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Fertility-sparing management for bulky cervical cancer with systemic chemotherapy and conization: a case report and review of the literature

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Summary

Herein the authors report the case of a patient with FIGO Stage Ib2 cervical cancer, experienced a complete response treated by neoadjuvant chemotherapy (NACT) followed by conization. Then she became pregnant and delivered a healthy boy at 38 weeks and exhibited no recurrent disease until July 2017 (82 months after surgery). To the present authors' knowledge, this is the first report describing this conservative treatment in locally advanced disease.

Key words: Locally advanced cervical cancer; Neoadjuvant chemotherapy; Pregnancy; Conization.

Introduction

Fertility-sparing surgical procedures such as neoadjuvant chemotherapy (NACT) plus surgery together with adjuvant post-surgical therapy have emerged as alternative treatments in young women with early-stage cervical cancer.

Case Report

A 31-year-old nulliparous Chinese woman was referred to this department in September 2010 because of vaginal bleeding. Cervical lesions were found during the uterine curettage scraping, and analysis of a biopsy specimen confirmed the presence of moderately differentiated squamous cell cervical carcinoma (Figure 1 A). Gynecologic pelvic examination revealed a large cervical lesion of 5 cm in its greatest diameter, releasing a foul stench. Blood cell counts were within the normal range and other examinations were normal except the SCC-Ag level was 2.6 (0-1.5) ng/mL. The patient was counseled about therapeutic options, including NACT followed by radical hysterectomy plus systematic pelvic lymphadenectomy or concurrent chemoradiation. The patient refused any image examinations or radical surgery because of a strong desire to preserve fertility since she was divorced and planned to remarry. The high risk of recurrence and potential obstetric problems were explained. Thereafter, the patient signed informed consent, and an individualized approach to the disease was planned. The case was discussed on a multidisciplinary basis by oncologists and chemotherapists. The basic chemotherapy regimen is cisplatin 75 mg/m^2, paclitaxel, 175 mg/m^2, every three weeks. Moderate hematologic and extra-hematologic toxicity was informed.

After the patient underwent the first cycle of NACT, the cervical lesion was reduced to a greatest diameter of 1.5 cm. Subsequently, after the second-time chemotherapy, to the authors' surprise, the cervical lesion had fallen off completely. Then after the third cycle, her SCC-Ag level was reduced to 0.7 ng/mL. The changes of SCC-Ag levels and FIGO Stage during the courses of chemotherapy are shown in Table 1. Reevaluation of disease after NACT, including gynecologic bimanual examination, colposcopy showed no lesion or metastasis. In November 2010, to preserve fertility and avert sexual dysfunction, conization was performed rather than radical trachelectomy or vaginal trachelectomy. The patient was discharged on postoperative day 2, in good general condition, with an intrauterine catheter, which was removed after four days, and no perioperative complications occurred. The final pathologic report stated the margins of resection were negative for disease, and a middle-grade squamous intraepithelial lesion was found in the anterior portion of the cervix (total of 18 series of pathological sections of HE, thickness, 2 um each slide, Figure 1B). After surgery, she accepted the following three chemotherapy cycles. No further adjuvant therapy was proposed. The patient was followed up closely including general and gynecologic examination, colposcopy, and thin prep cytology test (TCT) every three months within the first two years, then every six months. After seven years of follow-up, the patient had regular menses

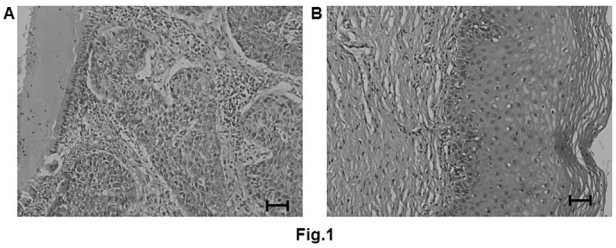

Fig.1

Figure 1. — A: Before chemotherapy: invasion of moderately differentiated squamous cell cervical carcinoma (×200). B: After chemotherapy: middle-grade squamous intraepithelial lesion in the anterior portion of the cervix (×200). Bar: 40 um

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Table 1. — *The changes of SCC-Ag levels, the greatest diameter of lesions, and FIGO stage during the course of chemotherapy.*

Chemotherapy cycle (Regimens: TP)	0	1	2	3	4	5	6
Diameter of the lesion (cm)	5	1.5	0	0	/	/	/
FIGO (2009)	|B2				/	/	/
SCC-Ag levels (ng/mL)	2.6	0.5	0.7	1.5	0.6	0.6	0.3

cancer were still controversial [2, 3].

In 2011, Marchiole *et al.* reported an innovative approach that NACT and vaginal radical trachelectomy for fertility-sparing treatment in women affected by cervical cancer (FIGO Stage IB–IIA1, tumors 2–5 cm), they were followed up 22 months (range 5–49 months), no relapse was reported, and one woman has attempted to conceive and was carrying a healthy baby at 17 gestational weeks in the pres-

Table 2. — *Summary of neoadjuvant chemotherapy and fertility-sparing surgery for cervical cancer with tumor size over 4 cm.*

Author, year	No. of patient	Tumour size (mm)	Chemotherapy regimen	Response	Surgery	Outcomes (median follow-up, months)	Pregnancy outcomes
Robova *et al.*, 22010, 2014 [1, 2]	7	>40	AP (SCC), PI(ACC) (3 courses)	NA	PLAE+SVT	One recurrence (42)	Unknown, about half of them became pregnant and delivered babies
Marchiole *et al.*, 2011[3]	3	42, 45, 45	TIP(SCC), TEP (ACC) (3 courses)	1 CR, 2 PR	PLAE+VRT	No recurrence (22)	One women attempted to conceive and delivered a healthy baby at 17 weeks
Palaia *et al.*, 2011 [4]	1	55	TIP (3 courses)	CR	PLAE+SVT	No recurrence (18)	No intention to become pregnant.
Tsubamoto *et al.*, 2012 [5]	2	43, 60	DDP+ irinotecan (3 courses)	CR	PLAE+SVT	No recurrence (103)	No intention to become pregnant.
Tsuji *et al.*, 2012 [6]	1	>40	DDP+MMC (2 courses)	CR	PLAE+ART	No recurrence (64)	Premature membrane ruptured after 27 weeks and delivered at 28 weeks
Hamed *et al.*, 2012 [7]	1	60	TP (4 courses)	CR	PLAE+VRT	No recurrence (16)	Unknown
Vercellino *et al.*, 2012 [8]	2	42, 42	TP or TIP (2 courses)	PR	LPPLND+VRT	No recurrence (43)	Unknown
Lanowska *et al.*, 2014 [9]	2	50, 41	TIP (2 or 3 courses)	CR	PLAE+VRT	No recurrence (42)	Unknown
Van Gent et al, 2014 [10]	1	42	TP (weekly in 6)	PR	PLAE+VRT (nerve sparing)	No recurrence (6.2)	No intention to become pregnant
Rawand Salihi *et al.*, 2015 [2]	1	52	TC	CR	PLAE+CON	No recurrence (58)	Did not become pregnant
Hauerberg *et al.*, 2015 [11]	1	45	Cisplatin+ ifosfamide + fluorouracil()	CR	PLAE+VRT	No recurrence (68)	Unknown
Salihi *et al.*, 2015 [2]	1	52	TC (weekly in 9)	CR	PLAE+CON	No recurrence	Failed to get pregnant
Feng *et al.*, 2016 [12]	1	60	TP	CR	PLAE+CON	No recurrence (72)	Premature membrane ruptured after 27 weeks and delivered at 29 weeks.
Present case	1	50	TP	CR	CON	No recurrence(84)	conceived and delivered a healthy baby at 38 weeks

TC: paclitaxel and carboplatin. TP: paclitaxel and cisplatin. AP: adriamyein and cisplatin. PI: cisplatin and ifosfamide. TEP: paclitaxel, epirubicin, cisplatin. TIP: paclitaxel, ifosfamide, cisplatin. VRT: vaginal radical trachelectomy. ART: abdominal radical trachelectomy. SVT: simple vaginal trachelectomy. PLAE: pelvic lymphadenectomy. CON: conisation. LPPLND: laparoscopic pelvic and para-aortic lymphadenectomy.

and was free of disease. After that, she had a new family and was pregnant naturally. In August 2015, a healthy boy was born without sequelae, which made her happier and are currently living a normal life.

Discussion

Fertility-sparing surgery (conization, chemoconization, or trachelectomy) is feasible and safe in patients with cervical cancer (diameter less than 2 cm) [1]. However, there were similar treatments for the patients with bulky cervical

ent report [4]. Subsequently, Palaia *et al.* [5], Tsubamoto *et al.* [6], and Robova *et al.* [7, 8] reported further progress in fertility-sparing management using NACT in Stage IB2, followed by the less extensive surgical approach of simple vaginal trachelectomy and pelvic lymphadenectomy. In Robova *et al.* study, 50% of women who accepted fertility-sparing procedure became pregnant and 40% delivered babies. Up to now, 24 cases of women diagnosed with cervical tumors > 4 cm and treated with NACT followed by conservative surgical management have been reported (Table 2) [1-12], and only one recurrence (1/ 24, 4.1%) has

been reported to date. The pathological response of most of them were complete disappearance except two got residual disease with 3 mm. However both of them had no recurrence during follow-up. Some of them achieved successful pregnancies and gave birth to healthy infants [4, 7, 9, 10]. Therefore, NACT should decrease tumor volume, which would enable the complete removal of the tumor with negative margins while preserving an adequate amount of cervical tissue [3, 11]. Such a procedure improves the chance of successful pregnancy in patients with Stage IB2.

The preoperative selection of young patients for fertility-sparing surgery is an important issue [12]. Bentivegna *et al.* proposed that in patients eligible for NACT, nodal dissection should be the first surgical step whichever later surgical approach is planned [1]. However, the patient with Stage IB2 squamous cell cervical carcinoma in the present report vehemently rejected any image examination because of impecunious family. When exhibited a good response to NACT, she urged to retain maximum fertility whatever the risks would be. After obtaining the patient's informed consent, the authors proceeded cautiously with the novel treatment and performed conization without pelvic lymphadenectomy, which has been never reported. Fortunately, CT detected no lymph node swelling or metastases in the pelvis during her follow-up process. Until now, only Kobayashi *et al.* reported one case of Stage IB1 cervical cancer who was only treated with NACT, followed by cold-knife conization [13]. The great thing is, after the conization surgery, she attempted to become pregnant and conceived immediately, and gave birth vaginally at 36 weeks. The patient has shown no evidence of recurrence after a disease-free interval of 48 months. Although pelvic lymphadenectomy following conization would have enabled the authors to determine if there was lymph node metastasis [14, 15], it was not clear what effect this procedure would have on potential pregnancies. Therefore, they believe that a pelvic lymph node biopsy by a less invasive method would be appropriate.

Chemo-conization [16] was first proposed as an alternative to fertility-sparing treatment with tumor ≤ 3 cm, aged ≤ 40 years. This approach can further reduce the extent of surgery, preserve a greater amount of cervical tissue, and is associated with improved pregnancy outcomes since it decreases the incidence of miscarriage in the second trimester, premature rupture of membranes, and preterm delivery often occurs after RT. In 2016, Feng *et al.* have reported a case of Stage IB2 treated with NACT, followed by conization and pelvic lymphadenectomy and finally gave birth at 29 weeks of gestation and exhibited no recurrent disease in 72 months after surgery [9]. Li *et al.* [17] suggested the argument that adjuvant chemotherapy alone after surgery does not sacrifice the survival outcome, even in the group of patients with high risk factors after surgery, compared with adjuvant radiotherapy. It was inferred that it would be safe to have adjuvant chemotherapy alone after surgery for this patient who had small-sized suspicious pelvic lymph nodes on PET/CT prior to surgery. Additionally, it may also be possible for patients to experience improved pregnancy and obstetrical outcomes without a concomitant sacrifice of oncologic outcomes even in cases of Stage IB2.

In conclusion, the present case shows a feasible method for controlling cervical cancer while maintaining fertility. Although the present conservative approach requires a larger number of patients and adequate follow-up to validate, the authors believe that these results, together with those of published articles, offer another perspective technique for conservative management for cervical cancer with a bulky mass.

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