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Is Ovarian Preservation Feasible in Early-Stage Adenocarcinoma of the Cervix?

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Background: In cervical adenocarcinoma, surgical treatment involves bilateral oophorectomy, which affects the long-term quality of life. The aim of our study was to assess the incidence of ovarian metastasis in early-stage cervical adenocarcinoma and to suggest an algorithm for the triage of these patients to preserve the ovaries.

Material/Methods: A total 101 patients with cervical adenocarcinoma who had undergone radical hysterectomy with pelvic lymphadenectomy and bilateral oophorectomy were included in this study. Data on the clinicopathologic characteristics of the cases were collected and low risk factors for ovarian metastasis in early-stage cervical adenocarcinoma were analyzed.

Results: The ovary metastasis rate of cervical adenocarcinoma in this study was 4.95%, while it is only 2% in stage IB1. Pathological grade, LSVI, lymph node status, tumor size, depth of stromal invasion, and involvement of the junction of the cervix and the body of the uterus were associated with ovarian metastasis, while LSVI, lymph node status, depth of stromal invasion, and involvement of the junction of the cervix and the body of the uterus were associated with ovarian metastasis in stage IB. Multivariate analysis revealed that LSVI and lymph node metastasis were independent risk factors for ovarian metastasis in all stages of cervical adenocarcinoma, but involvement of the junction of the cervix and the body of the uterus was an independent risk factor for ovarian metastasis in stage IB.

Conclusions: The incidence of ovarian metastasis in cervical adenocarcinoma is low. Our study suggests that ovarian preservation is safe and feasible in patients with no risk factors for ovarian metastasis. Further prospective studies are warranted.

MeSH Keywords: **Ovarian Neoplasms • Ovariectomy • Risk Factors • Uterine Cervical Neoplasms**

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Background

Cervical cancer is the leading malignant cancer of the female reproductive system, and its incidence in younger women has gradually increased as the sexual attitudes of society have changed. Approximately 40% of early cervical cancers occur in women of childbearing age [1]. Cervical adenocarcinoma accounts for 20–25% of cervical cancers [2]. Early cervical adenocarcinoma cancer has a good prognosis; the 5-year survival rate is greater than 80% [3]. However, surgical treatment of cervical adenocarcinoma involves oophorectomy, which affects the long-term quality of life, leading to menopausal syndrome, cardiovascular disease, or osteoporosis. In recent years, based on the ovarian metastasis rate in patients with cervical adenocarcinoma, some researchers have questioned whether bilateral oophorectomy is suitable for all patients; these researchers believe that the ovaries may be preserved in some patients to improve the quality of life after surgery. In this study, we analyzed ovarian metastasis in patients with cervical adenocarcinoma who underwent radical hysterectomy with pelvic lymphadenectomy and bilateral oophorectomy at our hospital and we explored methods of identifying cervical adenocarcinoma patients with a low risk of ovarian metastasis.

Material and Methods

Cervical adenocarcinoma patients who underwent extensive hysterectomy + pelvic lymphadenectomy between January 2008 and December 2014 at the Sun Yat-sen Memorial Hospital were included in this study. The inclusion criteria consisted of (1) patients undergoing initial treatment of the disease with no prior radiotherapy or chemotherapy before surgery; (2) cervical adenocarcinoma, confirmed by a post-operative pathological examination; and (3) no history of benign or malignant ovarian tumors.

This study was approved by the appropriate ethics committee and was therefore performed in accordance with ethics standards.

The clinical and pathological parameters included in this study were age, tumor size, tumor differentiation, lymph vascular space invasion (LSVI), parametrial invasion, lymph node status, depth of myometrial invasion, involvement of the junction of the cervix and the body of the uterus, vaginal involvement, involvement of the body of the uterus, involvement of the vaginal stump, and pre-operative serum levels of squamous cell carcinoma antigen (SCCA) and cancer antigen (CA)125.

Surgical specimens were routinely fixed, paraffin-embedded, and mounted on slides. Two pathologists examined the slides. Ovarian metastasis was diagnosed if cancer cells with

characteristics consistent with those found in the primary site were observed in ovarian tissue or ovarian vessels.

SPSS 19.0 statistical software was used for the data analysis. Continuous variables are expressed as the mean \pm standard deviation. For variables with a normal distribution, the *t* test was performed for intergroup comparisons; for non-normally distributed variables, the Wilcoxon test was performed for intergroup comparisons. Fisher's exact test was performed to compare rates between groups. A logistic regression analysis was performed to analyze the relationship between ovarian metastasis and other pathological parameters. A value of $P < 0.05$ was considered statistically significant.

Results

The clinical and pathological data of the enrolled patients

This study included 101 patients, with a mean age of 44.1 ± 9.32 (range, 23–70) years and a median age of 44 years. Among the 101 patients, 5 (4.95%) exhibited ovarian metastasis. The mean pre-operative SCCA level was 0.51 ± 0.59 $\mu\text{g/L}$, and the mean CA125 level was 34.62 ± 95.01 $\mu\text{g/L}$.

Ovarian metastasis of cervical adenocarcinoma and risk factors

The clinicopathologic characteristics of the patients are shown in Table 1. Pathological grade, LSVI, lymph node status, tumor size, depth of stromal invasion, and involvement of the junction of the cervix and the body of the uterus were associated with ovarian metastasis (all $P < 0.05$). The logistic regression analysis of ovarian metastasis and other pathological parameters showed that LSVI (hazard ratio [HR]: 14.759, 95% confidence interval [CI]: 1.381–157.756, $P = 0.026$) and lymph node metastasis (HR: 17.879, 95% CI: 1.682–190.052, $P = 0.017$) were independent risk factors for ovarian metastasis of cervical adenocarcinoma.

Ovary metastasis of stage IB cervical adenocarcinoma and risk factors

This portion of the study included data from 88 patients (87.1%) with stage IB cervical adenocarcinoma. For these 88 patients, the mean age was 43.61 ± 9.04 (range, 23–70) years, and the median age was 44 years. Four patients (4.5%) exhibited ovarian metastasis. The mean pre-operative SCCA level was 0.47 ± 0.50 $\mu\text{g/L}$, and the mean CA125 level was 37.45 ± 84.35 $\mu\text{g/L}$. The clinicopathologic characteristics of those patients are shown in Table 2. LSVI, lymph node status, depth of stromal invasion, and involvement of the junction of the cervix and the body of the uterus were associated

Table 1. Relationship between ovarian metastasis and other clinicopathologic characteristics in cervical adenocarcinoma.

Risk factors	Numbers		Ovarian metastasis		P
			Negative	Positive	
Age (years)					
≤45	57	(56.4%)	55	2	0.651
>45	44	(43.6%)	41	3	
Stage (FIGO 2009)					
IA2	1	(1.0%)	1	0	0.100
IB1	51	(50.5%)	50	1	
IB2	37	(36.6%)	34	3	
IIA1	4	(4.0%)	3	1	
IIA2	8	(7.9%)	8	0	
Grade					
G1	47	(46.5%)	47	0	0.047
G2	25	(24.8%)	23	2	
G3	29	(28.7%)	26	3	
Tumor size (cm)					
≤2	38	(37.6%)	38	0	0.000
>2, <4	18	(17.8%)	16	2	
≥4	45	(44.6%)	42	3	
LSVI					
Positive	25	(24.8%)	21	4	0.013
Negative	76	(75.2%)	75	1	
Lymph node status					
Positive	22	(21.8%)	18	4	0.008
Negative	79	(78.2%)	78	1	
Stromal invasion					
<1/2	56	(55.4%)	56	0	0.015
>1/2	45	(44.6%)	40	5	
Parametrial involvement					
Positive	8	(7.9%)	7	1	0.344
Negative	93	(92.1%)	89	4	
Involvement of the the junction of the cervix and uterus body					
Positive	23	(22.8%)	19	4	0.009
Negative	78	(77.2%)	77	1	
Involvement of the uterus body					
Positive	8	(7.9%)	7	1	0.344
Negative	93	(92.1%)	89	4	
Vaginal involvement					
Positive	14	(13.9%)	13	1	0.534
Negative	87	(86.1%)	83	4	
SCCA	101		0.52±0.60	0.32±0.22	0.123
CA125	101		36.6±81.74	51.4±47.1	0.541

Table 2. Relationship between ovarian metastasis and other clinicopathologic characteristics in stage IB cervical adenocarcinoma.

Risk factors	Numbers	Ovarian metastasis		P
		Negative	Positive	
Age (years)				
≤45	52 (59.1%)	50	2	1.00
>45	36 (40.9%)	34	2	
Satge (FIGO 2009)				
IB1	51 (57.95%)	50	1	0.305
IB2	37 (42.05%)	34	3	
Grade				
G1	42 (47.7%)	42	0	0.067
G2	21 (23.9%)	19	2	
G3	25 (28.4%)	23	2	
Tumor size (cm)				
≤2	36 (40.9%)	36	0	0.112
>2, <4	15 (17.0%)	14	1	
≥4	37 (42.1%)	34	3	
LSVI				
Positive	22 (25%)	19	3	0.047
Negative	66 (75%)	65	1	
Lymph node status				
Positive	17 (19.3%)	14	3	0.022
Negative	71 (80.7%)	70	1	
Stromal invasion				
<1/2	55 (62.5%)	55	0	0.018
>1/2	33 (37.5%)	29	4	
Parametrial involvement				
Positive	7 (7.95%)	6	1	0.287
Negative	81 (92.05%)	78	3	
Involvement of the the junction of the cervix and uterus body				
Positive	16 (18.2%)	13	3	0.018
Negative	72 (81.8%)	71	1	
Involvement of the uterus body				
Positive	5 (5.7%)	5	0	1.00
Negative	83 (94.3%)	79	4	
Vaginal involvement				
Positive	3 (3.4%)	3	0	1.00
Negative	85 (96.6%)	81	4	
SCCA	88	0.48±0.51	0.30±0.25	0.254
CA125	88	36.52±85.67	57.05±52.39	0.503

Table 3. Clinicpathologic characteristics of patients with ovarian metastasis of cervical adenocarcinoma.

No.	Age (years)	Stage	Tumor size (cm)	Grade	LVSI	Lymph node status	Stromal invasion	Involvement of the junction of the cervix and uterus body	Parametrial involvement	Involvement of the uterus body	Vaginal involvement
1	42	IB2	4	2	-	+	>1/2	-	-	-	-
2	47	IB2	6	3	+	+	>1/2	+	+	-	-
3	65	IIA1	3	3	+	+	>1/2	+	-	+	+
4	30	IB1	3	2	+	+	>1/2	+	-	-	-
5	48	IB2	4	3	+	-	>1/2	+	-	-	-

with ovarian metastasis (all $P < 0.05$). The logistic regression analysis of ovarian metastasis and other pathological parameters showed that involvement of the junction of the cervix and the body of the uterus ($HR: 16.385$, 95% $CI: 1.580-16.945$, $P=0.019$) was an independent risk factor for ovarian metastasis in stage IB cervical adenocarcinoma.

The clinical and pathological characteristics of ovarian metastasis in cervical adenocarcinoma

Among 5 cervical adenocarcinoma patients with ovarian metastasis, 2 patients were under 45 years of age and 3 patients were over 45 years of age; 1 patient was in stage IB1 and 4 patients were in stage >IB1. The tumor size was >2 cm in all 5 patients. Four patients were LVSI (+), 4 patients had lymph node metastases, 5 patients had tumor invasion of the outer half of the cervical muscles, 4 patients had involvement of the junction of the cervix and the body of the uterus, and 1 patient each had parametrial metastasis, involvement of the body of the uterus, and vaginal involvement. The data are shown in Table 3.

Discussion

Radical hysterectomy and pelvic lymphadenectomy are the standard surgical treatments for cervical cancer, and the decision to preserve the ovaries must be based on the pathological type of the tumor and the patient's age. The ovarian metastasis rate of squamous cervical cancer (SCC) is <1% according to published reports [4,5]; thus, clinicians have reached a consensus that if the patient is ≤ 45 years of age, the ovaries may be preserved. However, the ovarian metastasis rate of cervical adenocarcinoma is relatively higher; therefore, clinicians typically resect the ovaries in such cases during conventional treatment. In recent years, however, some researchers have questioned this practice because cervical adenocarcinoma occurs in younger women; approximately 34.6% of cervical

adenocarcinoma patients are <40 years of age and 60.3% are <50 years of age [6]. For Chinese women, the average menopausal age is 49 years, which suggests that in more than half of patients, their ovaries are still functioning at the time of diagnosis of cervical adenocarcinoma. For patients who want to have children after surgery, preserving the ovaries preserves their reproductive ability, as patients can choose whether to undergo extensive cervical excision while preserving the ovaries or to have children via a surrogate pregnancy. For patients without the need to preserve reproductive ability after surgery, preserving the ovaries helps to prevent menopausal symptoms, osteoporosis, and cardiovascular diseases associated with estrogen deficiency. Currently, reports vary regarding the ovarian metastasis rate of cervical adenocarcinoma, and most studies had small sample sizes without stratification; therefore, the ovarian metastasis rate of cervical adenocarcinoma is not clear. We aimed to analyze the clinical and pathological factors to identify low-risk factors for ovarian metastasis of cervical adenocarcinoma so that these patients may have the option to retain ovarian function, thereby improving their quality of life.

Due to a lack of large, randomized, controlled studies, no consensus on ovarian metastasis of cervical adenocarcinoma exists in China or in other countries. Existing data suggest that the ovarian metastasis rate of stage IA2-IIIB cervical adenocarcinoma is 0%–12.9% [5,7–11]. Landoni et al. [10] examined 380 patients with stage IA-IIA cervical adenocarcinoma and found that 9 patients (2.3%) exhibited ovarian metastasis. Yamamoto et al. [9] examined 98 patients with cervical adenocarcinoma, including 97 patients with FIGO stage \geq IB, and found that the ovarian metastasis rate was 10.2%. Natsume et al. [8] examined 61 patients with stage IIB cervical adenocarcinoma and 1 patient with stage IB cervical adenocarcinoma and found that 8 patients (12.9%) showed ovarian metastasis. Because of the relatively high metastasis rate, these researchers do not recommend preserving ovaries after cervical adenocarcinoma treatment. However, some researchers have a different opinion

because the previous studies did not consider the FIGO stage and most patients enrolled had locally advanced cervical adenocarcinoma. Kjørstad et al. [7] found that the ovarian metastasis rate of stage IB cervical adenocarcinoma was only 1.3%; therefore, the ovaries may be preserved in these patients. A Gynecological Oncology Group (GOG) study found that the ovarian metastasis rate was 1.6% for stage IB cervical adenocarcinoma and 0.5% for stage IB SCC, but the difference was not significantly significant [8]. Thus, the FIGO stage is a factor for ovarian metastasis of cervical adenocarcinoma, and the ovarian metastasis rate increases in patients with more advanced stages. The present study found that the overall ovarian metastasis rate was 4.95% in all cases of cervical adenocarcinoma and was 0% in stage IA2 cervical adenocarcinoma, 2% (1/50) in stage IB1 cervical adenocarcinoma, and 8.8% (3/34) in stage IB2 cervical adenocarcinoma; these results are consistent with the literature. Thus, we believe that the ovarian metastasis rate is low if the clinical stage is \leq IB1 and that some of those patients may benefit from ovarian preservation.

Studies have shown that the pathological factors associated with ovarian metastasis of cervical adenocarcinoma include age, FIGO stage, pathological grade, depth of cervical stromal invasion, LSVI, lymph node metastasis, parametrial metastasis, involvement of the body of the uterus, involvement of the junction of the cervix and the body of the uterus, and vaginal involvement [12–14]. Nakanishi et al. [15] conducted a retrospective analysis of 240 patients with cervical adenocarcinoma and found that the ovarian metastasis rate was 6.3% (15/240). A logistic regression analysis showed that intimal involvement, lymph node metastasis, parametrial metastasis, and tumor size > 30 mm were independent risk factors for ovarian metastasis. Ting et al. [16] conducted a multicenter study in China and found that among 183 patients with cervical adenocarcinoma, the ovarian metastasis rate was only 2.7%; lymph node metastasis, involvement of the body of the uterus, and parametrial involvement were independent risk factors, while pre-operative neoadjuvant chemotherapy was a protective factor for ovarian metastasis of cervical adenocarcinoma. Landoni et al. [10] found that age >45 years, deep cervical stromal invasion, and the FIGO stage were predictors of ovarian metastasis. However, some researchers reached different conclusions. Shimad et al. [17] suggested that ovarian metastasis was unrelated to lymph node metastasis or parametrial invasion and thus recommended ovariectomy during surgery. In the present study, the univariate analysis showed that ovarian metastasis of cervical adenocarcinoma was related to poor differentiation, LSVI (+), lymph node (+), tumor size >2 cm, depth of stromal invasion $>1/2$, and involvement of the junction of the cervix and the body of the uterus. The multivariate analysis showed that LSVI (+) and lymph node (+) were significant, independent risk factors for ovarian metastasis of cervical adenocarcinoma. Specifically, ovarian metastasis

in stage IB cervical adenocarcinoma was related to LSVI, lymph node status, depth of stromal invasion, and involvement of the junction of the cervix and the body of the uterus (all $P<0.05$). The multivariate analysis showed that involvement of the junction of the cervix and the body of the uterus ($HR: 16.385$, 95% $CI: 1.580-16.945$, $P=0.019$) was an independent risk factor for ovarian metastasis of stage IB cervical adenocarcinoma.

We then analyzed the pathological features of 5 patients with ovarian metastasis; of these, 3 patients showed LSVI (+) status, lymph node (+) status, depth of stromal invasion $>1/2$, and involvement of the junction of the cervix and the body of the uterus. Only 1 patient was in stage IB1, but she exhibited LSVI (+) status, lymph node (+) status, depth of stromal invasion $>1/2$, and involvement of the junction of the cervix and the body of the uterus. Based on these results and published reports, we believe that for patients with early-stage cervical adenocarcinoma, the ovarian metastasis rate is very low if the following conditions are met: age <45 years, stage \leq IB1, G1, tumor size <2 cm, LSVI (–), lymph node (–), depth of stromal invasion $<1/2$, and no involvement of the junction of the cervix and the body of the uterus.

It remains controversial whether preserving the ovaries in patients with cervical adenocarcinoma increases the risk of relapse. Several studies have been conducted on this topic. Tabata et al. [18] conducted a follow-up study of 706 patients with *in situ* cervical adenocarcinoma or FIGO stage IA cervical cancer (including adenocarcinoma) whose ovaries were preserved during surgery. The median follow-up time was 5 years, and no relapse was observed. Sutton et al. examined 41 patients with stage IB cervical adenocarcinoma in whom at least 1 ovary and its accessory tissue were preserved, and found no relapse during follow-up. Windbichler et al. [19] conducted a paired study based on tumor size in patients with stage I cervical cancer to compare the overall survival and progression-free survival of patients who had their ovaries preserved and those who did not, and found no significant difference in survival or relapse. Landoni et al. [10] examined 26 patients with FIGO stage IA2-IIA cervical adenocarcinoma who had at least 1 ovary and its accessory tissue preserved; the median follow-up time was 68 months, and no ovarian relapse was observed. The present study was a retrospective study in which both ovaries and the accessory tissues were resected in all patients; therefore, we were unable to obtain relapse data on patients who had their ovaries preserved, which is a limitation of this study.

Conclusions

In summary, the incidence of ovarian metastasis in cervical adenocarcinoma is low, and researchers have different opinions

regarding whether ovaries should be preserved in these patients. Previous studies and the present study suggest that ovarian preservation is safe and feasible in young patients with no risk factors for ovarian metastasis (age <45 years, stage ≤IB1, G1, tumor size <2 cm, LSVI (-), lymph node (-), depth of stromal invasion <1/2, and no involvement of the junction of the cervix and the body of the uterus). Large, randomized, controlled studies are needed to confirm these results.

Researching involving human participants

This study was approved by the appropriate ethics committee and was therefore performed in accordance with ethics standards.

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Disclosure of potential conflict of interests

The authors declare that they have no potential conflict of interests in this study.

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