Analysis of the risk factors for the recurrence of cervical cancer following ovarian transposition

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Summary

Purpose: To investigate the potential risk factors related to the recurrence of cervical cancer following ovarian transposition. *Materials and Methods:* A total of 105 patients with cervical carcinoma were retrospectively analyzed. Each patient underwent surgical therapy in combination with ovarian transposition from September 2000 to November 2009. The potential risk factors for recurrence following ovarian transposition were analyzed. *Results:* The average age of the 105 patients was 38.7 years. Twelve patients were in Stage IA, 65 in IB, 12 in Stage IIA, and 16 in Stage IIB. Twenty-five patients had well-differentiated cancer (G1). Forty-eight patients had moderately-differentiated cancer (G2), and 32 patients had poorly-differentiated cancer (G3). Ninety-seven cases were squamous cell carcinoma, three were adenocarcinoma, four were small cell carcinoma, and one case was adenosquamous carcinoma. Five patients (4.8%) had a recurrence, two of whom (1.9%) had ovarian metastasis. Univariate analysis showed that the pathological type ($p = 0.005$) and degree of differentiation ($p = 0.001$) were potential risk factors for recurrence of cervical carcinoma following ovarian transposition. Cancer embolus in vessels or lymphatic metastasis was observed in four of the five patients who suffered a recurrence. *Conclusion:* Pathological type, differentiated degree, and cancer embolus in vessels or lymphatic metastasis were identified as potential risk factors for the recurrence of cervical carcinoma after ovarian transposition.

Key words: Cervical carcinoma; Ovarian transposition; Recurrence.

Introduction

Cervical carcinoma is a common tumor, with the second highest incidence rate among female tumors. Globally, the number of patients has increased over time and 560,000 females were reported to be affected in 2006 [1]. The age of onset was found to peak at two age ranges, 35-39 years and 60-64 years. Moreover, there has been a growing concern worldwide regarding an increase in affected youths. Postoperative radiotherapy is required for some patients; however, the ovaries are very sensitive to this treatment. A single dose ≥ four Gy or ten-day doses ≥ 15 Gy can induce permanent ovarian castration. When treatment is limited to one ovary, the ovary distal to the radiation field is normally unaffected [2]. In 1985, McCall first described that ovarian transposition could reserve ovarian function following radical hysterectomy. Although radiotherapy has been shown to affect transposed ovaries, subsequent studies have reported that their function could be preserved [3-5]. Therefore, for young patients that require adjuvant radiotherapy following surgical resection, ovarian transposition out of the radiation field can prevent the damage resulting in ovarian function and increase the quality of life. Studies on the recurrence rate and recurrence-related risk factors, however, are rare. In this study, 105 patients with cervical carcinoma who underwent ovarian transposition within the past ten years were retrospectively analyzed, and the recurrence-related risk factors were investigated.

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Materials and Methods

A total of 105 patients with cervical carcinoma with an average age of 38.7 years (range 26-69) were enrolled in this study. All of the patients underwent surgical resection in combination with unilateral (n = 39) or bilateral (n = 66) ovarian transposition in the Department of Gynaecology and Obstetrics of Peking University People's Hospital between September 2000 and November 2009. Based on the staging criteria set by the International Federation of Gynecology and Obstetrics (FIGO) in 2009, 12 of the patients were staged in IA (nine in IA1 and three in IA2), 54 in IB1, 11 in IB2, 12 in IIA, and 16 in IIB. According to the differentiated degree, patients were categorized as having well-differentiated cancer (G1, n = 25), moderately-differentiated cancer (G2, n = 48) and poorly-differentiated cancer (G3, n = 32). Ninety-seven cases were squamous cell carcinoma, three cases were adenocarcinoma, four cases were small cell carcinoma, and one case was poorly-differentiated adenosquamous carcinoma. All carcinomas were verified by pathological examination.

Of the 105 patients, 97 (≥ Stage IA2) underwent radical/subradical hysterectomy plus a pelvic lymphadenectomy, seven (Stage IA1) underwent exofacial hysterectomy, and one was found to have cervical adenocarcinoma by pathological examination after complete hysterectomy and underwent a pelvic lymphadenectomy three weeks later. A total of 105 patients were also treated with ovarian transposition, 39 with unilateral ovarian transposition, and 66 with bilateral ovarian transposition. A total of 29 patients received postoperative radiotherapy (external irradiation of the entire pelvic and vaginal cavities following after-loading radiotherapy) with an average dose of 6,032 cGy (4,760 - 8,000 cGy).

All patients were followed up until October 2010 in one to three-month intervals during the first year postoperatively and every three to six months thereafter. The average follow-up period was 44.3 months (range 14-81). Gynecologic examination and transvaginal color Doppler sonography were per-

formed, and serum tumor markers (CA125, CA199, and SCC) were assayed at each visit. Abdominal ultrasonography or computed tomography/magnetic resonance imaging (CT/MRI) and chest X-rays were performed annually.

SPSS 13.0 was used for all statistical analyses. Potential risk factors of recurrence of cervical carcinoma following ovarian transposition were screened using COX regression univariate analysis. Survival analysis was performed using the Kaplan-Meier method.

Results

Of the 105 patients, five (4.8%) had a recurrence, including two (1.9%) patients who were diagnosed with ovarian metastasis. A 31-year-old patient with Stage IIB small cell carcinoma self-palpated the right abdominal lump six months postoperatively and subsequently underwent exploratory laparotomy. Frozen pathology showed metastatic carcinoma in the right ovary and a normal left ovary. As a result, both of the transposed ovaries were removed. Another patient was found to suffer from undifferentiated Stage IB1 cervical squamous cell carcinoma before surgery that was upgraded to poorly-differentiated Stage IB1 cervical squamous cell carcinoma after surgery by pathology. A PET scan at ten months post-surgery, however, indicated metastasis in the right ovary. As a result, an exploratory laparotomy and a right transposed ovariectomy were performed. The postoperative pathology demonstrated right transposed ovarian metastatic cancer.

Of the remaining three patients that suffered a recurrence, one patient with Stage IB1 poorly-differentiated squamous cell carcinoma was found to have multiple pelvic metastases, supraclavicular lymph nodes metastasis, and intestinal obstruction as determined by PET at 20 months postoperatively. This patient was given a single treatment of local alleviative radiotherapy plus chemotherapy, after which she developed severe myelosuppression and died 26 months later. Another patient with Stage IIB cervical small cell carcinoma who suffered a recurrence underwent initial surgery on July 15, 2008 and was treated with bleomycin, ifosfamide, and cisplatin (BIP) chemotherapy twice. Because of IV degree myelosuppression, however, the chemotherapy was stopped. Radiotherapy was administered at the local hospital from August 23 to September 23, 2008. After this treatment, the patient was tested for tumor markers, and a CT was given every three months; no abnormalities were found. CT at 17 months postoperatively showed an enlarged solid low-echo region in the bilateral ovaries, multiple nodular shadows, and multiple retroperitoneal lymphatic and epistropheus metastasis. In addition, the patient's CA125 also increased. After evaluation, the patient was not considered for a second surgery, and she abandoned the therapy. The last patient to suffer a recurrence was initially diagnosed with Stage IIA poorly-differentiated squamous cell carcinoma. The patient had received ten cycles of BIP chemotherapy 12 months before initial surgery. The patient refused to continue chemotherapy and is still being followed.

Table 1. — *Preliminary screening of potential risk factors by univariate analysis*.

Factors		Number	Recurrence (patient)	χ^2 value	p value
Age	≤ 40 years	55	2	0.323	0.57
	> 40 years	50	3		
FIGO Stage	≤ Stage IIA	89	3	2.492	0.114
	> Stage IIA	16	2		
Pathological type	Squamous	97	3	7.821	0.005
	Non-squamous	8	2		
Differentiation	G1-G2	73	0	11.977	0.001
	G3	32	5		
Lesion diameter	< 4 cm	75	3	0.366	0.522
	≥ 4 cm	30	2		
Infiltrating depth	< 1/2 muscular layer	70	4	0.42	0.517
	≥ 1/2 muscular layer	35	1		
Embolus in vessels or lymphatic metastasis	None	64	1	3.699	0.054
	Yes	41	4		

The potential factors identified by univariate analysis included pathological type ($p = 0.005$) and differentiation degree ($p = 0.001$). In addition, postoperative pathology showed cancer emboli in vessels in four of the five patients who had a recurrence, although the difference in the number of cancer emboli in the vessels was not statistically significant ($p = 0.054$). Given the trend, however, the number of cancer emboli in the vessels was considered a possible risk factor (Table 1). Multivariate analysis was not performed because only five patients had a recurrence during the follow-up period.

Using the Kaplan-Meier method, the authors found that the five-year survival rate was 98.1%, the recurrence rate was 4.8% (5/105), and the ovarian metastatic rate following transposition was 1.9% (2/105).

Discussion

The ovarian metastatic rate in patients with early-stage cervical carcinoma is very low. To evaluate the clinical pathological features of ovarian metastasis in cases of cervical carcinoma, Shimada *et al*. [6] studied 3,471 patients with Stage IB-IIB cervical carcinoma from 1981 to 2000 and found that for Stage IB, IIA, and IIB carcinoma, the ovarian metastatic rate of cervical squamous cell carcinoma was 0.22%, 0.75%, and 2.17%, respectively, while that of cervical adenocarcinoma was 3.72%, 5.26%, and 9.85%, respectively. Their results showed that the ovarian metastatic rate was only 1.5%, whereas the ovarian metastatic rate of Stage IIB squamous carcinoma increased significantly. Therefore, it was determined that for patients with Stage ≤ IIA cervical squamous cell carcinoma, the ovaries could be preserved. Furthermore, they found that the ovarian metastatic rate in patients with cervical adenocarcinoma increased significantly. Nakanishi *et al*. [7] conducted a study in 1,064 patients with cervical squamous cell carcinoma and 240 patients with cervical adenocarcinoma. They found that the metastatic rate of cervical adenocarcinoma was much

higher than that of squamous cell carcinoma (6.3% vs 1.3%). Therefore, patients with cervical adenocarcinoma should not be encouraged to preserve their ovaries. L'ubusky *et al*. [8] believed that the ovarian metastatic rate was determined by pathological types and the clinical stages of the tumor. They found that the postoperative ovarian dysfunction rate was low in young patients with Stage IA-IB squamous cell carcinoma and determined that there was a better chance to preserve the ovaries.

The ovary is very sensitive to radiation. For young patients requiring postoperative adjuvant radiotherapy, the ovary can be transposed outside of the radiation field to prevent damage to its function. The relationship between ovarian function following transposition and age, however, remains a concern. Morice *et al*. [9] reported that of 104 patients with cervical carcinoma who underwent ovarian transposition combined with radiotherapy or not. The ovarian function was preserved in 100% of the patients who did not receive radiotherapy, 90% of the patients who received intravaginal radiation, and 60% of the patients who received intracavitary radiation combined with extracorporeal radiation. Pahisa *et al*. [4] performed the surgery and laparoscopic ovarian transposition concurrently in 28 Stage IB cervical carcinoma patients who were younger than 45-years-old. Of these patients, 12 were supplemented with postoperative radiotherapy and the average follow-up period was 44 months. A total of 63.6% of the patients who had received radiotherapy and 93% of the patients who did not receive radiotherapy maintained normal ovarian function. Ishii *et al*. [10] explored the relationship between the function of transposed ovaries and age in patients with Stage IB-II cervical carcinoma and found that the incidence of menopausal symptoms was significantly lower in patients younger than 40 years of age (5/21) than in those older than 40 years of age (10/12). Ling Yan *et al*. [11] also observed that cervical carcinoma patients who were younger than 40 years of age had preserved ovarian function. Therefore, patients younger than 40 years of age should be considered for ovarian transposition.

Although lymph fluid of the uterine cervix can drain into the ileal and the parametrial lymph nodes, cervical carcinoma rarely spreads to the ovaries. Patients with cervical carcinoma and ovarian transposition, however, may still suffer from ovarian metastasis. Studies on the ovarian metastasis of cervical carcinoma following ovarian transposition are rare, and most are case reports. Ovarian metastasis can occur in cases of adenosquamous cell carcinoma, squamous cell carcinoma, and adenocarcinoma [12-14]. Yamamoto *et al*. [15] reported that the rate of ovarian metastasis was 0.4% for patients with cervical squamous cell carcinoma and 8.2% for other pathological types. Zhang Meiqing [16] indicated that only one out of 127 patients who did not opt to preserve the ovaries was diagnosed with ovarian metastatic squamous carcinoma and that the metastatic rate was 0.8%. Other studies [15, 17] also considered the pathology of cervical carcinoma and angiolymphoid infiltration to be factors affecting ovarian metastasis. In the current study, which included 105 patients with ovarian transposition, five patients suffered a recurrence (two with ovarian metastasis). Of the five cases involving recurrence, four of the patients had cancer emboli in vessels or lymphatic metastasis, suggesting that cancer emboli in vessels may be a crucial factor affecting recurrence following ovarian transposition.

Huang *et al*. [18] indicated that the surgical indications for ovarian transposition included (1) patients younger than 40 years of age, scheduled for radical hysterectomy due to cervical carcinoma, and that may require postoperative pelvic radiotherapy; (2) patients with a tumor diameter less than or equal to three cm; and (3) patients with no evidence of invasion into the parametrial, uterine, and/or lymph vessels. In this study, the five-year survival rate was high after ovarian transposition, but the risk of recurrence increased in patients with late-stage cervical carcinoma, non-squamous cell carcinoma, poorly-differentiated carcinoma, and cancer emboli in the vessels and lymphatic metastasis. It is unknown whether the rate of recurrence significantly changes when using 40 or 45 years as the cutoff age; however, it has been found that females older than 40 years of age are liable to have menopausal symptoms after transposition [10, 11]. Therefore, patients younger than 40 years of age are normally selected for ovarian transposition. Plante [19] followed 42 patients with Stage IA1-IIA cervical squamous cell carcinoma who were treated with extensive cervicectomy for an average of 60 months (range six to 156) and found that cervical adenocarcinoma was not a risk factor for recurrence. Therefore, young patients with cervical adenocarcinoma who wish to preserve ovarian function should be encouraged to undergo extensive cervicectomy or ovarian transposition.

Considering the present findings and those from previous studies [17, 20, 21], the authors believe that the indications for ovarian transposition may be as follows: (1) age younger than 40 years, a regular menstrual cycle before surgery, and no menopausal syndrome; (2) normal ovarian appearance during intraoperative exploration, and, when necessary, frost pathology should be performed to rule out metastasis; (3) Stage I-II highly or median-differentiated cervical squamous cell carcinoma; (4) no family history of breast or ovarian carcinoma; (5) no cancer emboli in vessels or lymphatic metastasis; and (6) patients who strongly wish to preserve ovarian function and sign an informed consent form.

Conclusion

Pathological type, differentiated degree, and cancer embolus in vessels or lymphatic metastasis were identified as potential risk factors for the recurrence of cervical carcinoma after ovarian transposition.

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