HUMAN BIOLOGY
2024, VOL. 94, ISSUE 1
ORIGINAL ARTICLE

OPEN ACCESS

Clinical Characteristics of Uterine Metastasis in Epithelial Ovarian Cancer

*Tianmei Wang, Cong Li**

ABSTRACT

Background: Epithelial malignancies of the ovary spread directly and easily to the serous coat of uterus. However, the occurrence of invasion and metastasis within the parenchyma of the uterus is unknown. The rate of metastasis and its associated clinical features provide objective data to support surgery for uterus-preserving ovarian cancer.

Methods: The data of patients with epithelial ovarian cancer (OC) who underwent hysterectomy from January 1, 2017, to March 31, 2022, were collected retrospectively. The study analyzed the distribution of uterine metastasis and identified risk factors related to clinical characteristics.

Results: A total of 393 patients were included, and the uterine metastasis rate confirmed by pathology was 34.35%, with 26.72% of metastasis of the serous coat of the uterus, and 5.85% of myometrial metastasis and 1.78% of endometrial metastasis. For stage II patients, there were only 12.5% uterine metastases, and only 4.8% had parenchymal metastases to the uterus. The occurrence of metastasis is negatively related to low CA125 and HE4 values, unilateral ovarian lesion, no involvement of fallopian tubes, non-grade 3 (G3), non-serous, without pelvic metastasis, and the presence of endometriosis. These factors were found to be protective against uterine metastasis. Among them, bilateral ovarian lesion, fallopian tubes involvement and pelvic metastasis are the main independent risk factors for uterine metastasis of ovarian cancer.

Conclusion: The incidence of uterine metastasis from ovarian cancer was 34.35%. For stage II patients, there were only 4.8% had parenchymal metastases to the uterus. The presence of unilateral ovarian lesions and the absence of involvement of the fallopian tubes and other pelvic organs were independent protective factors. This offers a new possibility to preserve fertility in patients with stage II ovarian cancer.

INTRODUCTION

Ovarian cancer (OC) is one of the most common gynecological malignant tumors, which can occur at any age. According to NCCN recommendations, fertility-sparing surgery (FSS) for OC is only indicated for early stage patients who want to retain fertility or patients with low-risk malignant tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, mucinous tumors, or malignant sex cord-stromal tumors). This mainly takes into account that OC is characterized by extensive dissemination in the abdominal cavity. Therefore, the uterus, fallopian tube, greater omentum, retroperitoneal lymph nodes, and other parts are most often involved. Because of this, hysterectomy is routinely performed for both patients who undergo comprehensive staging surgery in the early stage and patients who undergo tumor cell reduction in the middle and late stages Salvo et al. (2021).

However, with the postponement of the childbearing age, some patients may be diagnosed with malignant ovarian tumors before childbearing, and radical surgery may be difficult for them to accept. Moreover, hysterectomy also causes many other problems that affect women's quality of life and physical and mental health Pereira et al. (2017). Hysterectomy will affect the pelvic floor function of patients, causing pelvic organ prolapse, abnormal urination, and defecation. In addition, it will also have an impact on women's psychology, causing them to have psychogenic sexual dysfunction Monterrosa-Castro et al. (2018). Due to the differences in cultural backgrounds between China and the West, Chinese women, especially premenopausal women, are more dissatisfied with their self-image after hysterectomy, resulting in adverse psychological reactions Gabriel et al. (2021).

Department of Gynecology, First Affiliated Hospital of Chongqing Medical University
YouYi Road, YuZhong district, Chongqing city, China.

Correspondence to: Cong Li, YouYi Road, YuZhong district, Chongqing city, China.
E-mail: b05104@126.com.

Keywords: Carcinoma, Ovarian Epithelial; Neoplasm Metas; Fertility-sparing Surgery

This requires that doctors should constantly explore the possibility of more care while ensuring the oncological outcome of patients. At present, some studies believe that FSS is safer for patients of childbearing age with stage I grade 1-2 EOC. At the same time, in clinical practice, we found that in some patients in the middle and late stages, when suspected uterine metastasis was found by imaging and intraoperative observation before surgery, no microscopic metastasis could still be found by postoperative pathological examination. So, should hysterectomy be routinely performed in all cases of OC? This issue remains to be discussed.

MATERIALS AND METHODS

1.1 Research Objective:

Data were collected retrospectively who underwent hysterectomy for OC in our department from January 1, 2017, to March 31, 2022. Patients with metastatic OC, patients who had their uteri removed for other diseases before surgery, patients who had undergone another comprehensive staging operation in our hospital after tumor removal in other hospitals, patients with other incomplete data, and patients with stage I were excluded. All effective follow-up patients were informed consent to this clinical retrospective analysis, and through the Ethics Committee of First Affiliated Hospital of Chongqing Medical University (NO.2020-636). The informed consent was obtained from the study participants and the guidelines outlined in the Declaration of Helsinki were followed.

1.2 Methods:

Clinical information includes age, menopause, fertility, tumor marker value, and postoperative pathological results, all of which come from our electronic medical record system. Exclusion criteria include Patients with endometrial carcinoma (those with different pathological types of endometrium and ovary); no operative; the uterus has been removed due to benign diseases in the past (including total hysterectomy and subtotal hysterectomy); incomplete data; patients in stage I. Finally, 393 patients were included in the analysis.

1.3 Statistical processing:

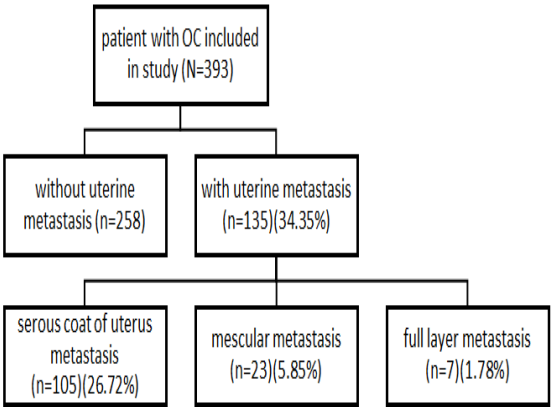
SPSS 26.0 statistics software were used for data analysis. Data information included both measurement data and count data. Measurement data obeying normal distribution were expressed as mean ± standard deviation and used two independent samples t-test, while non-normally distributed measurement data were expressed by median, maximum and minimum values with Mann-Whitney U rank-sum test; count data were tested by chi-square ($\chi 2$) test and ordinal categorical variable were tested by Mann-Whitney U rank-sum test. Binary logistic multifactorial regression was used to analyze the risk factors for uterine metastasis of OC. All statistical analyses were performed using a two-sided test, and $P<0.05$ were considered statistically significant.

RESULTS

2.1 The incidence of uterine metastasis in ovarian epithelial malignant tumors:

Among 393 cases, the overall rate of uterine metastasis confirmed by pathology was 34.45% (135/393). The metastasis of the serous coat of the uterus accounted for 26.72% (105/393). 5.85% (23/393) of patients with myometrial metastasis, the rate of endometrial metastasis was 1.78% (7/393). (Fig. 1).

Figure 1: Incidence of uterine metastasis in ovarian epithelial malignant tumors



2.2 Clinical characteristics of epithelial ovarian malignant tumors:

Two groups were divided based on the presence or absence of uterine metastasis, and the clinical characteristics of both groups were analyzed (Table 1). Uterine metastasis of OC is related to with several factors, including Ca125 and HE4 levels, presence of unilateral or bilateral ovarian lesions, clinical stage, involvement of the fallopian tube, pathological type, pathological grade, presence of extrauterine organ metastasis in the pelvic cavity, and the presence of endometriosis. It was not related to the age of onset, menopause, times of pregnancy and childbirth, the diameter of ovarian tumors, surgical opportunity (primary debulking surgery (PDS)/ neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS)), ascites/ peritoneal washout evidence, lymph node metastasis or history of breast cancer.

Table 1: Clinical characteristics of epithelial ovarian malignant tumors

	Group		P value
	without uterine metastasis (n=258) (%)	uterine metastasis (n=135) (%)	
Age	53.86±9.273	52.67±10.066	0.240*
Monopause			
NO	97(63.8)	55(36.2)	0.543†
YES	161(66.8)	80(33.2)	
Gravidity times			
0	7(63.6)	4(36.4)	0.982†
1-3	154(65.3)	82(34.7)	
＞3	93(66.0)	48(34.0)	
Unknown	4	1	
Delivery times			
0	14(66.7)	7(33.3)	0.929†
1	144(66.4)	73(33.6)	
＞1	100(64.5)	55(35.5)	
Ca125			
Mean rank	164.67(n=242)	224.88(n=128)	<0.001‡
Unknown	18	7	
HE4			
Mean rank	160.86(n=229)	204.42(n=122)	<0.001‡
Unknown	29	13	
Ovarian location			
Unilateral	151(79.9)	38(20.1)	<0.001†
Bilateral	103(51.5)	97(48.5)	
Unknown	4	0	
Diameter			
＜10cm	153(62.4)	92(37.6)	0.086†
≥10cm	105(70.9)	43(29.1)	
Stage			
Mean rank	171.4(n=247)	221.24(n=129)	<0.001‡
II	91(87.5)	13(12.5)	
III	119(57.2)	89(42.8)	
IV	37(57.8)	27(42.2)	
Unknown	11	6	
Grade 3			
NO	97(78.2)	27(21.8)	<0.001†
YES	161(59.9)	108(40.1)	
Pathological type			
Serous	186(61.8)	115(38.2)	<0.003†
Others	70(78.7)	19(21.3)	
Unknown	2	1	
fallopian tube involved			
NO	171(79.5)	44(20.5)	<0.001†
YES	86(48.9)	90(51.1)	
Unknown	1	1	
Ascites/ Peritoneal washout evidence			
NO	191(68.0)	90(32.0)	0.125†
YES	67(59.8)	45(40.2)	
Lymph node metastasis§			
NO	217(65.8)	113(34.2)	0.917†
YES	41(65.1)	22(34.9)	
Pelvic metastasis‖			
NO	93(86.9)	14(13.1)	<0.001†
YES	165(57.7)	121(42.3)	
PDS/IDS			
PDS	150(68.5)	69(31.5)	0.183†
NACT+IDS	108(62.1)	66(37.9)	
Endometriosis			
NO	220(62.9)	130(37.1)	0.001†
YES	38(88.4)	5(11.6)	
History of breast cancer			
NO	252(65.5)	133(34.5)	0.574†
YES	6(75.0)	2(25.0)	

* T test; † Chi-square test; ‡ Mann-Whitney U rank-sum test; § Lymph node metastasis refers to metastasis confirmed by pathology, excluding imaging lymph node metastasis; ‖ Pelvic metastasis refers to other organ metastasis in pelvic cavity except uterus

Table 2: Logistic regression analysis of risk factors for uterine metastasis of OC

	OR (95%CI)	P value
Ca125	NS	0.372
HE4	NS	0.257
Ovarian location	3.482(1.966-6.167)	<0.001
Stage	NS	0.277
G3	NS	0.667
Pathological type	NS	0.263
Fallopian tube involved	2.825(1.625-4.914)	<0.001
Pelvic metastasis	4.328(1.657-11.302)	0.003
Endometriosis	NS	0.203
NS= non significant; OR= Odds Ratio; CI= Confidence Interval.		

Although the uterine metastasis rate was as high as 42.8% and 42.2% in patients with stage III and IV, the uterine metastasis rate was only 12.5% in stage II OC patients. Moreover, in stage II patients, serous coat of uterus metastasis was 7.7%, and uterine parenchyma metastasis was only 4.8%. Low CA125 and HE4 values, unilateral ovarian lesion, stage II, no involvement of fallopian tubes, non-G3, non-serous, without pelvic metastasis, and the presence of endometriosis were the factors that were found to be protective for uterine metastasis.

2.3 Multi-factor coupling of OC with uterine metastasis:

The 12 variables that were statistically different in our table 1 were subjected to binary logistic regression analysis (Table 2). From the logistic regression result, bilateral ovarian lesions (OR=3.482), fallopian tube involvement (OR=2.825) and pelvic metastasis (OR=4.328) were identified as the main independent risk factors for uterine metastasis of OC.

DISCUSSIONS

3.1 Analysis of clinical characteristics of possible low-risk factors of uterine metastasis:

In OC, the presence of unilateral ovarian lesions and the absence of involvement of the fallopian tubes and other pelvic organs were independent protective factors. Low CA125 and HE4 values, non-G3 and non-serous are secondary protective factors. In clinical practice, if there are stage II patients with a strong desire to retain the uterus, preoperative determination of no other lesions in the uterus, it can be considered to retain the uterus during the operation, if the patient's lesion is present only in one ovary or the fallopian tube and other pelvic organs are not involved. Or if an ovarian malignant tumor is found accidentally after an operation, whether the uterus is retained in the subsequent staging operation can also be further discussed.

The history of endometriosis may be the low risk factors of uterine metastasis, suggesting that it may be protective factors for uterine metastasis, or because patients need to see doctors repeatedly due to related diseases, their OC was easy to identify early, and the risk of metastasis in other parts was reduced.

3.2 Possible effects for diagnosis of uterine metastasis in epithelial OC:

OC is classified as the surgical and pathological stage. Its staging is based on surgical pathology. According to FIGO staging in 2017, stage IIA refers to the tumor spreading to and/or planting in the uterus and/or fallopian tube and/or ovary. Stage II OC is still controversial and difficult to define Janda et al. (2019). It includes a group of patients with OC, whose tumor directly spread to other pelvic organs, but there is no evidence of spread, and it cannot be confirmed by the results of disease examination after surgery Doubeni et al. (2016).

Therefore, the staging of Phase II was diagnosed generally based on the following: before the operation: ultrosound, CT or MRI were certain judgment basis. During the operation: the description of the scope of pelvic and peritoneal lesions, such as: lesions on the serous surface of the uterus was generally presence in the vesical peritoneal reflection, posterior wall of the uterus, Douglascul-de-sac and the dense adhesion, thickening and shortening between uterine ligaments and lesions. After the operation: pathologic confirmation should be done to determine whether there is tumor involvement, based on the remarks made during the operation. So, if the patient has preoperative neoadjuvant chemotherapy or has had incomplete staging surgery in the past, the positive rate of the medical examination results will also be affected, which poses a challenge in determining whether there is uterine metastasis in advanced OC.

Among the 104 patients of stage II included in our study, there were 24 patients in stage IIA, including 14 patients in stage IIA due to uterine metastasis, 10 patients in stage IIA due to serous coat of uterus metastasis, and 2 of muscular layer, 2 of full layer,

which could not be statistically analyzed due to the small number of patients, and were not listed in the results. More stage II staging was due to the extension of organs in pelvic besides the uterus, such as intestines and bladder. Some scholars believe that the disease of stage II intestinal metastasis that invades intestinal mucosa through the intestinal wall should be upgraded to stage IVB Javadi et al. (2016).

According to the analysis of the uterus parts involved, the extension of the serous surface is consistent with the biological behavior of the direct spread of OC. According to the purpose of tumor cell reduction, it is not always necessary to remove and replace the affected organs as long as the surgery successfully eliminates all visible lesions. For patients with endometrial invasion indicated by preoperative imaging, the presence of tumor involvement can be confirmed by hysteroscopy before surgery, and the occurrence of OC combined with endometrial cancer can be ruled out. In the case of uterine substantial metastasis, it is necessary to remove the uterus to prevent myometrial metastasis, which helps reduce the tumor's spread. This retrospective analysis found that 5.85% of patients with myometrial metastasis were confirmed after surgery, indicating a low probability occurrence.

3.3 possible effects for the treatment of epithelial OC:

Early epithelial OC and low malignant potential tumors can be operated on with fertility preservation Nasioudis et al. (2020), that is, unilateral adnexectomy or bilateral adnexectomy can be performed to preserve the uterus Goeckenjan et al. (2020). For young patients who hope to retain their reproductive function, the affected side can be resected+ comprehensive staging surgery in IA stage; In stage IB, bilateral adnexectomy (uterus preservation) and comprehensive staging operation are feasible Baek et al. (2020). However, in the actual clinical work, there were only few cases of reserving the uterus in patients who diagnosed with stage II during the operation. OC occurred at a slightly older age, and patients often had children. It was rare for patients to insist on reserving the uterus because of the requirement of reproduction. Patients removed bilateral ovaries, and there was no consensus on the preservation of oocyte in OC. At the same time, based on the patient's fear of malignant tumor, they hope to be resected to the maximum extent. Even young patients may give up childbearing and choose simultaneous hysterectomy of double appendages. Therefore, in the choice of whether cut or not, simultaneous resection is selected to a large extent. And there is no definite answer whether the retention of the uterus will affect the five-year survival of patients.

A retrospective analysis of 9017 patients Bercow et al. (2021) showed that the 5-year survival period of OC patients aged 15-44 years was lower than that of the whole population group, and its influencing factors might be the fertility-preserving surgery.

However, there were also several other high-risk factors during this period, making it impossible to solely analyze the impact of fertility-preserving surgery on the 5-year survival rate. A meta-analysis found that Liu et al. (2020) the hazard ratio (HR) of patients undergoing fertility-preserving surgery in Phase I patients of 2223 patients in 8 centers decreased slightly, but the decrease was not statistically significant. There was no statistical difference in the specific stage and pathological type, and no difference in the overall survival.

For those patients who have retained fertility, the five-year survival time of most patients with borderline tumors and germ cell tumors is lower than that of those who have undergone radical surgery Canlorbe et al. (2021). The follow-up study on the fertility and prognosis of 25 cases of borderline epithelial ovarian tumors found that Kim et al. (2021) the risk of premature ovarian failure in fertility-preserving patients was higher than the control group, and the number of people who needed assisted reproductive technology increased. There was no significant impact on fertility, but there was no confirmed data for the five-year survival. The report on the re-pregnancy rate of 153 patients with fertility preservation can be seen Nitecki et al. (2021). Among these patients, epithelial ovarian cancer accounts for 55%. There is no difference in the postoperative pregnancy outcome, delivery mode and newborn with non-tumor patients.

According to this retrospective analysis, the rate of uterine parenchyma metastasis of OC is low. Patients who have the desire to retain the uterus, or patients who have difficulty with uterus removal during surgery, or patients who have been diagnosed with OC but have not been fully staged after surgery, the uterus can be retained when making the next operation plan. It is important to determine whether this will impact the five-year survival rate of the patients.

3.4 The influence of hysterectomy on patients' quality of life:

Take hysterectomy for benign diseases such as uterine leiomyoma as an example, the impact of hysterectomy on the quality of life, exercise ability, and sexual function of patients has also attracted attention. Compared to women without hysterectomy, women with hysterectomy-bilateral oophorectomy were found to have an increased risk of substantial Physical Functioning (PF) limitations versus minimal PF limitations over 18 years of follow-up Wilson et al. (2018). At the 17-year follow-up, the route of hysterectomy is not associated with a difference in recurrence, grade, or subsequent treatment of prolapse when the indication for hysterectomy is considered. Prolapse, as an indication of hysterectomy, increases the risk for recurrence. Women planning a hysterectomy should be counseled

appropriately about the risk of subsequent prolapse Wilson et al. (2018). The prevalence of hysterectomy is disproportionately higher among women with disabilities compared with women without disabilities. These differences are most noticeable in women of childbearing age Scime et al. (2021).

CONCLUSION

In OC, the rate of uterine metastasis was 34.35%. For stage II patients, there were only 12.5% uterine metastases, 7.7% were plasma surface metastases, and only 4.8% had parenchymal metastases to the uterus. And the presence of unilateral ovarian lesions and without the involvement of the fallopian tubes and other pelvic organs were independent protective factors. Low CA125 and HE4 values, non-G3 and non-serous are secondary protective factors. The history of endometriosis may be the low risk factors of uterine metastasis. This offers a new possibility to preserve fertility in patients with stage II OC.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

REFERENCES

1. Salvo G, Falconer H, Pareja R. 2021 Mar. Beyond oncologic outcomes: fertility and ovarian preservation as key priorities. Int J Gynecol Cancer. 31(3):313.

2. Pereira N, Schattman GL. 2017 Oct. Fertility Preservation and Sexual Health After Cancer Therapy. J Oncol Pract. 13(10):643-651.

3. Monterrosa-Castro A, Monterrosa-Blanco A, Beltrán-Barrios T. 2018 Mar-Apr. Insomnia and sexual dysfunction associated with severe worsening of the quality of life in sexually active hysterectomized women. Sleep Sci. 11(2):99-105.

4. Gabriel I, Kalousdian A, Brito LG, et al. 2021 May. Pelvic organ prolapse after 3 modes of hysterectomy: long-term follow-up. Am J Obstet Gynecol. 224(5): 496.e1-496.e10.

5. Janda M, McGrath S, Obermair A. 2019 Feb. Challenges and controversies in the conservative management of uterine and ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 55:93-108.

6. Doubeni CA, Doubeni AR, Myers AE. 2016 Jun 1 .Diagnosis and Management of Ovarian Cancer. Am Fam Physician. 93(11):937-44.

7. Javadi S, Ganeshan DM, Qayyum A, et al. 2016 Jun. Ovarian Cancer, the Revised FIGO Staging System, and the Role of Imaging. AJR Am J Roentgenol. 206(6):1351-60.

8. Nasioudis D, Mastroyannis SA, Haggerty AF, et al. 2020 May.Fertility preserving surgery for high-grade epithelial ovarian carcinoma confined to the ovary. Eur J Obstet Gynecol Reprod Biol. 248:63-70.

9. Goeckenjan M, Freis A, Glaß K, et al. 2020 Jun. Motherhood after cancer: fertility and utilisation of fertility-preservation methods. Arch Gynecol Obstet. 301(6):1579-1588.

10. Baek MH, Park JY, Kim DY, et al. 2020 Nov. Feasibility and safety of fertility-sparing surgery in epithelial ovarian cancer with dense adhesion: a long-term result from a single institution. J Gynecol Oncol. 31(6): e85.

11. Bercow A, Nitecki R, Brady PC, et al. 2021 Mar. Outcomes after Fertility-sparing Surgery for Women with Ovarian Cancer: A Systematic Review of the Literature. J Minim Invasive Gynecol. 28(3):527-536.

12. Liu D, Cai J, Gao A, et al. 2020 Apr 15. Fertility sparing surgery vs radical surgery for epithelial ovarian cancer: a meta-analysis of overall survival and disease-free survival. BMC Cancer. 20(1):320.

13. Canlorbe G, Chabbert-Buffet N, Uzan C. 2021. Fertility-Sparing Surgery for Ovarian Cancer. J Clin Med. 10(18):4235.

14. Kim SS. 2021 Jan. Fertility preservation for women with borderline ovarian tumors: fertility-sparing surgery. Fertil Steril. 115(1):83-84.

15. Nitecki R, Clapp MA, Fu S, et al. 2021 Jun 1. Outcomes of the First Pregnancy After Fertility-Sparing Surgery for Early-Stage Ovarian Cancer. Obstet Gynecol. 137(6):1109-1118.

16. Wilson LF, Pandeya N, Byles J, et al. 2018 Jun. Hysterectomy and perceived physical function in middle-aged Australian women: a 20-year population-based prospective cohort study. Qual Life Res. 27(6):1501-1511.

17. Wilson L, Pandeya N, Byles J, et al. 2018 Aug. Hysterectomy and incidence of depressive symptoms in midlife women: the Australian Longitudinal Study on Women's Health. Epidemiol Psychiatr Sci. 27(4):381-392.

18. Scime NV, Brown HK, Metcalfe A, et al. 2021 Nov 29. Prevalence of Hysterectomy by Self-Reported Disability Among Canadian Women: Findings from a National Cross-Sectional Survey. Womens Health Rep (New Rochelle). 2(1):557-565.