

Analysis of Risk Factors and Prognosis for Ovarian Metastasis in Patients with Endometrial Carcinoma

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Abstract

Objective: To investigate the risk factors and prognosis for ovarian metastasis in patients with endometrial carcinoma.

Methods of study: Seven hundred sixty-four cases of endometrial carcinoma treated in Beijing Obstetrics and Gynecology Hospital (BOGH) during the period between September, 1970 and August, 2011 were retrospectively analyzed. All the cases had complete surgical and pathological records.

Results: Among 764 cases of endometrial carcinoma analyzed, 23 (3.01%) cases had ovarian metastasis. Univariate analyses found that the depth of muscular invasion, peritoneal lavage cytology, histological grading, cervical migration, parametrial metastasis, fallopian tube metastasis and lymph node metastasis were significantly different between two groups with (n=23) or without (n=741) ovarian metastasis. Multivariate Logistic regression analysis revealed that factors predictive of ovarian metastasis included peritoneal lavage cytology and the depth of muscular invasion. Endometrial carcinoma patients with ovarian metastasis had poorer five-year survival rate and higher recurrent rate than those without ovarian metastasis.

Conclusion: Parametrial metastasis, positive tumor cells in peritoneal lavage and deep muscular invasion are independent risk factors for ovarian metastasis of endometrial carcinoma. Endometrial carcinoma patients with ovarian metastasis are more poorly prognostic.

Keywords: Endometrial carcinoma; Ovarian metastasis; Risk factors; Prognosis

Recently, the morbidity of endometrial carcinoma tends to increase. With a rise in the number of young patients and demand of life quality, ovary preservation is increasingly demanded by women who suffered from gynecological cancers, and it has become a common practice to reserve ovaries in patients inflicted with cervical squamous cell carcinoma and of young women with early stage of ovarian cancer. Controversies, however, remain on whether ovary preservation should be observed in endometrial carcinoma patients [1]. In this study we retrospectively analyzed the risk factors and prognosis of endometrial carcinoma associated with ovarian metastasis, and attempt in this article to discuss whether ovary preservation in endometrial carcinoma patients.

Materials and Methods

Patient information

The clinical information of 764 cases of endometrial carcinoma patients who were surgically treated at BOGH from September, 1970 through August, 2011 was collected. The pathological diagnosis of ovarian metastasis was made according to standard diagnostic criteria as described by Uibright and Roth [2] as the following: 1) The growth of ovarian tumor is multi-nodular (the main criterion); 2) The ovarian tumor meets two or more of following feature, namely, the diameter of ovary is less than 5 cm; Both sides of ovary were involved; The deep layer of uterine were invaded; The vessels were invaded; The fallopian tube were invaded. Dominant metastasis: in operation, metastasis lesions on ovary could be seen by naked eye. Recessive metastasis: in operation, the ovaries appear normal, but pathology examination proofs ovary metastasis.

Treatment

All patients were treated by surgery (hysterectomy and bilateral adnexectomy and pelvic lymphadenectomy). If the patient had high risk factors of relapse, such as deep muscular invasion, cervical invasion, parametrial metastasis, lymph node metastasis, adjuvant

treatments were given, including radiotherapy, chemotherapy and hormone therapy.

Statistic methods

Statistical analysis was performed using the SPSS11.5 software. The *t* Test and Chi-square test were used for univariate analysis, and for multivariate analysis, logistic regression was employed. $p < 0.05$ was used as the cut-off value for significant difference.

Results

General information of patients

Among 764 cases of endometrial carcinoma analyzed, 23 (3.01%) cases had ovarian metastasis. The age range of group with ovarian metastasis was 32-78 (average 52.81 ± 9.26), and the age range of group without ovarian metastasis was 28-82 (average 52.69 ± 9.51). There were 256 patients were premenopausal (7 patients in group with ovarian metastasis) and 508 patients were postmenopausal (16 patients in group with ovarian metastasis). No significant difference was found in age of incidence, age of menarche, Body Mass Index (BMI), age of menopause, bleeding duration and family history of tumor between groups with and without ovarian metastasis (Table 1).

Univariate analysis

There were significant differences in the depth of muscular

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invasion, cytology of peritoneal lavage, grade of cell differentiation, cervical metastasis, parametrial metastasis, vaginal metastasis, oviduct metastasis and lymphatic metastasis between the group of endometrial carcinoma with metastasis and the group of endometrial carcinoma without metastasis. However, no significant difference was identified in the depth of uterine, gross type, pathological type, ligament metastasis and vascular carcinoma embolism between two groups (Table 2).

Multi-factor analysis

By performing multivariate analysis, we found that parametrial metastasis, cytology of peritoneal lavage and the depth of muscular invasion represent three independent risk factors for patients of endometrial carcinoma with ovarian metastasis (Table 3).

Analysis of prognosis

The five-year survival rate of endometrial carcinoma patients with ovarian metastasis is 86.96%, in contrast to the 95.94% five-year survival rate for those without ovarian metastasis, demonstrating a statistically significant difference between the two groups ($p = 0.037$). Furthermore, the relapse rates in endometrial carcinoma patients with and without ovarian metastasis, respectively, is 21.73% (5/23) and 7.59% (58/706) ($p = 0.014$). It is of note that among 5 cases of relapse patients, lymph nodes ($n = 2$), vaginal residual ($n = 1$), liver ($n = 1$) and colon ($n = 1$) were the sites in which metastases were found. The mean interval between incidence and recurrence was 17.4 and 33.7 months, respectively, for patients with or without ovarian metastasis, but such a difference was statistically not significant $p = 0.310$.

	Group without ovarian metastasis (Mean ± SD)	Group with ovarian metastasis (Mean ± SD)	<i>p</i>
Age of incidence	52.81 ± 9.26	52.69 ± 9.51	0.951
Age of menarche	15.01 ± 2.19	14.56 ± 1.63	0.414
BWI	26.74 ± 4.21	24.29 ± 1.78	0.084
Duration of bleeding	16.49 ± 25.56	19.14 ± 19.49	0.699
Depth of uterine	7.87 ± 1.42	8.5 ± 1.71	0.251

Table 1: Comparison of measurement data of between endometrial carcinoma patients with and without ovarian metastasis.

		Group without ovarian metastasis N (%)	Group with ovarian metastasis N (%)	<i>p</i>
Family history of tumor	No	669 (87.57)	20 (86.96)	0.931
	Yes	95 (12.43)	3 (13.04)	
Gross type	Localized	380 (73.22)	9 (64.29)	0.458
	Diffuse	139 (26.78)	5 (35.71)	
Depth of muscular invasion	No	179 (25.98)	2 (9.09)	0.01
	<1/2	350 (50.80)	9 (40.91)	
	≥1/2	160 (23.22)	11 (50)	
Cytology of ascites	Negative	330 (89.67)	5 (55.56)	0.001
	Positive	38 (10.33)	4 (44.44)	
Pathological type	Endometrioid	679 (88.99)	18 (88.68)	0.11
	Special types*	84 (11.01)	5 (21.74)	
Grade of cell differentiation	G1	252 (37.11)	4 (19.05)	0.028
	G2	313 (46.10)	9 (42.86)	
	G3	114 (16.79)	8 (38.10)	
Cervical metastasis	No	700 (91.62)	15 (65.22)	0
	Yes	64 (8.38)	8 (34.78)	
Parametrial metastasis	No	739 (96.73)	19 (82.61)	0
	Yes	25 (3.27)	4 (17.39)	
Vaginal metastasis	No	760 (99.48)	22 (95.65)	0.023
	Yes	4 (0.52)	1 (4.35)	
Oviduct metastasis	No	746 (97.64)	20 (86.96)	0.002
	Yes	18 (2.36)	3 (13.04)	
Ligament metastasis	No	753 (98.56)	22 (95.65)	0.262
	Yes	11 (1.44)	1 (4.35)	
Vascular carcinoma embolism	No	733 (95.94)	21 (91.3)	0.274
	Yes	31 (4.06)	2 (8.7)	
Lymphatic metastasis	No	750 (98.17)	20 (86.96)	0
	Yes	14 (1.83)	3 (13.04)	

*Special pathological types include serous papillary adenocarcinoma, clear cell carcinoma and adenosquamous carcinoma

Table 2: Comparative clinicopathological features of endometrial carcinoma patients with and without ovarian metastasis.

Risk factors of relapse	<i>P</i>	OR	95%CI
Parametrial metastasis	0.002	15.31	2.81-83.36
Cytology of ascites	0.005	16.02	2.33-110.07
Depth of muscular invasion	0.038	8.81	1.12-69.07

Table 3: Logistic regression of factors of endometrial carcinoma with ovarian metastasis.

Discussion

Previous reports have indicated that ovarian metastasis occurs at rates of 2.4% to 14.1% in endometrial carcinoma [3-7]. In this study, 23 cases of ovarian metastasis were found among a total of 764 cases of endometrial carcinoma surgically treated between September 1970 and August 2011 at BOGH, presenting ovarian metastasis incidence of 3.01%.

Two mechanisms have been proposed for endometrial carcinoma to develop ovarian metastasis. Firstly, tumor cell can be implanted in ovaries by directly spreading through fallopian tube or uterine muscular layer, which is considered to be a common route for ovarian superficial metastases. Such a metastatic mechanism is usually associated with positive cytology of peritoneal lavage but not the pelvic lymph nodes. Watanabe et al. [8] showed that parametrial spread occurred in uterine endometrial cancer with ovarian metastasis. The second mechanism of ovarian metastasis is believed to be through formation of lymph channels of uterine fundus, via which tumor cells invade the inner portion of ovaries. In the second manner of metastasis, positive pelvic lymph nodes and negative cytology of peritoneal lavage are commonly present [6]. The relapse risk factors of endometrial carcinoma with ovarian metastasis have been reported to be different by different studies. Creasman et al. [9] suggested that pathological grading, depth of muscular invasion and the location of primary lesion were among the determining risk factors, with the depth of muscular invasion being most closely relevant. Connell et al. [10] reported that presence of metastasis lesions (including peritoneal implantation and distant metastasis), positive peritoneal lavage, cervical invasion and special pathological type were all independence risk factors. Ying et al. [5] showed that pelvic lymph metastasis, depth of muscular invasion, pathological grading and cervical invasion were independent risk factors for endometrial carcinoma with ovarian metastasis. Interestingly, Gemer et al. [11] analyzed 67 cases of endometrial carcinoma and found that the relapse risk was very low for the patients of grades 1-2 disease, muscular invasion <1/2, negative peritoneal lavage and lack of lymph metastasis. Vita et al. [12] reported that the dedifferentiated endometrioid adenocarcinoma of the uterus had a relationship with ovarian metastasis. Karube et al. [13] also indicated that histopathological prognostic factors predicted ovarian metastasis and para-aortic lymph node metastasis in patients with endometrioid uterine cancer. Our study showed that parametrial metastasis, positive peritoneal lavage and deep muscular invasion account for three major risk factors, and this finding appears to support that the main route of ovarian metastasis in endometrial carcinoma might be through muscular invasion that subsequently causes parametrial metastasis and consequently, ovarian metastasis. Correlations between ovarian metastasis and cervical metastasis, vaginal metastasis and lymph metastasis were identified, suggesting that lymphatic route might contribute to ovarian metastasis as an assisting route.

Debate exists as for whether ovaries should be reserved in younger endometrial carcinoma patients. Gemer et al. [11] comparatively analyzed patients younger and older than 40 years old and found that younger patients developed ovarian metastasis more readily, providing an argument against ovary preservation in young patients. Lee et al. [14] analyzed 260 cases of endometrial carcinoma and found that 19 cases were associated with ovarian malignant tumors, among which 12 cases were metastasized from uterus and 7 belonged to primary ovarian original cancer. Among 206 cases without lesions outside the uterus, patients who were younger than the 45-year-old did not carry any ovarian malignant tumor. Furthermore, 35 patients with reserved ovaries did not relapse or die from cancer in the following visits.

Apparently, the latter report supports the strategy of ovary preservation in younger patients with early stage of endometrial carcinoma.

Based upon the results of our current study, there appears no correlation between the incidence of endometrial carcinoma with ovarian metastasis and age, and therefore age is not a relapse risk factor for ovarian metastasis in endometrial carcinoma. Patients at all ages who present risk factors for ovarian metastasis, including parametrial metastasis, positive peritoneal lavage and deep muscular invasion, therefore should not have their ovaries reserved in surgery. Young patients diagnosed with negative peritoneal lavage, normal ovarian appearance and no muscular or parametrial invasion are those to be considered for ovary preservation. For these patients, however, recessive metastasis should be precluded by rapid pathological examination of frozen tissues. Lax et al. [15] also stresses the importance of intraoperative frozen sections in diseases of the female genital tract. Turan et al. [16] evaluated medical records of 816 patients with stage IA-IVB endometrial carcinoma and indicated that the accuracy of intraoperative pathologic evaluation in endometrial cancer was reasonably high. Kisu et al. [17] studied 201 women diagnosed with endometrial carcinoma and found that in assessment of myometrial invasion, the accuracy of frozen sections was significantly higher than that of MRI.

So we get the conclusion that parametrial metastasis, positive tumor cells in peritoneal lavage and deep muscular invasion are independent risk factors for ovarian metastasis of endometrial carcinoma. Endometrial carcinoma patients with ovarian metastasis are more poorly prognostic. During the operation, rapid pathological examination of frozen tissues of ovarian is suggested to preclude ovarian recessive metastasis.

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