

# Neoadjuvant chemotherapy followed by fertility-sparing surgery for women with stage IB1 cervical cancer

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Fertility-sparing surgery was optimal to patients with tumor diameter smaller than 2 cm. For patients with larger tumors, neoadjuvant chemotherapy can debulk the tumor and offer the chance of surgery. We report 2 cases of stage IB1 cervical cancer treated by neoadjuvant chemotherapy and fertility-sparing surgery. Relevant literature was reviewed. Its safety, efficacy, and reproductive outcome need to be validated in the future.

**Keywords:** Fertility-sparing surgery, Neoadjuvant chemotherapy, Uterine cervical neoplasms

## INTRODUCTION

In 1994, Dargent et al. [1] first presented their results of a series of patients with early cervical cancer treated by vaginal radical trachelectomy (VRT). The purpose of this technique is to maintain patients' fertility without decreasing disease-free survival and overall survival. However, Dargent's operation is optimal to patients with tumor diameter smaller than 2 cm. Patients with larger sizes are denied this conservative treatment. In 2005, Kobayashi et al. [2] first presented one patient with stage IB1 cervical (3 cm diameter) cancer treated with chemotherapy and conization which maintained her fertility. Then in 2006, Plante et al. [3] presented their preliminary reports in bulky cervical cancer treated by neoadjuvant chemotherapy (NACT) with VRT. With time and experience, several reports showed the possibility of the conservative treatment. During 2003–2005, there were 2 young patients treated by NACT before fertility-sparing surgery in Peking Union Medical College Hospital. The objective of the present study was to

review case reports of women with cervical cancer treated by NACT and fertility-sparing surgery.

## CASE REPORTS

### 1. Case 1

A 29-year-old woman G0P0 was presented in November 25th 2005. In October 12th, she was admitted to local hospital with abdominal pain. The gynecologic physical examination revealed a tumor measured 2.5 cm × 2.5 cm. Colposcopy and biopsy specimen showed squamous cell carcinoma of non-keratinizing type. In November, she was given one cycle chemotherapy (PF regimen: cisplatin 100 mg/m<sup>2</sup>, day 1; 5-fluorouracil (5-FU) 1,000 mg/m<sup>2</sup>, day 1–4). Repeat gynecologic physical examination showed no tumor and magnetic resonance imaging (MRI) showed no metastatic lymph nodes. In November 29th 2005, she underwent surgery. Laparoscopy pelvic lymphadenectomy was done first and the frozen section was negative. Then it was followed by VRT. The final histopathological examination revealed carcinoma *in situ* without evidence of invasive cancer. The 11 removed lymph nodes confirmed negative. The patient was followed up via gynecologic physical examination, colposcopy every month and positron-emission tomography each year. The patient is free of disease for 69 months. However, she has not attempted to conceive.

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## 2. Case 2

A 31-year-old G1P0 was admitted to hospital for intermenstrual bleeding for 5 months. The gynecologic physical examination revealed a tumor measuring 3.5 cm × 3.5 cm, and the biopsy showed invasive squamous cell carcinoma (moderate-low differentiation). She was given one cycle chemotherapy (PB regimen: bleomycin 15 mg/m<sup>2</sup>, day 1; cisplatin 25 mg/m<sup>2</sup>, day 1–3) on November 12nd–14th 2003. The side effect was fever (grade 1). The repeat gynecologic physical examination showed that the tumor had shrunk to 2 cm, and the doctor suggested she underwent a radical hysterectomy. But she wanted to reserve her fertility and refused the surgery. We told her that the possibility of recurrence and she signed the consent. On December 15th 2003, she underwent the surgery. First she underwent pelvic lymphadenectomy and the frozen sections of lymph nodes were negative. Then she underwent VRT. The final histopathology confirmed a squamous cell carcinoma (moderate differentiation, 6 mm in depth, 12 mm in width, which involved more than half of the cervical stroma). The final histology of 8 lymph nodes was negative. After surgery, she was given three cycles of adjuvant chemotherapy using the same regimen of bleomycin and cisplatin. The side effect was vomiting (grade 2) which was tolerable. She was followed up via gynecologic physical examination, colposcopy every month in the first 6 months and positron-emission tomography each year. The Thinprep cytologic test (TCT) and serum level of squamous cell carcinoma (SCC) was normal. The patient did not desire pregnancy at the time of this writing.

## DISCUSSION

We performed a Medline search from January 1994 to October 2011 with the key words *neoadjuvant chemotherapy*, *fertility-sparing surgery*, and *cervical cancer*. References from the identified articles were investigated for relevance, and the systemic English search suggested 11 articles [2–12] about NACT plus fertility-sparing surgery. The results were showed in Table 1.

Radical hysterectomy and pelvic lymphadenectomy is the standard therapy for patients with early stage cervical cancer (IB–IIA). However radical surgery does not spare fertility and decreases quality of life. Young patients with early cervical cancer always have a strong desire to maintain fertility. Fertility-sparing surgery (which includes conization, chemoconization, and trachelectomy) is safe and feasible for early invasive cervical cancer in well selected patients [12]. The limitation is that the technique is usually confined to small cervical lesions which are less than 2 cm as adequate vaginal margin can be

obtained. However, more and more reports have showed that the inclusion criteria have been expanded [2,13]. Tumor sizes measuring between 2.5 to 4 cm are sometimes considered indication for VRT [10]. As our cases show that fertility-sparing surgery is feasible and safe for patients with tumor diameter more than 2 cm. After reviewing the literature, we found that 42 patients (IB1–IIA1) with cervical cancer ≥2 cm were treated with NACT followed by fertility-sparing surgery (Table 1). Three recurrences (5.6%) have been reported to date.

NACT followed by radical hysterectomy is always used as an alternative treatment to radiotherapy in locally advanced cervical cancer. NACT can eradicate micrometastasis, reduce number of positive nodes, debulk the tumor, downstage the disease, and offer the chance of surgery. Cervical cancer is a highly chemosensitive disease and it is reasonable to present a good response to NACT. In the literature, 44 of 54 patients (81.5%) show the complete response or optimal pathological response after NACT using different chemotherapy regimens.

The crucial factor in second-trimester abortion or premature labor is the amount of remaining stromal tissue [7]. Reduction of tumor volume after neoadjuvant chemotherapy can permit increased possibility of obtaining a wider uninvolved margin, less radical removal of cervical stroma which can improve the chance for successful pregnancy [13,14]. Pregnancy outcome is good and neoadjuvant chemotherapy showed no effect on fertility. In total, there are 28 pregnancies. There was one first-trimester loss and five premature deliveries (Table 1).

In most published articles, SCCs were treated with paclitaxel, ifosfamide, and cisplatin (TIP) chemotherapy. Though the regimen showed a good response, it sometimes was correlated with grade 3 hematological toxicities and ovarian fibrosis which may lead to premature ovarian failure [3]. There were no previous reports about the chemotherapy results of PF regimens in fertility-sparing surgery. NACT including cisplatin and 5-FU showed comparable clinical response rate and an acceptable acute toxicity [15]. In our hospital, cisplatin and 5-FU (PF) were chosen as a first line regimen before surgery to improve the possibility of performing surgery. Cao et al. [16] have also used this combination in 147 patients with locally advanced cervical cancer (IB2–IIB) and reported an 82% clinical response. In our cases, 1 patient treated with PF regimen showed complete response. The regimen is well tolerated and no hematological complications were observed. The other patient was treated with bleomycin, cisplatin (BP) regimen. In the report of Liu et al. [5], BP showed an optimal pathological response which was not present in our case.

Our limitation is that the tumor diameters were measured on visual inspection not on objective tools such as MRI which is a more accurate measurement. So in the patients who may be

**Table 1.** Clinical and pathological characteristics, oncological outcome, and pregnancy outcome in patients with neoadjuvant chemotherapy plus fertility-sparing surgery

Author	Year	Tumor size ≥2 cm	No. of conservative surgery	Stage	Neoadjuvant chemotherapy	Pathological response (%)	Fertility-sparing surgery	Recurrence	Pregnancy
Kobayashi et al. [2]	2005	1	1	IB1	SCC:BOMP	1/1 (100) CR, 1	Conization	0	1 VD at 36 wk
Plante et al. [3]	2006	3	3	IB1	SCC:TIP	3/3 (100) CR, 2; PR1, 1	PLN, VRT	0	1 preterm, 2 term
Landoni et al. [4]	2007	2	2	IB1	AC:TEP	2/2 (100) CR, 2	PLN, conization	0	NA
Liu et al. [5]	2008	1	1	IB1	SCC:BP	1/1 (100) PR1, 1	PLN, ART	0	1 preterm
Maneo et al. [6]	2008	6	16	IB1	SCC:TIP; AC:TEP	15/16 (93.8) CR, 5; PR1, 10	PLN, conization	0	1 spontaneous abortion, 2 VDs at term; 7 CSs
Rob et al. [7]	2008	6	7	IB1	SCC:IP; AC:AP	6/7 (85.7) CR, 2; PR1, 4	PLN, SVT	0	1 term, 2 in progress
Robova et al. [8]	2010	11	12	IB1	SCC:IP; AC:AP	9/12 (75) CR, 4; PR1, 5	PLN, SVT	3	2 preterm, 4 term, 1 in progress
Singh et al. [9]	2010	1	1	IB1	CCAC:TC	1/1 (100) PR2, 1	PLN, ART	0	NA
Gottschalk et al. [10]	2011	1	1	IB1	AS:TP	1/1 (100) PR1, 1	PLN, VRT	0	CS at 38 wk, one ectopic pregnancy
Marchiole et al. [11]	2011	7	7	IB1, 2 IB2, 3 IIA1, 2	SCC:TIP; AC:TEP	4/7 (57.1) CR, 3; PR1, 1	PLN, VRT	0	1 in progress
Palaia et al. [11]	2011	1	1	IB2	SCC:TIP	1/1 (100) CR, 1	PLN, SVT	0	NA
Present case	2011	2	2	IB1	SCC:PF; BP	1/2 (50) PR1, 1; PR2, 1	PLN, VRT	0	NA
<b>Total</b>		<b>42</b>	<b>54</b>	<b>IB1–IIA1</b>		<b>44/54 (81.5)</b>		<b>3</b>	<b>28</b>

AC, adenocarcinoma; AP, doxorubicin, cisplatin; ART, abdominal radical trachelectomy; AS, adenosquamous carcinoma; BOMP, bleomycin, vincristine, mitomycin, and cisplatin; BP, bleomycin, cisplatin; CCAC, clear cell of adenocarcinoma of the cervix; CR, complete disappearance of tumor in the cervix with negative lymph nodes; CS, cesarean section; IP, ifosfamide, cisplatin; NA, not available; PF, cisplatin, 5-fluorouracil; PLN, pelvic lymphadenectomy; PR1, residual disease with less than 3 mm stromal invasion including in situ carcinoma; PR2, persistent residual disease with >3 mm stromal invasion on surgical specimen; SCC, squamous cell carcinoma; SVT, simple vaginal trachelectomy; TC, paclitaxel, carboplatin; TEP, paclitaxel, epirubicin, cisplatin; TIP, paclitaxel, ifosfamide, cisplatin; TP, paclitaxel, cisplatin; VD, vaginal delivery; VRT, vaginal radical trachelectomy.

offered fertility-sparing surgery, MRI or other objective tools are suggested to measure tumor diameter.

In conclusion, NACT followed by fertility-sparing surgery offer an innovative technique for conservative management for young women with cervical cancers who do not meet the criteria for primary surgical treatment (tumors larger than 2 cm). We think this is a valuable option in selected patients. It is an experimental concept and long-term results are not confirmed. Further studies are required to validate the safety, efficacy, and reproductive outcome of this approach.

### CONFLICT OF INTEREST

No potential conflict of interests relevant to this article was reported.

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