

# Multicenter research on tumor and pregnancy outcomes in patients with early-stage cervical cancer after fertility-sparing surgery

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## Abstract

**Objective:** To investigate tumor and pregnancy outcomes after fertility-sparing surgery for cervical cancer.

**Methods:** A total of 83 patients with cervical cancer who received fertility-sparing surgery at 10 gynecologic cancer research centers in Henan Province were enrolled from January 2010 to June 2016. Clinical data and follow-up results were collected. Of them, 78 had cervical squamous carcinoma and five had cervical adenocarcinoma. International Federation of Gynecology and Obstetrics (2009) staging showed that 26 patients had stage IA1, 11 had stage IA2, and 46 had stage IB1. Seventy-two patients underwent radical trachelectomy and retroperitoneal lymphadenectomy, whereas 11 underwent subradical trachelectomy and retroperitoneal lymphadenectomy. Moreover, 17 patients received one to two courses of preoperative neoadjuvant chemotherapy and five received two to four courses of postoperative chemotherapy. Eighty-three patients were followed up postoperatively (median follow-up duration, 36.2 months).

**Results:** With regard to tumor outcomes, one (1.2%) patient showed recurrence following fertility-sparing surgery. In 69 patients with planned pregnancy after treatment, 54 had 58 pregnancies, including 42 full-term births and eight premature births. Seventy-nine patients were satisfied with their quality of life.

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**Conclusions:** Radical/subradical trachelectomy is safe and effective as fertility-sparing surgery for young patients with early cervical cancer, with good pregnancy outcomes.

### **Keywords**

Early cervical cancer, fertility preservation, pregnancy outcome, tumor prognosis, trachelectomy, chemotherapy, lymphadenectomy

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## **Introduction**

Cervical cancer is the fourth most common malignant disease in women worldwide.<sup>1</sup> The incidence of cervical cancer is correlated with the regional economic level, and 85% of cervical cancer cases are found in developing countries. China has a huge population of patients with cervical cancer. Following improvement in the widespread use of cervical cancer screening technology, this condition is being increasingly detected in young patients and in those with early stages of this disease. Epidemiological studies have indicated that the average age of onset has been reduced by 5 to 10 years compared with that found 10 years previously.<sup>2</sup> Therefore, an increasing number of patients are at a reproductive age when diagnosed. Age distribution studies have shown that 57.7% of patients with cervical cancer in China are aged < 45 years when diagnosed, and 42.4% of these patients have one or no children.<sup>3</sup> In this population, preservation of reproductive function has a long-term effect on their life and psychology. At present, radical hysterectomy (RH) is the standard procedure for treatment of cervical cancer. Although this method has a high cure rate, it results in the loss of reproductive function because of the requirement of complete uterine removal. Therefore, a safe and effective fertility-sparing surgery is important for treating cervical cancer.

However, the safety, postoperative efficacy, and pregnancy outcomes of fertility-sparing surgery remain controversial, and should be further investigated. In the present study, we examined cases of cervical cancer with feasible assessment results before fertility-sparing surgery from multiple research centers. We examined the patients' postoperative tumor and pregnancy outcomes to provide better guidance for preserving reproductive function in patients with early-stage cervical cancer.

## **Materials and methods**

### **Patients**

For this study, we selected 88 cervical cancer cases with feasible assessment results before fertility-sparing surgery from 10 gynecologic cancer research centers in Henan province from January 2010 to June 2016. These 10 research centers included Henan Cancer Hospital, First Affiliated Hospital of Zhengzhou University, Second Affiliated Hospital of Zhengzhou University, Third Affiliated Hospital of Zhengzhou University, First Affiliated Hospital of Henan University of Science and Technology, Luoyang Central Hospital, Nanyang Central Hospital, First Affiliated Hospital of Xinxiang Medical College, Anyang City Cancer Hospital, and the First People's Hospital of Anyang City.

The study was approved by the Ethical Committee of the First Affiliated Hospital and the College of Clinical Medicine of Henan University of Science and Technology. All of the patients signed written informed consent.

### *Inclusion criteria*

The inclusion criteria were as follows: age  $\leq 40$  years; nulliparous or parous with child-bearing requirement; no infertility or other diseases that are difficult to treat; able to undergo long-term follow-up after surgery; cervical squamous cell carcinoma or adenocarcinoma confirmed by pathology; clinical diagnosis in accordance with one of the following conditions (International Federation of Gynecology and Obstetrics staging, 2009): 1) stage IA1, 2) stage IA2, IB1, or IIA1 (focal diameter  $\leq 2$  cm), and 3) stage IB1 or IIA1 (focal diameter  $> 2$  cm and  $\leq 4$  cm, which shrank after intravenous chemotherapy); consent to participate in this study and undergo surgery; and able to fill in the satisfaction questionnaire regarding quality of life.

### *Exclusion criteria*

The exclusion criteria were as follows: age  $> 40$  years; no child-bearing requirement; complications with other infertility factors that were difficult to treat; clinical diagnosis of stage IB2 or IIA2 or any of the above-mentioned stages; and clinical diagnosis of stage IB1 or IIA1 (focal diameter  $> 2$  cm and  $\leq 4$  cm, which did not shrink after intravenous chemotherapy). Patients with a tumor diameter  $> 2$  cm or interstitial infiltration  $> 1/2$  muscle layer cannot receive fertility preservation surgery, and such patients with cervical cancer were not included in our clinical study. This study aimed to include patients with early cervical cancer and patients with tumor shrinkage  $< 2$  cm after chemotherapy. Therefore,

the size of the tumor and the diameter of the specimen after surgery are not described again in our study.

### *Fertility-sparing therapy*

For laparoscopic vaginal radical trachelectomy (VRT), patients underwent laparoscopy, pelvic lymphadenectomy, and a rapid pathological examination was performed to determine no lymph node metastasis. VRT was then performed. If there was metastasis on the lymph nodes or tumors at the cervical margin, RH was performed. The pelvic lymph nodes were removed under laparoscopy, the uterine artery was freely preserved, and the para-uterine tissue was removed. The cervix was removed by the vagina, cervical cerclage was performed, and the vaginal stump was sutured.

The pelvic lymph nodes were cleaned as follows. Along the left ovary pelvic funnel ligaments, an ultrasonic scalpel was used to open the lateral peritoneum to the round ligament and the posterior lobe of the broad ligament to the uterus, and to clear the lymph nodes according to the order from outside to inside, from top to bottom, and from shallow to deep. The right pelvic lymph nodes were treated in the same manner. For extensive trachelectomy, when the cervix was removed, the upper one quarter to one third of the vagina was removed. The main ligament was cut at the pelvic wall and the sacral ligament was cut close to the sacrum. For subtotal trachelectomy, vaginal resection was performed without resection of the cervix. The ureteral tunnel was not involved, and the main ligament and uterine ligament were severed beside the cervix.

Adjuvant chemotherapy was based on the US National Comprehensive Cancer Network, which published the 2017 cervical cancer clinical practice guidelines as a guideline for adjuvant chemotherapy. Of 83 patients with cervical cancer,

17 (20.4%) received preoperative neoadjuvant chemotherapy with one to two courses of cisplatin + vincristine + bleomycin intravenous chemotherapy. The remaining 66 (79.5%) patients directly underwent treatment without any preoperative and postoperative radiotherapy. A total of 72 (86.7%) patients were scheduled to undergo extensive trachelectomy and retroperitoneal lymphadenectomy, whereas 11 (13.3%) patients underwent subtotal trachelectomy and retroperitoneal lymphadenectomy. The median amount of intraoperative bleeding was 200 mL (range, 50–1000 mL). A postoperative pathology examination confirmed that no cancer cells were detected at the surgical margin in all patients. The mean number of retroperitoneal lymph nodes removed was  $18.9 \pm 9.6$  and no cancer metastasis was observed. A total of seven (8.4%) patients had lymphovascular space involvement. Among these, five patients had two to four courses of postoperative intravenous chemotherapy with the bleomycin + ifosfamide + cisplatin regimen, and gonadotropin-releasing hormone agonist class drugs were used to protect ovarian function during chemotherapy in these patients. Although complete informed consent was obtained, two patients required close follow-up and did not undergo adjuvant therapy. A total of six (7.2%) patients had postoperative complications, including infection in one (1.2%), urinary retention in three (3.6%), and intestinal obstruction in two (2.4%). All of these conditions improved following symptomatic and supportive treatment.

### **Follow-up**

Follow-up examinations were performed at 3-month intervals, including a pelvic examination, the Thinprep cytological test, transvaginal ultrasonography, an abdominal ultrasound scan, chest radiography, and serum tumor marker (squamous-cell

carcinoma and CA125) detection. A human papillomavirus examination was recommended at 6 to 12-month intervals. Once recurrence or metastasis was suspected, colposcopy, biopsy, a pathological examination, fractional curettage, pelvic and abdominal computed tomography, magnetic resonance imaging, positron emission tomography-computed tomography, and a bone scan were conducted, as appropriate. Each research center had a specially assigned staff member for follow-up, psychological counseling, and conception guidance, who also collected and processed clinical data (on menstrual recovery and pregnancy outcomes) and reviewed the results. Until September 2017, 80 patients had completed follow-up without any withdrawal. The follow-up rate was 100% and the median follow-up time was 36.2 months (2–8 years). The patients who participated in the study are still in follow-up.

### **Statistical analysis**

Data processing was performed using SPSS 20.0 statistical software (IBM, Armonk, NY, USA). The chi-square test was used for comparison of enumeration data. A P value < 0.05 was considered significant.

## **Results**

### **Patients' characteristics**

Of the 88 patients with cervical cancer, two underwent RH because of intraoperative findings of pelvic lymph node metastases and three received radiation therapy because of postoperative pathological findings of lymph node metastases. These five patients were excluded. Of the 83 patients included in the study, 78 (93.9%) had cervical squamous carcinoma and five (6.0%) had cervical adenocarcinoma. The mean ( $\pm$ standard deviation) age of the patients was  $31.6 \pm 4.7$  years and the median

number of pregnancies was 2.0 (range, 0–7). Sixty-nine (83.1%) patients were non-parous, 12 (14.5%) had a single delivery, and two (2.4%) had two deliveries. With regard to complications, one (1.2%) had hypertension, one (1.2%) had diabetes mellitus, and the remaining patients did not have any complications. Among the patients, 26 (31.3%) were classified as stage IA1, 11 (13.3%) were classified as stage IA2, and 46 (55.4%) were classified as stage IB1. Histological differentiation showed that 37 (44.6%) patients had G1 (poor), 31 (37.3%) had G2 (moderate), and 15 (18.1%) had G3 (high).

### Recovery of menstruation after surgery

Of the 83 patients with cervical cancer who underwent fertility-preserving surgery, 80 (96.4%) showed recovery of regular menstruation. Among the other three (3.6%) patients, one showed recovery of menstruation, although it remained irregular until 8 months after the end of the last chemotherapy. The other two patients did not show recovery of menstruation at 6 months and 13 months after the end of the last chemotherapy.

### Tumor outcome

Of the 88 patients, 83 successfully underwent fertility-preserving surgery (success rate, 94.3%). None of the patients were lost to follow-up and recurrence was found in one patient (recurrence rate, 1.2%). The median follow-up duration was 36.2 months in 83 patients and all of the tumors were progression-free.

### Postoperative pregnancy

Among the 83 patients who received complete follow-up, 69 (83.1%) had planned to conceive, whereas 14 (16.9%) chose to use contraception for personal reasons without unexpected pregnancy. Of the 69 patients who planned to conceive, 54 (84.1%) became pregnant (50 [72.5%] with 1 pregnancy and 4 [5.8%] with 2 pregnancies), and all were a result of natural conception. There was no significance difference among the different treatments on pregnancy outcome (Table 1). Moreover, there was no significant effect of histological type on pregnancy outcome (Table 2). Because of the low incidence of cervical adenocarcinoma, it is more likely to relapse than squamous cell carcinoma. Therefore, fertility preservation surgery is still dominated by

**Table 1.** Effect of different treatments on pregnancy outcome.

Different treatments	No. of cases	Complications	Satisfaction rate	Number of pregnancies
A + C	14	2	12	8
A + D	58	2	57	43
B + C	3	1	2	1
B + D	8	1	8	6
$\chi^2$ value		6.433	7.782	3.645
P value		0.06	0.025	0.283

A: Radical trachelectomy and retroperitoneal lymphadenectomy.

B: Subradical trachelectomy and retroperitoneal lymphadenectomy.

C: Neoadjuvant chemotherapy.

D: Without neoadjuvant chemotherapy.

**Table 2.** Effect of different histological types on pregnancy outcome.

Different treatments	No. of cases	Complications	Satisfaction rate	Number of pregnancies
Poor differentiation	37	3	35	18
Moderate differentiation	41	2	40	28
High differentiation	15	1	14	12
$\chi^2$ value	0.592	1.133	5.567	
P value	0.86	0.657	0.063	

cervical squamous cell carcinoma. We found that in patients with cervical cancer with reserved fertility, adenocarcinoma and squamous cell carcinoma were similar in treatment outcome after surgery, and there was no significant difference in the recurrence rate. Additionally, only one patient with cervical adenocarcinoma conceived among five of these patients in our study. Therefore, this could not be statistically analyzed. Consequently, the pathological features are not described in detail.

The average duration from the median time of surgery until the first pregnancy was 15.0 months (range, 3–99 months), whereas that until the second pregnancy in four patients was 16, 25, 36, and 60 months. Fifteen (21.7%) patients did not become pregnant, and the overall mean length of time that conception was attempted was  $7.9 \pm 6.3$  months in these patients. Four (5.8%) patients attempted to conceive for >1 year, and the reasons for infertility might have included ovarian factors (1 case), fallopian tube factors (1 case), and unknown factors (2 cases). In particular, a patient who received laparoscopic surgery because of fallopian tube adhesion did not conceive after surgery.

### Pregnancy outcome

Following fertility-sparing surgery in the 69 patients, 54 (78.3%) had a total of 58 pregnancies, including 42 (72.4%) full-term births, eight (13.8%) premature births, four (6.9%) spontaneous abortions

(10–14 weeks), two (3.4%) induced abortions (6–8 weeks), and two (3.4%) drug abortions (5–6 weeks). The median gestational age at delivery was 37.5 weeks (range, 28.6–39.0 weeks) and all of the patients delivered via cesarean section. Pregnancy complications included threatened premature deliveries in eight (16.0%) and premature rupture of membranes in four (8.0%) patients. The other 38 (76%) patients experienced a successful pregnancy. The mean birth weight of the newborns was  $2932.5 \pm 772.4$  g, which was appropriate for the gestational age, and all were alive and healthy.

### Degree of satisfaction with postoperative quality of life

Of the 83 patients with complete follow-up, 79 (95.2%) were satisfied with the current quality of life and four (4.8%) were not. The degree of satisfaction regarding quality of life was significantly higher in patients who received radical trachelectomy and retroperitoneal lymphadenectomy, but without neoadjuvant chemotherapy, compared with the other groups ( $P = 0.025$ , Table 1).

### Discussion

With an increase in the marital and reproductive age in modern society, the incidence of cervical cancer in young women has been increasing.<sup>2</sup> Therefore, methods for preserving fertility and physiological function of patients with cancer, in addition to good



tumor outcomes, have become a major objective for gynecologic oncologists. For young patients with early-stage cervical cancer, preservation of reproductive function not only has academic value, but also has social significance.

The application of laparoscopic VRT, which includes laparoscopic pelvic lymphadenectomy and VRT, was first reported by Dargent et al.<sup>4</sup> in 1994. This procedure facilitates full-term pregnancy success in patients by retaining the reproductive function of patients with early-stage cervical cancer. The efforts of Smith<sup>5</sup> and Shepherd et al.<sup>6</sup> led to development of radical trachelectomy combined with laparotomy, laparoscopy, robots, and other different approaches. In the present study, we chose radical trachelectomy under laparoscopy as the method for preserving reproductive function in young patients. We found that there was no significant difference among the different treatments on pregnancy outcomes and no significant difference of different histological types on pregnancy outcomes. Because this type of surgery is not standard for cervical cancer surgery, there are many restrictions with this process, which may limit its application worldwide. Therefore, summarizing and evaluating experience and outcome of this type of surgery are important.

At present, the recurrence and mortality rates of radical trachelectomy are similar to those of RH in patients with early-stage cervical cancer.<sup>7-9</sup> In the present study, only one patient with poorly differentiated adenocarcinoma received RH because of recurrence after radical trachelectomy. The resultant recurrence rate of 1.2% is significantly lower than that in the literature. The recurrence rate in patients with early-stage cervical tumors >2 cm in diameter can reach 20%, particularly among those receiving fertility-sparing therapy without preoperative chemotherapy.<sup>10</sup> The low recurrence rate in the present study may

be due to the relatively low number of cases with tumors >2 cm in diameter and the follow-up duration was not sufficient to identify other recurrences.

Different pregnancy outcomes have been found in patients with early-stage cervical cancer following fertility-sparing therapy.<sup>11-14</sup> Okugawa et al.<sup>11</sup> reported that the pregnancy rate was 25% in 61 patients who attempted to conceive after trachelectomy. In 2015, Pareja et al.<sup>12</sup> summarized the pregnancy rates of patients with early-stage cervical cancer worldwide, and found values of 16.2% and 11.24% in those who had undergone abdominal and vaginal radical trachelectomy, respectively. The pregnancy rate was 69.9% (58/83) in the present study, which is higher than both of the values from the previous studies.<sup>11,12</sup> Furthermore, in our study, the full-term birth rate was higher, and the premature birth and abortion rates were lower than those found in the literature.<sup>15</sup> This discrepancy between studies may be associated with the number of cases enrolled, surgical techniques used, follow-up time, postoperative psychological counseling, sample size, and other factors. The pregnancy rate and birth rate may be affected by the patient's own psychological factors and family and social factors. Therefore, proper case selection, appropriate surgical technique, and normative postoperative follow-up and evaluation are increasingly attracting clinical attention. Accordingly, we aim to conduct a large-scale research study with a longer follow-up time to further investigate how early intervention treatment can improve the pregnancy rate and parturition rate in patients following fertility-sparing therapy. We also wish to further confirm the safety and feasibility of reproductive preservation in patients with early-stage cervical cancer. Development and progression of cervical cancer is the result of multiple factors and steps. Prevention of this condition in young

patients may become a clinical goal in the future because the ultimate objective in medicine is not how to survive, but how to live better.

### Author contributions

Aihong Wang, Canhui Jin, Xiaoyu Tian: Project development, data collection, and manuscript writing.

Ying Wang: Data collection.

Guanyi Cui, Canhui Jin: Data analysis.

Aihong Wang, Xiaoyu Tian: Manuscript writing.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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