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Treatment and prognosis of cervical cancer associated with pregnancy: analysis of 20 cases from a Chinese tumor institution

Xiang ZHANG[1,2], Yong-liang GAO[1], Yue YANG[†‡1]

([1]*Department of Gynecological Oncology, Zhejiang Cancer Hospital, Hangzhou 310022, China*)

([2]*Zhejiang Key Laboratory of Radiation Oncology, Hangzhou 310022, China*)

[†]E-mail: yangyue@zjcc.org.cn

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Abstract: This study was designed to investigate the therapeutic approaches and prognosis for cervical cancer associated with pregnancy. Clinical information, therapeutic strategies, and follow-up results of 20 patients with cervical cancer associated with pregnancy from Jan. 2000 to June 2009 in the Zhejiang Cancer Hospital were retrospectively analyzed. The International Federation of Gynecology and Obstetrics (FIGO) stages were: *in situ* (*n*=1), stage IA1 (*n*=1), stage IB1 (*n*=5), stage IB2 (*n*=1), stage IIA (*n*=8), stage IIB (*n*=3), and stage IIIB (*n*=1). Eight patients were in the first trimester of pregnancy, four in the second, two in the third, and six at postpartum when diagnosed. The therapeutic strategies were either single or combined modalities, including surgery, radiotherapy, and chemotherapy. Fourteen patients survived, five patients died (four of remote metastasis and one of uremia), and one patient was lost to follow-up. One newborn from a patient at stage IIA carcinoma in the third trimester with postponed therapy six weeks after diagnosis survived. Retarded fetal growth was observed in one patient receiving neoadjuvant chemotherapy and cesarean section. Out of the six postpartum patients, three underwent cesarean section and survived, whereas only one out of the three who underwent vaginal delivery survived. The remaining two died of remote metastasis. Therefore, personalized treatment is necessary for cervical cancer associated with pregnancy. Cervical cancer patients in the third trimester of pregnancy can continue the pregnancy for a short period of time. There may be potential risk for the fetus by chemotherapy during pregnancy. Cesarean section is the preferred mode of delivery for pregnant cervical cancer patients.

Key words: Cervical cancer, Pregnancy, Treatment, Prognosis
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1 Introduction

Cervical cancer associated with pregnancy is one of the most common cancers found during pregnancy or postpartum, and occurs in approximately 0.004% to 0.1% of pregnant and postpartum women (Sood and Sorosky, 1998; Pentheroudakis and Pavlidis, 2006). Approximately 28.8% of the global incidence of cervical cancer associated with pregnancy is reported in China every year (Noordhuis *et al.*, 2011). While the incidence of cervical cancer associated with pregnancy is relatively low, the absolute number of cervical cancer patients is considerable given the large population of China.

Currently, there is a lack of unified standard protocol for treatment of cervical cancer associated with pregnancy. Treatment is presently the same for pregnant and non-pregnant women. Surgery is the primary treatment for early-stage cervical cancer. Radiotherapy or chemoradiotherapy is often used for patients with advanced-stage cervical cancer. In the case of cervical cancer associated with pregnancy, further treatment strategies are required according to

‡ Corresponding author
ORCID: Xiang ZHANG, http://orcid.org/0000-0002-6706-3925; Yue YANG, http://orcid.org/0000-0001-8438-6905

the size of the tumor, the diagnostic image findings, gestational stage at the time of diagnosis, and the personal intention of whether or not to continue the pregnancy (Morice *et al.*, 2012). Consequently, individualized therapy is preferred for the treatment of cervical cancer associated with pregnancy.

The treatment strategy for cervical cancer associated with pregnancy has gradually changed from aggressive tumor therapy to the current fertility-sparing treatment, particularly for patients in the first or second trimesters with early-stage cancer. Retrospective studies with small patient numbers showed that only 5% (4/76) of pregnant patients died of cervical cancer after postponing therapy for an average of 16 weeks, indicating the satisfactory safety profile of postponed therapy, especially for early-stage tumor (Lee *et al.*, 1981; Takushi *et al.*, 2002; Hunter *et al.*, 2008). Postponed therapy for stage IB1 cancer patients did not promote tumor recurrence in cases with no pelvic lymph node metastasis visible by laparoscopy (Nisker and Shubat, 1983; Greer *et al.*, 1989; Alouini *et al.*, 2008; Lee *et al.*, 2008). Furthermore, it has been reported that tumor growth can be well controlled by neoadjuvant chemotherapy with little adverse effects on pregnancy (Marana *et al.*, 2001; Caluwaerts *et al.*, 2006; Boyd *et al.*, 2009; Chun *et al.*, 2010; Favero *et al.*, 2010; Rabaiotti *et al.*, 2010; Smyth *et al.*, 2010). However, the majority of published data on cervical cancer associated with pregnancy consist of case reports or retrospective studies based on small sample sizes. Therefore, studies regarding the impact of pregnancy on the progression of cervical cancer, the timing of therapy determination and the effect of delivery mode on both the patient and the fetus are required.

To address the above questions, a retrospective analysis was carried out to collect clinical information, therapeutic strategies, and the follow-up results of 20 patients with cervical cancer associated with pregnancy. All patients were admitted to the Zhejiang Cancer Hospital (Hangzhou, China) between Jan. 2000 and June 2009. The objective of the current study was to investigate the therapeutic approaches, including the procedure to sustain the pregnancy, individualized tumor therapy, appropriate mode of delivery, and the corresponding prognosis.

2 Materials and methods

Out of 7718 cervical cancer patients, the records of 20 pregnant cervical cancer patients (approximately 0.25% of total cervical cancer) hospitalized between Jan. 2000 and June 2009 in Zhejiang Cancer Hospital (Hangzhou, China) were analyzed. The diagnoses were confirmed by pathological study, either during their gestational period or within six months after delivery. Clinical information was collected, including age, gestational phase, clinical stage of tumor according to the standard of the International Federation of Gynecology and Obstetrics (FIGO), tumor size, histological diagnosis, therapeutic approach, pregnancy outcome, fetus health, and follow-up information. This study was approved by the Zhejiang Cancer Hospital Institutional Review Board.

Individualized therapy was performed for each patient. The strategy was designed according to the clinical stage of the tumor, tumor size, and the gestational phase of the patient. The putative therapeutic approaches and the corresponding outcomes were all clarified with the patients, and the therapeutic timing and approach were agreed and decided by both patients and doctors.

According to the general therapeutic principle, the pregnancy could be continued for the patients of *in situ* carcinoma or at stage IA, under close medical monitoring. Postponed therapy could be performed for the patients in the third trimester until the fetus was mature enough for delivery. There were two means to terminate pregnancy for cervical cancer associated with pregnancy, including artificial abortion and cesarean section followed by immediate total hysterectomy or radical surgery. The cesarean section to terminate pregnancy was suggested for patients with a viable infant. In the current report, either vaginal delivery or cesarean section was adopted by the patients who were diagnosed with the cervical cancer after childbirth.

There are several approaches for tumor treatment, including surgery, radiotherapy, and chemotherapy, either alone or in combination. The major therapeutic strategies include surgery followed by adjuvant radiotherapy (or chemo-radiotherapy), radiotherapy alone, concurrent chemo-radiotherapy, and

the neoadjuvant chemotherapy in combination with surgery and radiotherapy (or chemo-radiotherapy) for those patients with post-operative high-risk factors. Surgery, including hysterectomy (for *in situ* carcinoma) or radical surgery, is the major approach for patients with early-stage cervical cancer, while radiotherapy or chemo-radiotherapy is mainly used for patients with locally advanced cervical cancer. The pelvic external radiotherapy in combination of brachytherapy is usually performed as routine radiotherapy strategy, and the platinum-based chemical reagents are commonly used in the chemotherapy regimens.

3 Results

The clinical information of the 20 patients is listed in Table 1. The age of the patients ranged between 29 and 45 years, with a median age of 33 years. According to the classification of pathological type, there were 18 patients with squamous cell carcinoma (including one *in situ* carcinoma), one patient with adeno-squamous carcinoma and one patient of small cell carcinoma. According to the FIGO clinical stage classification, one patient presented with *in situ* carcinoma (5%), one patient with stage IA1 (5%), five at stage IB1 (25%), one at stage IB2 (5%), eight at stage IIA (40%), three at stage IIB (15%), and one at stage IIIB (5%). Tumor size ranged between 2 and 10 cm in diameter except for the *in situ* and IA1 carcinoma. Twelve patients presented with a tumor size larger than 4 cm. According to the classification of the gestational phase at diagnosis, eight patients were in the first trimester of pregnancy, four in the second, two in the third, and six at postpartum.

Table 1 Clinical information of 20 patients

Clinical information	Value*
Median age (range) (year)	33 (29–45)
Pathological type (*n*)	
Squamous	18
In situ carcinoma	1
Invasive carcinoma	17
Adeno-squamous	1
Small cell squamous	1
Clinical stage of FIGO 2000 (*n*)	
In situ carcinoma	1
Stage IA1	1
Stage IB1	5
Stage IB2	1
Stage IIA	8
Stage IIB	3
Stage IIIB	1
Tumor size (diameter, cm)	2–10
Larger than 4 cm (*n*)	12
Timing of diagnosis (*n*)	
First trimester	8
Second trimester	4
Third trimester	2
Postpartum	6

* Data are expressed as number of patients except for age (median (range)) and tumor size (range)

Tumor treatment strategy was designed according to the clinical stage and tumor size. Surgery alone or neoadjuvant chemotherapy followed by surgery was suggested for patients with early-stage tumor (stage IIA or earlier). Neoadjuvant chemotherapy mainly consisted of platinum-containing drugs. Adjuvant therapy was applied to the patients who had high-risk factors as revealed by post-operative pathological study. High-risk factors were defined post-operatively, including tumor size, lymphatic vascular space involvement, deep stromal invasion, positive lymph nodes and positive surgical margins or positive parametrium. Radical therapy included radiotherapy or concurrent radio-chemotherapy containing platinum, predominantly for patients with stage IIB or more advanced carcinoma.

Treatment strategies differed among the eight patients in the first trimester pregnancy. Six of the eight patients underwent direct radical surgery, one underwent induced abortion followed with radical surgery, and one underwent induced abortion followed by concurrent chemo-radiotherapy. Out of the four patients in the second trimester pregnancy, two underwent pregnancy termination by cesarean section followed by radical surgery while the remaining two underwent direct radical surgery. Of the two patients in the third trimester pregnancy, one was diagnosed with stage IIA cervical carcinoma at 28 weeks of gestation and therapy was postponed until 34 weeks of gestation when cesarean section was safely performed. The other patient decided to terminate the pregnancy, and received neoadjuvant radiotherapy followed by cesarean section to remove the fetus, in which retarded growth was observed. Six patients were diagnosed with cervical cancer at postpartum. Three underwent cesarean section, while the remaining three patients underwent vaginal delivery.

Therapy strategies for these six patients included surgery or radiotherapy (chemo-radiotherapy) according to the clinical stage of the tumor.

The follow-up program was maintained up to Dec. 2013. The shortest follow-up period was 14 months and the longest 142 months, with a median time of 68 months. Only one patient was lost to follow-up. Seven out of eight first trimester patients survived without tumor. One patient died of lung metastases 11 months after therapy. Two out of four second trimester patients survived. One patient with small cell cancer died of lung metastases one year after therapy and one patient was lost during the follow-up period. Of the two third trimester patients, one patient survived tumor-free while the other patient suffered from pelvic tumor recurrence 13 months after therapy, and died of uremia. Three out of the six postpartum patients underwent cesarean section and survived tumor-free. Of the remaining three patients undergoing vaginal delivery, one survived tumor-free, one died of lung and bone metastases 8 months after therapy and one died of lung metastases 12 months after therapy. The newborns, one from the third trimester patient and six from postpartum patients, were healthy (Table 2).

4 Discussion

Four patients in the present study (one with *in situ* carcinoma, one with stage IA1 carcinoma and two in the third trimester of pregnancy) were informed that they could continue the pregnancy under close medical monitoring until the fetus matured

Table 2 Therapy strategy, pregnancy outcomes and follow-up results

Stage	Diagnosis timing[a]	Number	Therapy strategy[b]	Chemotherapy regimen[c]	Outcome of pregnancy[d]	Fetus or neonate	Follow-up result[e]	Reason of Death
In situ	2nd	1	Surgery		Abandoned		DFS	
IA1	1st	1	Surgery		Abandoned		DFS	
IB1	1st	1	Surgery		Abandoned		DFS	
	1st	1	Surgery+RT		Abandoned		DFS	
	1st	1	Surgery+CCRT	FP	Abandoned		DFS	
	2nd	1	Surgery+CCRT	EP	Abandoned		Died	Lung metastasis
	3rd	1	NACT+surgery+CCRT	NACT: BVP CCRT: FP	Abandoned	Retarded fetus	Died	Uremia
IB2	2nd	1	Surgery+CCRT	FP	Abandoned		Lost	
IIA	1st	1	Surgery+RT		Abandoned		DFS	
	1st	1	Surgery+CCRT	FP	Abandoned		DFS	
	1st	1	Surgery+CCRT+CT	CCRT: FP CT: BIP	Abandoned		Died	Lung metastasis
	2nd	1	Surgery+RT		Abandoned		DFS	
	3rd	1	NACT+surgery+CT	NACT: TP CT: BIP	CS	Good	DFS	
	Post	1	Surgery+CCRT+CT	CCRT: FP CT: BVP	VD	Good	Died	Lung metastasis
	Post	1	Surgery+CCRT	FP	CS	Good	DFS	
	Post	1	NACT+CCRT	NACT: BIP CCRT: TP	CS	Good	DFS	
IIB	1st	1	CCRT	FP	Abandoned		DFS	
	Post	1	RT		VD	Good	Died	Lung and bone metastasis
	Post	1	CCRT	FP	CS	Good	DFS	
IIIB	Post	1	CCRT+CT	CCRT: TP CT: TP	VD	Good	DFS	

[a] 1st: first trimester; 2nd: second trimester; 3rd: third trimester; Post: postpartum. [b] RT: radiotherapy; CT: chemotherapy; NACT: neoadjuvant chemotherapy; CCRT: concurrent chemo-radiotherapy. [c] FP: 5-fluorouracil+cisplatin; EP: etoposide+cisplatin; BVP: bleomycin+vincristine+cisplatine; BIP: bleomycin+ifosfamide+cisplatin; TP: paclitaxel+cisplatin. [d] CS: cesarean section; VD: vaginal delivery. [e] DFS: disease-free survival

for birth. Only one patient however, at Week 28 of gestation with stage IIA carcinoma, decided to continue pregnancy and postpone anti-tumor therapy. One healthy female baby was born by cesarean section at Week 34 with fetal lung maturation supported by medical intervention. The follow-up result showed that the patient was tumor-free and the baby was in good health, indicating that patients with stage IIA cervical cancer can continue pregnancy and postpone therapy for six weeks with satisfactory outcomes. Indeed, 70% of cervical cancers associated with pregnancy cases are diagnosed at tumor clinical stage I (Lee *et al.*, 1981; Takushi *et al.*, 2002; Hunter *et al.*, 2008). Reports investigating postponed therapy for patients with stage II or more advanced tumor remain limited. It has been suggested that therapy should not be postponed more than six to eight weeks for patients with stage II or more advanced tumor (Amant *et al.*, 2009). In the current report, only 25% (1/4) of patients who fulfilled the postponed therapy criteria decided to continue pregnancy. This may reflect the reality in China that radical therapy is preferred by patients owing to financial pressures or limited medical resources, with life quality (for instance, to continue pregnancy) sacrificed.

It has been suggested that neoadjuvant chemotherapy to control tumor growth is a viable option for second or third trimester patients with locally advanced cervical cancer (stage IB2 or more advanced) (Amant *et al.*, 2009; Pentheroudakis *et al.*, 2010). Fruscio *et al.* (2012) reported that chemotherapy during the second or third trimester of pregnancy has no obvious adverse effect on the fetus, even though the putative risk is to promote the progress of the tumor since chemotherapy is not the radical treatment for cervical cancer (Lai *et al.*, 1997; Benhaim *et al.*, 2008; Favero *et al.*, 2010). No patient in the current report received neoadjuvant chemotherapy with the purpose of continuing the pregnancy. Rather, one patient in the third trimester of pregnancy with stage IB2 tumor underwent chemotherapy combination of bleomycin, vincristine plus cisplatin followed by pregnancy termination by cesarean section. In this case, fetal growth was retarded and the developmental stage was not in accordance with gestational age, indicating that certain chemical agents may have a potential adverse effect on fetal development even in the third trimester. Guo *et al*. (2012) reported that one out of two neonates, whose mothers received chemotherapy (5-fluorouracil plus cisplatin) before delivery, died 4 d after birth. Though other reasons, like disorders associated with pregnancy, may also induce retarded fetus, caution is required when selecting chemotherapy agents for patients who opt to continue pregnancy.

Cesarean section is suggested to patients who have the birth canal blocked by cervical tumor (Amant *et al.*, 2009). The outcomes of the six patients in the current study differed greatly, and interestingly three patients who underwent cesarean section had successful tumor-free survival, whereas two patients who had vaginal delivery died of remote metastasis. These findings confirm that cesarean section may be a safer delivery mode for cervical cancer patients. The association between remote metastasis and vaginal delivery remains unclear. It is possible that the extrusion and hemorrhage of the vagina during childbirth may be responsible for remote metastasis.

In general, it has been demonstrated that the pathogenesis or progress of cervical cancer is not obviously influenced by pregnancy (Takushi *et al.*, 2002; Germann *et al.*, 2005; Stensheim *et al.*, 2009). The six postpartum patients in the present study were diagnosed with cervical cancer within six months of delivery, with stage II or more advanced tumor. This suggests that cervical cancer may have been present in these patients prior to them delivery because of the long course of cervical tumor formation. Consequently, cervical cancer screening before and during pregnancy is essential to avoid unnecessary pregnancy termination or poor cancer prognosis after delivery.

The treatment strategies and prognosis of cervical cancer associated with pregnancy, where there is no need to continue pregnancy or pregnancy has been terminated, are generally the same as for non-pregnant women (Sood and Sorosky, 1998; Takushi *et al.*, 2002; Germann *et al.*, 2005; Stensheim *et al.*, 2009). In the current study, the incidence of remote metastasis was significantly higher than that of the local recurrence (4:1). The incidence of metastasis in the present investigation was also higher than that of previously reported non-pregnant cervical cancers (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008). The high incidence of remote metastasis in the current study may be

attributed to limited patient sample size, the patients in the current report presenting with relatively advanced tumors (60% were stage II or more advanced), and putative individual differences such as local blood supply, sex hormone levels, and altered immune function.

5 Conclusions

The current study confirms the feasibility to continue pregnancy for selected cervical cancer patients, indicates that there may be potential risk for fetus by chemotherapy during pregnancy, and reveals relationship between cervical cancer prognosis and delivery mode. The current study, however, is a retrospective analysis and this does not give ideal evidence for therapeutic guidelines. Furthermore, the patient sample size was limited and there was a particular lack of patients who chose to postpone therapy until childbirth. Future studies are required, focusing on the outcomes of postponed therapy in pregnant women and prospective investigations.

Compliance with ethics guidelines

Xiang ZHANG, Yong-liang GAO, and Yue YANG declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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中文概要

题　目：妊娠相关性宫颈癌 20 例临床分析

目　的：探讨妊娠相关性宫颈癌合适的治疗方式，包括维持妊娠、针对肿瘤的治疗、分娩方式，以及预后。

创新点：在发展中国家对妊娠相关性宫颈癌治疗和分娩方式的选择，以及相关预后。

方　法：回顾性分析 2000 年到 2009 年浙江省肿瘤医院收治的 20 例妊娠相关性宫颈癌患者的临床资料、治疗方案及随访结果。

结　论：妊娠中晚期患者可选择在短期内继续妊娠；新辅助化疗对胎儿可能有影响；对合并宫颈癌的患者，剖宫产术是较阴道分娩更合适的方式。

关键词：宫颈癌；妊娠；治疗；预后