 128 months; (iv) the median survival of G1-2 cohort was 109 months while there were invalid results for G3 EEC patients due to small sample size.

Stratification analysis for risk factors in lymphatic metastasis

The LM rate (16.6%, 30 out of 181) in G3 population is around twice higher than that of G1-2 (9.4%, 99 out of 1054). Patients over 70 years old in G1-2 group presented with the highest LM rate. There is no obvious difference among the subgroups of G3 with different ages. The risk of LM G3 EEC patients with any of the following risk factors would be increased by 3 to 5 folds, which included LVSI, CSI, AI, or MI [Table 1].

After adjusting for age, PI and TS in multivariate analysis, we found that LVSI, AI, and CSI were independent risk factors for LM (adjusted OR = 3.4, 5.8, 8.9; 95% CI: 1.1–10.64, 1.5–22.4, 2.8–28.0, respectively) in G3 EEC cohort. LVSI, AI, MELF, and MI (adjusted OR = 8.8, 3.4, 2.2, 5.0; 95% CI: 4.9–16.0, 1.3–8.9, 1.3–3.9, 2.9–8.6, respectively) were independent risk factors amongst G1-2 cohort [Figure 2]. The overall population presented with similar trends with G1-2 subgroup (adjusted OR = 7.0, 3.2, 2.7, 4.3; 95% CI: 4.1–11.7, 1.5–6.8, 1.6–4.5, 2.7–6.9, respectively) [Figure 2]. From our data, we observed that TS increased LM risk for G1-2 other than G3.

Among 181 G3 EEC patients, general LM rate was 16.6% (30/181). With negative LVSI, CSI, and AI, the LM rate was 3.3% (3/92). When combining with single positive LVSI or CSI or AI, the LM rate was 14.5% (8/55) or 2/7 or 1/2, respectively. The LM rate increased to 75% (9/12) combining with positive LVSI and CSI. Likewise, with positive LVSI and AI, the LM rate reached 60% (6/10). LM rate regarding G3 EEC patient with positive LVSI, CSI, and AI was 33% (1/3) [Table 2].

Survival analysis

From January 2009 to June 2018, no patients died with EC. 1.8% (7/381) patients had recurrence [Supplementary Table 1, http://links.lww.com/SLA/D394]. Five-year OS was 100.0% and 5-year PFS was 98.2% (374/381). Kaplan-Meier curves illustrated that the OS or PFS of G3 group was not significantly shorter than compared with G1-2 group (log-rank $P > 0.05$) [Figure 3]. In G3 EEC patients at stage I or II, OS and PFS analysis showed that there was no distinct difference between two subgroups.

Table 1: Clinical characteristics of lymphatic metastasis in grade 3 cohort *vs.* grade 1 and grade 2 cohort.

Variables	G3 cohort ($n=181$)				G1-2 cohort ($n=1054$)			
	LM negative	LM positive	χ^2	*P*	LM negative	LM positive	χ^2	*P*
Age at diagnosis, *n* (%)			17.757	0.142*			12.039	0.856*
≤30 years	2 (2/3)	1 (1/3)			19 (90.5)	2 (9.5)		
31–40 years	5 (5/8)	3 (3/8)			65 (91.5)	6 (8.5)		
41–50 years	26 (72.2)	10 (27.8)			264 (91.7)	24 (8.3)		
51–60 years	71 (87.7)	10 (12.3)			421 (90.3)	45 (9.7)		
61–70 years	44 (89.8)	5 (10.2)			167 (90.3)	18 (9.7)		
>70 years	3 (3/4)	1 (1/4)			19 (82.6)	4 (17.4)		
MELF, *n* (%)			6.846	0.093*			10.801	<0.001
No	148 (84.6)	27 (15.4)			880 (94.1)	55 (5.9)		
Yes	3 (3/6)	3 (3/6)			75 (63.0)	44 (37.0)		
LVSI, *n* (%)			11.389	<0.001			42.052	<0.001
No	95 (94.1)	6 (95.9)			805 (97.5)	21 (2.5)		
Yes	56 (70.0)	24 (30.0)			150 (65.8)	78 (34.2)		
CSI, *n* (%)			16.947	<0.001			3.274	<0.001
No	141 (88.7)	18 (11.3)			856 (91.8)	76 (8.1)		
Yes	10 (45.5)	12 (54.5)			99 (81.1)	23 (18.9)		
AI, *n* (%)			2.777	<0.001			6.900	0.002
No	144 (86.7)	22 (13.3)			924 (91.2)	89 (8.8)		
Yes	7 (7/15)	8 (8/15)			31 (75.6)	10 (24.4)		
PI, *n* (%)			2.365	0.413*			8.417	1.000*
No	148 (84.1)	28 (15.9)			950 (90.6)	98 (9.4)		
Yes	3 (3/5)	2 (2/5)			5 (5/6)	1 (1/6)		
TS, *n* (%)			5.060	0.338			9.786	<0.001
≤2cm	54 (87.1)	8 (12.9)			467 (94.7)	26 (5.3)		
>2cm	97 (81.5)	22 (18.5)			488 (87.0)	73 (13.0)		
MI, *n* (%)			31.904	<0.001			36.627	<0.001
Shallow (MI ≤ 50%)	101 (91.8)	9 (8.2)			801 (96.4)	30 (3.6)		
Deep (MI >50%)	50 (70.4)	21 (29.6)			154 (69.1)	69 (30.9)		
Stage, *n*			NA	NA			NA	NA
IA	98	–			733	–		
IB	33	–			115	–		
II	7	–			70	–		
IIIA	8	–			32	–		
IIIB	5	–			5	–		
IIIC1	–	12			–	55		
IIIC2	–	17			–	42		
IV	–	1			–	2		

*Yates' adjusted Chi^2 test; Bold font indicates $P < 0.05$. AI: Adnexal involvement; CSI: Cervical stroma involvement; LVSI: Lymph vascular space invasion; MELF: Endo, Microcystic, Elongated, and Fragmented endometrioid carcinoma; MI: Myometrium involvement; NA: Not available; PI: Parametrium involvement; TS: Tumor size.

The first group was divided into chemotherapy, radiotherapy, and chemoradiotherapy (log-rank $P > 0.05$). The second group was classified as pelvic LND and pelvic + para-aortic LND (log-rank $P > 0.05$) [Supplementary Figure 1, http://links.lww.com/SLA/D395].

Discussion

Establishing a simple risk prediction model for clinician is of significance. Age, grade, MI, LVSI, and TS have been elucidated to have effects upon LM predictions, which might provide insights to physicians for better clinical and diagnosis decisions.[16,21-23] SLN technique helps us to achieve a balance between the maximum resection of lesions and the minimum injury. Even with rare chance, G3 EEC patients had around 20% less chance for SLN mapping than G1-2 according to a survey involving gynecology oncologists.[24] We believe that pathologic grade should be the most reliable and accessible factor. That is the reason why G3 was selected as indicator to evaluate the probability of LM in this investigation.

Inconsistent standards were published by different institutions. Mayo and FIGO guidelines tend to categorize TS >2 cm as high-risk. While according to National Comprehensive Cancer Network (NCCN) and Europe's Leading Medical Oncology Society guidelines, TS was not regarded as a high-risk factor.[5,25,26] In fact, it is non-trivial to determinate the TS due to its irregular shape of lesion and

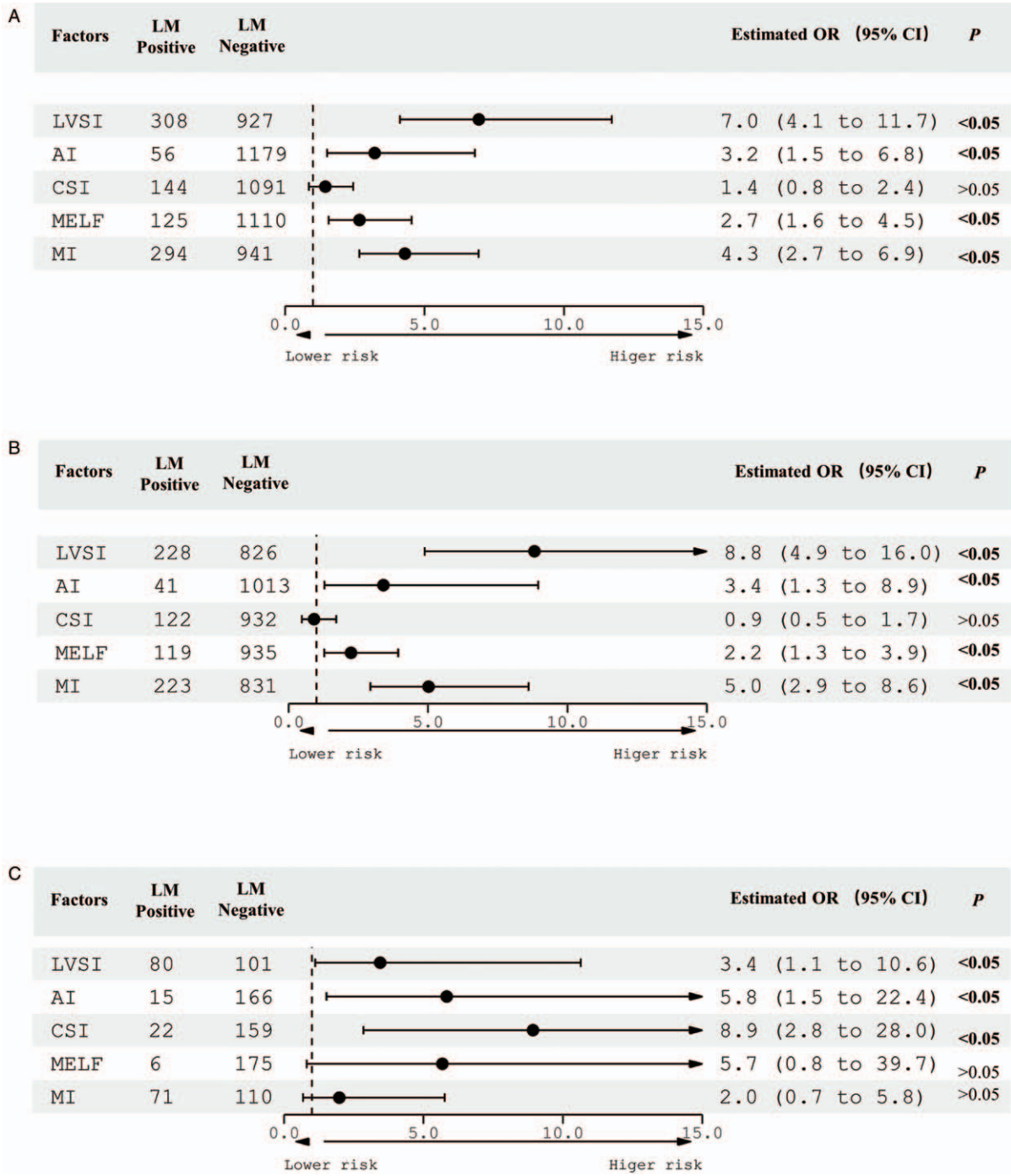

Figure 2: Multivariate analysis of lymphatic metastasis related risk factors of endometroid endometrial cancer patients. (A). The multivariate analysis of all endometroid endometrial cancer patients. (B). The multivariate analysis of grade 1 and grade 2 endometroid endometrial cancer patients. (C). The multivariate analysis of grade 3 endometroid endometrial cancer patients. Data shown as numbers. AI: Adnexal involvement; CI: Confidence interval; CSI: Cervical stroma involvement; LM: Lymphatic metastasis; LVSI: Lymphovascular space invasion; MELF: Endo, Microcystic, Elongated, and Fragmented; MI: Myometrium invasion; OR: Odds ratio.

therefore the latest NCCN guideline had removed this factor.[25]

Based on report results from international or national guidelines as well as other literatures,[25-28] it is true that deep myometrial invasion (MI >50%) increased the risk of lymph nodes metastasis. However, accurate evaluation of deep myometrial invasion before operation is challenging. Though the NCCN guidelines recommend the usage of pelvic enhanced magnetic resonance imaging (MRI) to determine the myometrial invasion (myoinvasion >50% is considered as a risk factor) depth,[25] the MRI accuracy is about 68% for T2-weighted imaging.[28]

As for age, it was considered that higher age was associated with higher LM chance; however, the age cut-off was still inconsistent. According to the latest NCCN guidelines, "age ≥60" was considered as an age cut-off[25] though in

Table 2: Lymphatic metastasis rates stratified by lymph vascular space invasion (LVSI), cervical stroma involvement (CSI), and adnexal involvement (AI) in grade 3 endometrial cancer patients.

Number of risk related factors	Subgroup	LM negative ($n = 151$)	LM positive ($n = 30$)
0	LVSI− CSI− AI−	89 (96.7)	3 (3.3)
1	LVSI+ CSI− AI−	47 (85.5)	8 (14.5)
1	LVSI− CSI+ AI−	5 (5/7)	2 (2/7)
1	LVSI− CSI− AI+	1 (1/2)	1 (1/2)
2	LVSI+ CSI+ AI−	3 (3/12)	9 (9/12)
2	LVSI− CSI+ AI+	0 (0)	0 (0)
2	LVSI+ CSI− AI+	4 (4/10)	6 (6/10)
3	LVSI+ CSI+ AI+	2 (2/3)	1 (1/3)

Data are presented as *n* (%). +: Positive pathology; −: Negative pathology. AI: Adnexal involvement; CSI: Cervical stroma involvement; LM: Lymphatic metastasis; LVSI: Lymph vascular space invasion.

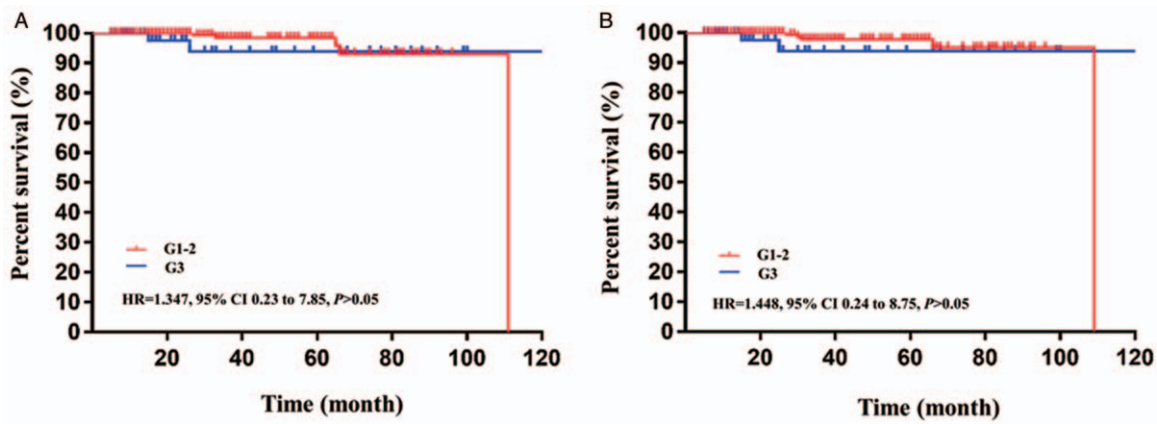

Figure 3: Survival analysis of grade 3 cohort versus grade 1 and grade 2 cohorts. (A). Overall survival of grade 3 versus grade1 and grade 2 cohorts (B). Progression free survival of grade 3 versus grade 1 and grade 2 cohorts. Data shown as percentage survival (%).CI: Confidence interval; G1-2: Grade 1 and grade 2; G3: Grade 3; HR: Hazard ratio.

our data, "≥70-year-old" seemed to have significant impacts upon LM.

For LVSI, it is indispensable in EC carcinogenesis, which has been emphasized again recently. LVSI is a potential predictor for EC recurrence,[16,29] which is associated with significantly higher rate of paraaortic LM with OR of 5.[30] A retrospective study showcased that there was no OS difference between adjuvant external beam radiation therapy and vaginal brachytherapy for LVSI-positive patients, while it was associated with increased risk of mortality (hazard ratio of 1.94).[31] Unfortunately, it is quite difficult to get LVSI before operation.

Finally, we selected G3 as our first concern to make decisions prior to operations of EC patients. We discovered that G3 EEC patients without any extra risk factor (LVSI, AI, or CSI) had an LM rate of 3.3% (3/92), which is remarkably lower than other risk factors. In this regard, LND might not be needed. On the contrary, G3 EEC patients with one or more extra risk factors had higher chances of lymph node metastasis, which could be explained by synergetic effects due to these risk factors. G3 EEC patients with only one risk factor presented with LM rate ranging from 14.5% (8/55) to 1/2. If there were two extra risk factors, LM rate would increase to 6/10 and 75% (9/12). G3 EEC patients with positive LVSI, AI, and CSI were found to have lower LMN incidence at 1/3. We assumed that it was due to the limited sample size.

The categorization of three tiers of LVSI was investigated by pathologists to evaluate its potential risk.[29] Although our study failed to categorize LVSI into three tiers, our results are consistent with previous opinions. LVSI was independent risk factors in G3 and G1-2 subgroups, which increased the LM rates to more than three folds and eight folds, respectively. Therefore, we recommend G3 EEC patients with LVSI to receive lymph node evaluation. G3 EEC patients with no other risk factors could be evaluated only with imaging. While G3 EEC patients with positive LVSI in their final pathological diagnosis should be evaluated by both imaging and comprehensive staging surgery if they were not done previously, which is consistent with the latest NCCN guidelines.[25]

There are debates on surgical procedures among EC patients. Recent systematic analysis proposed superior benefits of combined pelvic and para-aortic rather than pelvic LND alone.[24] While two randomized trials indicated that systematic pelvic LND had no survival benefits compared with non-LND in early EC patients.[8,9] A recent Israeli group study advised that surgical staging

by pelvic LND is not associated with higher metastatic rates or better survival of EC patients.[32] Consistently, our data showed no survival difference between G3 and G1-2 patients, which informed that "grade" might not influence patients prognosis although G3 patients had higher rate of LM than G1-2 patients. Similarly, patients with pelvic and para-aortic lymph node dissection had similar OS and PFS to patients with only pelvic lymph node dissection in G3 population at early stage, which suggested that less traumatic treatment could be considered for these patients.

In addition, we found that MELF and MI only increased the LM rate among G1-2 population, while CSI increased the LM risk of G3 patients. This might indicate different metastasis pathways in EC patients with various grades, for which further investigations should be carried out.

In this study, our strength was based upon the follow-up duration of almost ten years. In addition, the independent high-risk factors were robust to adjustments. We provided clinically friendly data by stratifying these risk factors, which proposed certain evidence for clinical practice especially in areas with poor medical resources. Nevertheless, this study still had limitations. Since this is a retrospective analysis, selection bias may have influenced the treatments given to G3 patients. Only 381 (30.9%) patients were discovered to have complete follow-up data due to technical reasons, which might lead to certain bias of survival analysis. However, there might be no important bias when randomly missing follow-up in cohort studies even if the loss rate reached 60%.[33] Studies with larger sample sizes along with prospective clinical trial designs with novel molecular classifications warrant more considerations.

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Conflicts of interest

The design, data collection and analysis, and manuscript writing of this study were all independently completed by researchers of Obstetrics and Gynecology Hospital of Fudan University, and clinical data were independently kept by Obstetrics and Gynecology Hospital of Fudan University. The authors have full access to clinical data and are responsible for the originality and the accuracy.

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