EJGO European Journal of Gynaecological Oncology

Original Research

Criteria for predicting ovarian metastasis in early-stage cervical adenocarcinoma

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Summary

Objectives: To evaluate the clinicopathologic risk factors for and construct criteria to predict the risk of ovarian metastasis in early-stage cervical adenocarcinoma. *Materials and Methods:* Subjects were cervical adenocarcinoma patients with International Federation of Gynecology and Obstetrics (FIGO) Stage less than or equal to IIB who underwent hysterectomy and bilateral salpingo-oophorectomy and pelvic lymphadenectomy at this institution between January 2010 and December 2017. Clinicopathologic variables were studied by univariate and logistic regression analysis to identify the risk factors, and then criteria were built. *Results:* Four hundred and nineteen patients were enrolled in the study, and ovarian metastasis rate was 4.50% (19/419). Eight patients had normal appearance, and 14 patients had bilateral ovarian metastases. Univariate analysis revealed that clinical stage ($p < 0.001$), preoperative hemoglobin ($p = 0.017$), preoperative red blood cell count ($p = 0.001$), histology type ($p < 0.001$), deep cervical stromal invasion ($p < 0.001$), lymphatic vascular space invasion ($p < 0.001$), parametrial invasion ($p < 0.001$), marginal invasion ($p < 0.001$), vaginal invasion ($p < 0.001$), uterine corpus invasion ($p < 0.001$) , fallopian tube invasion ($p < 0.001$), and pelvic lymph node metastasis ($p < 0.001$) were associated with ovarian metastasis. The logistic regression analysis revealed that clinical stage (odds ratio, OR, 11.747; 95% confidence interval, CI, 1.969-70.082), histology type (OR, 5.069; 95% CI, 1.249-24.904), lymphatic vascular space invasion (OR, 13.369; 95% CI, 2.194-81.469,) and fallopian tube invasion (OR, 124.305; 95% CI, 20.969-736.871) were independently associated with ovarian metastasis. When the clinical stage, histology type, lymphatic vascular space invasion, and fallopian tube invasion were considered as high-risk factors for ovarian metastasis, the sensitivity, specificity, positive predictive value, and negative predictive value were found to be 100.00%, 58.76%, 10.00%, 100.00%, and 60.57%, respectively. *Conclusion:* Clinical stage, histology type, lymphatic vascular space invasion, and fallopian tube metastasis may be used in the prediction of ovarian metastasis in early-stage cervical adenocarcinoma.

Key words: Adenocarcinoma; Ovarian metastasis; Ovarian preservation; Clinical risk factors.

Introduction

Cervical cancer is the fourth most common malignancy of the female reproductive system and the fourth leading cause of cancer death in women in the United States [1]. In developing countries, cervical cancer is the second most common malignancy and the third leading cause of cancer death in women [2]. The above studies show that the mortality rate of cervical cancer can be effectively reduced along with the screening, prevention of HPV infection, better treatment, but the constitution of pathological types is changing. Smith *et al.* [3] reported that, after adjusting for age, the incidence of squamous cell carcinoma (SCC) decreased by 41.9% over time, while the incidence of cervical adenocarcinoma (ADC) increased by 29.1%. Bray *et al.* [4] also confirmed that the age-adjusted incidence of ADC patients increased by 0.5% to more than 3% each year in Europe. The incidence of SCC patients is decreasing, while that of ADC patients is increasing with proportion of ADC patients in cervical cancer as high as 23% in a prior report [5].

A systematic review found that the incidence of ovarian metastasis (OM) in patients with SCC and ADC was 0.4% and 2%, respectively [6]. The incidence of OM in ADC patients was 4.98% to 8.1% in China [7, 8]. Since Shimada *et al.* [9] found that the rate of ovarian metastasis in ADC patients was 5.31%, bilateral salpingo-oophorectomy (BSO) was recommended for ADC patients. However, it had been observed that nearly 50 percent of ADC patients were premenopausal and younger than 45 years old [10]. For young ADC patients, BSO caused lower estrogen levels which may lead to menopausal symptoms such as hot flashes, night sweats, and osteoporosis and may decrease quality of life. Although there were non-hormonal interventions available to improve menopausal symptoms [11, 12], the larger issue was the lack of protective effects of estrogen on the cardiovascular and motor systems. It had been suggested that HRT could be used to improve low estrogen status in patients with SCC after BSO, but it was not mentioned for ADC patients [13]. Estrogen is

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Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XLI, n. 5, 2020
doi: 10.31083/j.ejgo.2020.05.5219

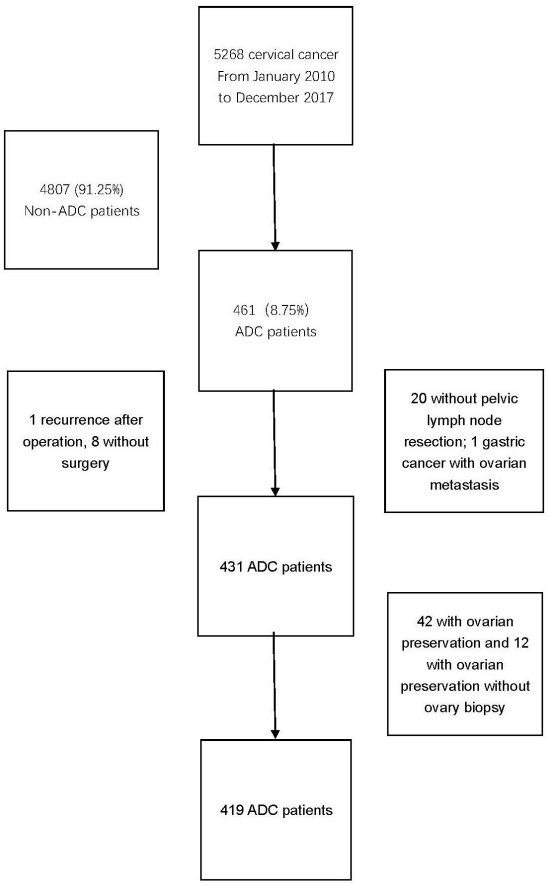

Figure 1. — Patient screening flow chart.

needed to preserve the ovaries in young ADC patients to improve the quality of life. Laparoscopic ovarian transposition has been reported safe and effective in preserving ovarian function [14]. The purpose of this article was to clarify high-risk factors for OM and establish prediction criteria for these factors in ADC patients.

Materials and Methods

The data of all cervical cancer patients diagnosed in West China Second University Hospital between January 2010 to December 2017 was reviewed retrospectively. All cases were confirmed by histological pathological examination, we included only ADC patients and used the standard WHO classification of cervical cancer (2014) as the diagnostic criteria for staging. Patients with stage IA-IIB (International Federation of Gynecology and Obstetrics (FIGO)) tumors were included. For ADC patients with FIGO Stage IA, sub-radical hysterectomy and pelvic lymph node dissection were performed. For patients with Stage IB-IIB, primary treatment consisted of radical hysterectomy, BSO, pelvic lymph node dissection, and/or para-aortic lymph node sampling. All surgical procedures were performed by gynecologic oncologists. We also included patients that had preoperative neoadjuvant chemotherapy, ovarian biopsy, or resection of only one ovary without another ovary biopsy. The patients with recurrent tumors or that had OM from other cancers were excluded. Clinicopathological data was extracted from medical records after obtaining informed consent from all patients.

Table 1. — *Clinicopathological features of cervical adenocarcinoma patients (n = 419).*

Characteristics	Value$^{\alpha}$
Age (year)	44.54 ± 8.15
BMI$^{\beta}$ (Kg/M^2)	22.46 ± 2.80
Preoperative red blood cell count (*10^{12}/L)	4.31 ± 0.40
Preoperative hemoglobin (g/L)	126.37 ± 14.91
Pelvic lymph node number	21.18 ± 7.96
Overweight (BMI $\geq$ 23)	162 (38.7)
Tumor family history	38 (9.1)
Neoadjuvant chemotherapy	97 (23.2)
FIGO stage	
IA	11 (2.6)
IB1	244 (58.2)
IB2	46 (11.0)
IIA1	54 (12.9)
IIA2	42 (10.0)
IIB	22 (5.3)
Histological types	
Mucinous carcinoma (common type)	217 (51.8)
Mucinous carcinoma (gastric type)	27 (6.4)
Villoglandular carcinoma	12 (2.9)
Endometrioid carcinoma	121 (28.9)
Clear cell carcinoma	14 (3.3)
Others$^{\gamma}$	28 (6.7)
Pelvic lymph node status	
No	345 (82.3)
Yes	74 (17.7)
Ovarian status	
No	400 (95.5)
Yes	19 (4.5)

BMI: body mass index; FIGO: International Federation of Gynecology and Obstetrics; α: the value is the mean $\pm$ standard deviation or percentage; β: the weight is divided by the square of the height; γ: 11 cases including mucinous carcinoma (intestinal type), two case of mucinous adenocarcinoma (signet ring type), one case of serous carcinoma, two cases of early invasive adenocarcinoma; one case of mesonephric carcinoma; 11 cases of adenocarcinoma admixed with neuroendocrine carcinoma.

The role of clinicopathological factors in the prediction of OM was evaluated. Factors included body mass index ($<$ 23 *vs.* $\geq$ 23), neoadjuvant chemotherapy (NACT), tumor family history, tumor diameter ($<$ 4 cm *vs.* $\geq$ 4 cm), FIGO staging (I *vs.* II), preoperative hemoglobin (Hb $\geq$ 120 g/L *vs.* Hb $<$ 120 g/L), preoperative red blood cell count (RBC $\geq$ 4.0*10^{12}/L *vs.* RBC$<$ 4.0*10^{12}/L), preoperative white blood cell counts ($<10\times10^9$/L *vs.* $\geq 10\times10^9$/L), preoperative platelet counts ($<390\times10^9$/L *vs.* $\geq 390\times10^9$/L),

preoperative fibrinogen ($<$ 258 mg/L *vs.* $\geq$ 258 mg/L), gross lesion types (exogenous, infiltrative, and ulcerative), histological grade, histological types (gastric-type endocervical adenocarcinoma, GAS *vs.* non-GAS), depths cervical stroma invasion (DSI), lymphatic vascular space invasion (LVSI), parametrial invasion (PMI), marginal invasion (MI), uterine corpus invasion (UCI), vaginal invasion (VI), fallopian tube invasion (FTI), and pelvic lymph node metastasis (PLNM). Clinical stage was determined according to FIGO guidelines revised in 2014. Histological grade was categorized as low (high to moderate differentiation, early invasive adenocarcinoma, GAS, and villoglandular carcinoma) or high (low differentiation or clear cell carcinomas). Information of DSI was classified as $<$ 1/2 or $\geq$ 1/2. Histological types were categorized as GAS (minimal deviation adenocarcinoma was included) *vs.* non-GAS.

Based on the results of logistic regression analysis, the prediction criteria were established and then the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the criteria were evaluated. All statistical analyses were performed by using SPSS version 22 and p values less than 0.05 were considered statistically significant. Pearson chi-square test was used to compare categorical data. Logistic regression analysis was used to detect independent risk factors of ovarian metastasis. Odds ratios with 95% CIs were used to display the strength of association.

Results

Cervical cancer patients (n = 5268) were admitted to our institution from January 2010 to December 2017 (Figure 1), and 4,807 patients were excluded because of non-ADC tumors. Twenty patients without pelvic lymph node dissection were considered ineligible. Other exclusions were 1 patient with a recurrent tumor, 8 nonsurgical patients, 1 gastric cancer with ovarian metastasis, 12 patients with surgeries preserving ovaries without performing ovary biopsy. In the present study, 8 patients had normal appearance during operation, and 14 patients had bilateral ovarian metastases. A total of 419 patients were enrolled into the study. The OM rate was 4.50% (19/419). Pelvic lymph node metastasis rate was 17.70%. Characteristics of other clinicopathological features are shown in Table 1.

Table 2 shows the clinicopathological features of ADC in patients with and without OM. The OM rates in GAS and non-GAS patients were 25.93% (7/27) and 3.06% (12/392), respectively. Univariate analysis revealed that clinical stage ($p < 0.001$), preoperative hemoglobin ($p = 0.017$), preoperative red blood cell count ($p = 0.001$), histology type ($p < 0.001$), deep cervical stromal invasion ($p < 0.001$), lymphatic vascular space invasion ($p < 0.001$), parametrial invasion ($p < 0.001$), marginal invasion ($p < 0.001$), vaginal invasion ($p < 0.001$), uterine corpus invasion ($p < 0.001$), fallopian tube invasion ($p < 0.001$), and pelvic lymph node metastasis ($p < 0.001$) were associated with ovarian metastasis.

Significant variables from univariate analysis were entered into a logistic regression model. Logistic regression revealed that clinic stage (odds ratio, OR, 11.747; 95% confidence interval, CI, 1.969-70.082), histology type (OR, 5.069; 95% CI, 1.249-24.904), lymphatic vascular space invasion (OR, 13.369; 95% CI, 2.194-81.469,) and fallopian tube invasion (OR, 124.305; 95% CI, 20.969-736.871) were independently associated with ovarian metastasis.

Table 3 shows the diagnostic performance of high-risk factors alone or combination together to predict OM. When the authors considered FIGO clinical Stage II, GAS, LVSI, and FTI as high-risk factors for ovarian metastasis, the specificity and NPV were 59.00% and 100%, respectively. Ovarian metastasis was correctly estimated in 255 (60.86%) women, overestimated in 164 women (39.14%) and no underestimated patients.

Discussion

In the current study, the percentage of ADC was 8.75% in cervical cancer patients. Our results differed from a systematic review that found that the percentage of ADC was 19.14% [6]. The lower proportion of ADC patients in our study may be related to the fact that this study was based on the WHO histological classification of cervical cancer in 2014 and cervical adenosquamous carcinoma and neuroendocrine carcinoma were not included. In the current study, the OM incidence rate in ADC patients was 4.50%, similar to literature reports of 2%-5.31% [6, 9]. The above results confirm that the OM incidence rate was high in ADC patients. Ovarian invasion tended to be bilateral and the appearance was normal in some cases of ADC patients. It had been reported that 56.25% (9/16) of patients with ADC had micro-metastasis and 66.67% (10/ 15) had bilateral ovary invasion [15]. Wen *et al.* also found that 50% (8/16) of patients with ovarian metastasis had normal ovarian appearance [8]. Our results found that 42.11% (8/19) of patients with ovarian metastasis had a normal ovarian appearance and 73.68% (14/19) had bilateral ovary metastases. This might be related to the pathway of OM, speculated to be lymphatic spread, transtubal implantation or via hematogenous spread [16, 17]. The present authors believed that perform ovarian biopsy was needed even if with normal ovarian appearance when intended to keep ovaries. Although patient quality of life could be improved by preserving ovaries in young ADC women, significant challenges remained in defining low-risk populations for OM to avoid residual ovarian foci. Prior studies identified neoadjuvant chemotherapy, FIGO staging, tumor diameter $\geq$ 4 cm, DSI $\geq$ 1/2, LVSI, PMI, UCI, FTI, and PLNM as risk factors for OM in ADC patients [7, 18, 19]. In the present study, logistic regression showed that clinical stage, histology type, LVSI and FTI were significantly associated with OM in ADC patients.

In the current study, histological type was an important variable affecting OM in ADC. The OM rate was found to be 25.93% in GAS patients and 3.06% in non-GAS pa-

Table 2. — *Relationship between ovarian metastasis and clinicopathological variables (n = 419).*

Variables	Without OM n (%)	With OM n (%)	*p*
Neoadjuvant chemotherapy			0.015
Yes	88/419 (22.0)	9/419 (2.1)	
No	312/419 (74.5)	10/419 (2.4)	
FIGO stage			< 0.001
I	298/419 (71.1)	3/419 (0.7)	
II	102/419 (24.3)	16/419 (3.8)	
Preoperative hemoglobin (g/L)			0.017
≥ 110	356/419 (85.0)	13/419 (3.1)	
< 110	44/419 (10.5)	6/419 (1.4)	
Preoperative red blood cell count (*10^{12}/L)			0.001
≥ 4	330/419 (78.8)	9/419 (2.1)	
< 4	70/419 (16.7)	10/419 (2.4)	
histological types			< 0.001
non-GAS	380/419 (90.7)	12/419 (2.9)	
GAS	20/419 (4.8)	7/419 (1.7)	
Depths cervical stroma invasion			< 0.001
$<$ 1/2 or no invasion	225/419 (53.7)	2/419 (0.5)	
$\geq$ 1/2	175/419 (41.8)	17/419 (4.1)	
Lymphatic vascular space invasion			< 0.001
No	304/419 (72.6)	4/419 (1.0)	
Yes	96/419 (22.9)	15/419 (3.6)	
Parametrial invasion			< 0.001
No	373/419 (89.0)	11/419 (2.6)	
Yes	27/419 (6.4)	8/419 (1.9)	
Marginal invasion			$< 0.001^*$
No	397/419 (94.7)	14/419 (3.3)	
Yes	3/419 (0.7)	5/419 (1.2)	
Vaginal invasion			< 0.001
No	339/419 (80.9)	9/419 (2.1)	
Yes	61/419 (14.6)	10/419 (2.4)	
Uterine corpus invasion			< 0.001
No	302/419 (72.1)	3/419 (0.7)	
Yes	98/419 (23.4)	16/419 (3.8)	
Fallopian tube invasion			$< 0.001^*$
No	395/419 (94.3)	8/419 (1.9)	
Yes	5/419 (1.2)	11/419 (2.6)	
Pelvic lymph node metastasis			< 0.001
No	340/419 (81.1)	5/419 (1.2)	
Yes	60/419 (14.3)	14/419 (3.3)	

*OM: ovarian metastasis; FIGO: International Federation of Gynecology and Obstetrics; GAS: gastric-type endocervical adenocarcinoma. *Fisher Exact Test.*

tients, similar to literature reporting 30%-35% [8, 20]. The present authors believed that it was not appropriate to preserve ovaries in GAS due to the relatively high OM rate.

Relatively little knowledge was available related to the diagnostic efficacy of criteria for ovarian metastasis in ADC patients. According to the present authors' knowledge, only Touhami *et al.* [21] mentioned in a systemic review that if ADC patients are younger than 45-years-old, eager to preserve ovarian function, have no family history of ovarian cancer, MRI suggests that FIGO staging is less than or equal to IB, tumor diameter $\leq$ 4 cm, no PMI, no CUI, no DSI, no LNM, no LVSI in pathology, and no extrauterine infiltration, no lymph node metastasis, and normal ovarian appearance were confirmed during surgery, 96.7% of ADC patients had no OM (30/31). In the present study, when FIGO clinical Stage II, GAS, LVSI, and FTI were considered as high-risk factors for OM, the specificity and NPV were 59.00%, and 100.00%. These criteria had better diagnostic effectiveness possibly caused by the fact that our predictors were mostly derived from postoperative patho-

Table 3. — *Prediction of ovarian metastasis in cervical adenocarcinoma using clinicopathological variables (n = 419).*

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy	LR+	LR-n
FIGO Stage	84.21%	74.50%	13.56%	99.00%	74.94%	3.30	0.21
Histology type	36.84%	95.00%	25.93%	96.94%	92.36%	7.37	0.66
LVSI	78.95%	76.00%	13.51%	98.70%	76.13%	3.29	0.28
FTI	57.89%	98.75%	68.75%	98.01%	96.90%	46.32	0.43
FIGO Stage + Histology type	84.21%	71.75%	12.40%	98.97%	72.32%	2.98	0.22
FIGO Stage + Histology type+ LVSI	100.00%	59.25%	10.44%	100.00%	61.10%	2.45	0.00
FIGO Stage + Histology type+ FTI	100.00%	71.25%	14.18%	100.00%	72.55%	3.48	0.00
FIGO Stage + Histology type+ LVSI+FTI	100.00%	59.00%	10.38%	100.00%	60.86%	2.44	0.00

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; FIGO: International Federation of Gynecology and Obstetrics.

logical results, while the previous study used MRI variables as predictors. Given the difficulty of accurately accessing the invasion of fallopian tube and LVSI by frozen pathological examination, the authors used clinical stage and histological type as diagnostic criteria. The NPV was 98.97%, 72.32% patients were correctly estimated, and 0.72% patients were underestimated. In the present study, when the authors considered FIGO clinical Stage II, GAS, LVSI, and FTI as high-risk factors for ovarian metastasis, the specificity and NPV were 59.00% and 100%, respectively. The preserved ovaries did not require resection in patients with FIGO clinical Stage < IIA, histological type of non-GAS, no LVSI, and no FTI.

We acknowledge several inherent limitations to this study. First, selection bias exists in this retrospective study. The level of evidence was relatively weak, and there was a lack of external validation of our creating classification. Second, most of the variables in this study were based on postoperative pathological findings and could only be used to assess whether there a relationship with ovarian metastasis. Considering the difference between preoperative or intraoperative pathological results and the final pathological results, the diagnostic efficacy of FIGO Stage and preoperative histological type should be evaluated in the future.

In conclusion, we believe it was not appropriate to preserve ovaries in GAS due to the relatively high OM rate. If clinical Stage < IIA and histological type was non-GAS, it could be considered to preserve ovarian in young ADC patients. Patients with FIGO clinical Stage < IIA, histological type of non-GAS, no LVSI, and no FTI have a low risk of ovarian metastasis and do not require resecting the preserved ovarian. To further reduce the risk of residual ovarian foci, suspicious lesions and ovarian biopsies should be performed.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

Acknowledgments

Thanks to all the peer reviewers and editors for their opinions and suggestions.

Conflict of Interest

The authors report no conflicts of interest in this work.

Submitted: February 05, 2020
Accepted: April 01, 2020
Published: October 15, 2020

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