

Outcomes of fertility and pregnancy in patients with early-stage cervical cancer after undergoing neoadjuvant chemotherapy

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Summary

Objective: To explore the outcomes of oncology, fertility, and pregnancy in patients after undergoing neoadjuvant chemotherapy (NACT) followed by fertility-sparing operations with cervical cancer, and its value in clinical treatment. **Materials and Methods:** A total of 11 patients from seven hospitals in Beijing with cervical cancer since August 2009 to December 2011, who had undergone fertility-sparing treatments were recruited in this study. **Results:** Among the 11 patients, there were nine cases of squamous cell carcinoma, two cases of adenocarcinoma, one case in Stage IA2, and ten cases in Stage IB1 (FIGO, 2009). All of the 11 patients were treated with NACT of one to two cycles before the operations, and then they underwent radical trachelectomy (RT) + retroperitoneal lymphadenectomy. Eleven patients had completed the follow-up (100%) and the mean follow-up was 24.4 months. The outcomes of the oncology and pregnancy are as follows: no patient recurred after fertility-sparing treatments; in seven patients seeking pregnancy after the treatments, three pregnancies occurred in two women. **Conclusions:** NACT+RT, as a fertility-sparing treatment for young women with bulky early-stage cervical cancer and its outcomes in fertility and pregnancy are satisfactory, however its safety needs to be studied further.

Key Words: Early-stage cervical cancer; Neoadjuvant chemotherapy; Fertility-sparing; Pregnancy.

Introduction

Carcinoma of the cervix remains the leading cause of death worldwide among all gynecologic malignancies. In developed countries, however, cervical cancer screening has dramatically reduced the incidence of this disease. Approximately 15% of all cervical cancers and 45% of surgically treated Stage IB cancers occur in women under the age of 40 [1]. Therefore, many women of reproductive age will be diagnosed with this disease at an early stage.

Radical surgery has been the primary treatment options for women with cervical cancer of more than three mm invasion (International Federation of Gynecology and Obstetrics [FIGO] Stage IA2 and more). Most young patients with cervical cancer are diagnosed in the early stages of the disease and the number of these patients that are completely cured is high. However, radical surgery does not spare fertility and both methods can lead to psychosexual dysfunction and decreased quality of life. Furthermore, infertility increases the frequency of depression, stress, and sexual dysfunction [2, 3]. This leads to the question of whether it is possible to preserve the uterus without increasing the risk of recurrence and to afford the opportunity for pregnancy.

Radical trachelectomy (RT) was introduced in clinical practice in 1997 by an international group [4]. Furthermore, over the past ten years, many studies have been published

on neoadjuvant chemotherapy (NACT) and fertility sparing surgery in women with larger cancers [5-7], and they have described procedures that reduce the radicality of paracervical resection [8, 9]. With these procedures, women have an opportunity to retain their childbearing potential. This paper reviews the authors' present knowledge of fertility sparing procedures in patients with cervical cancer, and presents an analysis of oncological and pregnancy results of 11 patients.

Materials and Methods

Subjects

From August 2009 to December 2011, 11 young patients underwent conservative treatment (NACT followed by RT) affected by invasive tumor. These patients were enrolled from seven hospitals: Peking University People's Hospital, Peking University Third Hospital, Peking Union Medical College Hospital, Chinese PLA General Hospital, Beijing Chao-yang Hospital, Beijing Obstetrics and Gynecology Hospital, and Beijing Hospital.

Inclusion criteria

Eligibility criteria for this treatment included: age < 40 years, childbearing demand, no infertility, agreed with long-term follow-up, pathologically confirmed cervical squamous carcinoma, adenocarcinoma or adenosquamous carcinoma, cervical cancer in Stages IA2, IB1, and IIA1 (diameter ≤ 4cm, including patients who had received chemotherapy or embolization). Informed consent was obtained from all women and patients were counseled

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Table 1. — *Demographics and pregnancy outcomes.*

No.	Age (years)	Pathology	FIGO	Histology	Pre-NACT diameter (cm)	Post-NACT diameter (cm)	NACT regimen× cycles	Post-op chemotherapy× cycles	Pregnancy willingness	Pregnancies
1	24	Squamous carcinoma	IB1	G3	4	0	PVB×2	TP×2	Yes	1
2	29	Squamous carcinoma	IB1	G2	2.5	0	PVB×1	No	No	0
3	30	Adenocarcinoma	IB1	G2	2.5	0	PF×2	No	Yes	2
4	27	Squamous carcinoma	IB1	G3	2.5	0	PMV×2	PMV×1	Yes	0
5	28	Squamous carcinoma	IB1	G2	2.5	0	PMV×1	No	No	0
6	31	Squamous carcinoma	IB1	G3	2.5	1	PMV×1	PMV×1	Yes	0
7	24	Adenocarcinoma	IB1	G3	2.5	1	PMV×1	No	Yes	0
8	31	Squamous carcinoma	IB1	G3	3	0	PMB×2	No	No	0
9	27	Squamous carcinoma	IB1	G3	3	1	PMB×2	TP×6	Yes	0
10	36	Squamous carcinoma	IB1	G3	3	0	TP×2	TP×2	Yes	0
11	30	Squamous carcinoma	IA2	G2	Not observed	0	TP×1	No	No	0

about the potential risks involved and the fact that the procedure was not the standard of care at that time.

Medical records and follow-up data of all patients were reviewed and collected for this analysis. Data collected include age, gestational age at diagnosis, FIGO stage, histology, type and date of treatment, clinical and pathological responses to chemotherapy, duration of treatment delay, surgical data, children outcome and maternal follow-up including adjuvant therapies, relapses and vital status. This analysis was approved by the local ethical committee.

NACT efficacy

NACT consisted of five combined chemotherapeutic regimens. These regimens included DDP (50-70 mg/m²), VCR (one mg/m²), BLM (15-20 mg/m²), 5-FU (1,000 mg/m²), MMC (ten mg/m²), and paclitaxel (175 mg/m²). DDP was given as intravenous drip or intra-arterial intervention. One or two cycles of these chemotherapeutic regimens were given at a three- to four-week intervals.

Clinical response was determined by clinical pelvic examination and colposcopy two weeks after the last cycle of NACT. Responses to chemotherapy were recorded according to the World Health Organization criteria [10]. Complete response (CR) was defined as disappearance of the tumor, partial response (PR) indicated 50% or more decrease in total tumor size, stable disease (SD) referred to tumor size decreases less than 50% or increases no more than 25%, and progressive disease (PD) indicated tumor size increase over 25%. The patients who showed CR or PR to neoadjuvant treatment were planned for surgery, while patients experiencing no change or PD were offered salvage chemotherapy. Fertility sparing operation was indicated when the maximum diameter of the lesion was less than two cm, or the treatment regimen would be changed.

Follow-up

Follow-up was performed every three months for two years, every six months for three years, and then annually. Each follow-up visit entailed a physical and pelvic examination, including pap-test and colposcopic examination. SCC, CA125, HPV, and abdominal ultrasound performed every six months. Pelvic MRI was offered to each patient once a year. PET scan was indicated only in cases of clinical suspicion of recurrence. By September 2012, all the 11 patients received full term follow-up, and follow-up duration was 24.4 ± 17.5 months.

Statistics

The SPSS 16.0 was used for data analysis and $p < 0.05$ was considered statistically significant.

Results

Demographics

From August 2009 to December 2011, 11 young women (aged 28.8 ± 3.4 years) diagnosed with cervical cancer were evaluated for a conservative treatment. Pathologic analysis of the biopsy demonstrated squamous-cell carcinoma in nine cases, and adenocarcinoma in two cases. Among them, seven patients were not pregnant previously, and four patients had one child previously. Median parity was 3.0 (0-six). All the patients did not have hypertension, diabetes mellitus, and other comorbidities. According to the FIGO (2009) classification: one case with IA2 (9.1%) and the other ten cases were with IB1 (90.9%). The histological classification indicated: four cases with G2 (moderate grade) and seven cases with G3 (high grade). Except for one case with IA2, the other ten cases had lesions: < 2.5 cm (six cases), three cm (three cases), and four cm (one case). One patient had pathologically confirmed lymphovascular space involvement (LVSI) before surgery.

Fertility sparing treatment

Preoperative treatment

All 11 patients received NACT, including those in Stage IA2 patient with LVSI. Six patients underwent uterine artery interventional chemotherapy, and then received chemotherapy intravenously; the other five patients only received intravenous chemotherapy. All the regimens were platinum-based chemotherapy and Table 1 shows the details. After one to two cycles of treatment, eight patients reached CR, three patients reached PR, which indicated that the NACT reached 100% in efficacy. Meanwhile, the maximum diameter of the lesion was less than two cm (Table 1). All the patients did not receive radiotherapy.

Operational treatment

All the patients underwent radical trachelectomy with retroperitoneal lymphadenectomy, and one patient received cervical cerclage. The operations included open surgery and

Table 2. — Tumor and pregnancy outcomes after fertility sparing operations

Author	Case number	Average (median) follow up duration (month)	Relapse	Deliveries	Pregnancies
Maneo A., <i>et al.</i> [11]	16	69	0	6	10
Robova H., <i>et al.</i> [12]	12	76.5	3	7	7
Gottschalk E., <i>et al.</i> [13]	1	60	0	1	1
Marchiole P., <i>et al.</i> [14]	7	22	0	1	1

transvaginal and laparoscopic surgeries. The intraoperative blood loss volume was 259.1 ± 182.8 ml, the intraoperative fast frozen pathology indicated that the lymph nodes were all negative, and the pathology showed that the surgical margin was negative. The average number of retroperitoneal lymph nodes was 18.7 ± 9.4 . No blood transfusion was required in the perioperative time and no intraoperative complications occurred.

Postoperative treatment

The indications for postoperative chemotherapy were: tumor size reaching four cm, high grade tumor, deep invasion, and LVSI. After obtaining the patient's consent, five patients underwent one to six cycles of platinum-based chemotherapy, and Table 1 shows the details. GnRH-a was used to protect ovarian function during chemotherapy. One patient refused chemotherapy, although she was confirmed with LVSI. After a mean follow up of 24.4 ± 17.5 months, no relapse was observed.

Pregnancy

In the 11 patients, seven patients had planned to conceive, while the other four patients chose contraception. In the seven patients, two patients successfully conceived, and one patient had one childbirth, and the second had two childbirths. The durations between first conception and operation were 11 months and 15 months, respectively. The other five patients were not pregnant until last follow-up, and the average pregnancy attempting duration was 8.4 ± 5.4 months, and two patients had attempted for over 12 months. The possible infertility causes were ovarian factor and unknown cause, respectively. Table 1 shows the pregnancy outcomes.

Discussion

NACT followed by radical hysterectomy for the treatment of locally invasive cervical cancer has emerged in the recent years. The main advantages of this approach are the possibility to evaluate the efficacy of drugs after each cycle, the reduction of tumor burden, thus making it operable, and the possibility to conserve the patient's conceivability.

NACT in fertility sparing surgery would not be an experimental concept in the future; however, it currently requires verification, especially concerning oncological findings. Pregnancy results are very good and NACT has

no effect on fertility. The present study has shown some promising results. Data on pregnancy and neonatal outcome are similar to other studies, and Table 2 shows the details [11-14]. All babies had a birth weight adequate to the correspondent gestational age. However, there is no clear consensus regarding postoperative adjuvant chemotherapy after initial NACT. Postoperative adjuvant chemotherapy alone instead of adjuvant radiotherapy may reduce the risk of recurrence [15]. Furthermore, it is still controversial to conduct fertility sparing operation when LVSI is confirmed preoperatively. Roy *et al.* [16] summarized 100 patients who received RT, of whom five patients developed relapse and four of them had LVSI. Therefore, LVSI may be a contraindication of fertility sparing operation. However, other studies show that only 5% the patients with LVSI developed lymph node metastasis after fertility sparing operation [17]. Therefore, some researchers believe that LVSI could be a risk factor for poor prognosis, but if lymph node metastasis does not occur, LVSI should not be a contraindication for RT. In the present report, one patient with LVSI did not have tumor relapse.

RT with laparoscopic pelvic lymphadenectomy is currently the standard fertility preserving procedure. Fertility sparing procedures in tumors less than two cm in size are now considered to be safe surgical procedures. Down-staging by NACT is still an experimental procedure and will require multicentre cooperation to verify its oncological safety [18]. However, chemotherapy neither affects fertility nor decreases the chance of pregnancy.

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