



Original research

Effect of preoperative radiotherapy on stage IB2 and IIA2 cervical cancer: A retrospective cohort study



Tongqing Zhang, Weimin Kong^{*}, Fengshuang Li, Dan Song, Tingting Liu, Chao Han, Simeng Jiao, Jiao Chen

Department of Gynecological Oncology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, 100006, China

HIGHLIGHTS

- Efficiency of the preoperative radiotherapy on early stage CC was evaluated.
- There was no difference for complication, blood loss and surgery time between two groups.
- Preoperative radiotherapy did not improve the postoperative pathology.
- 1-, 3- and 5-year survival rates were similar between two groups.
- 3- and 5-year locoregional control rates were much higher in radiotherapy group.

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ABSTRACT

Introduction: The aim of the retrospective study was to investigate the therapeutic efficiency of the preoperative intracavitary radiotherapy combined with radical surgery on postoperative complications and long-term survival in patients with stage IB2 and IIA2 cervical cancer (CC).

Methods: From January 1995 to December 2012, a total of 171 patients with stage IB2 or IIA2 CC were recruited into the study. They were divided into two groups according to the treatment modality provided: preoperative radiotherapy followed by radical surgery ($n = 80$), and radical surgery alone ($n = 91$). The clinical curative effect, postoperative complications and the postoperative prognosis of patients were evaluated and compared in two groups. The tumor response and survival of patients in two groups were observed in follow-up study.

Results: There were no significant differences in the incidence of postoperative complications, intra-operative blood loss and surgery duration ($P > 0.05$) between the two groups. Preoperative radiotherapy did not improve the postoperative prognosis yet. Though patients undergoing preoperative radiotherapy showed the similar 1- (92.50% vs. 84.62%), 3- (85.00% vs. 81.32%) and 5-year (80.00% vs. 74.72%) survival rates, the 3- and 5-year locoregional control rates of them were much higher than those undergoing surgery alone ($P < 0.05$).

Conclusion: Preoperative radiotherapy combined with radical surgery could improve locoregional control rate and would not increase the risk of postoperative complications. It may be a feasible treatment mode for early stage CC carcinoma.

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1. Introduction

Cervical cancer (CC) is the third most commonly diagnosed

primary carcinoma and the leading cause of cancer death among women in the world [1]. The prognosis of patients with early stage CC (stage IB2 and IIA2) is usually poor due to high risk of recurrence and metastasis of CC [2].

Traditionally, patients with early stage cancer are treated with radiation therapy and surgery. Radical hysterectomy followed by primary chemoradiation therapy and tailored adjuvant therapy has been suggested in the treatment of early stage IB2 and IIA2 CC [3]. However, there were some inconsistencies on curative effects of

^{*} Corresponding author. Department of Gynecological Oncology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Qihelou Road, Dongcheng District, Beijing, 100006, China.

E-mail address: WeiminKongwk@163.com (W. Kong).

surgery and radiotherapy in patients with stage IB2 or stage IIA2 CC. Previous studies have proved that radical surgery and radiotherapy are equally effective in the treatment of stage IB2 and IIA CC, but the type and rate of complications and morbidity between them were different [4,5]. Rungruang and his partners found that early stage CC patients treated with surgery first had improved outcomes than those treated with radiation first [6]. Park et al. [7] suggested that radical hysterectomy had better survival outcomes and lower treatment-related morbidities as compared to primary chemoradiation therapy in patients with IB2 and IIA2 CC. Therefore, the roles of radical hysterectomy and primary chemoradiation therapy in early stage CC patients should be re-evaluated.

To investigate the curative effect of preoperative radiotherapy plus immediate radical surgery, a retrospective cohort study was performed to compare it with radical hysterectomy alone in stage IB2 and IIA2 CC patients.

2. Materials and methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (<http://www.strobe-statement.org/>) [8] for cohort studies was developed to enhance the quality of the present study.

2.1. Inclusion and exclusion criteria and group assignment

From January 1995 to December 2012, the consecutive medical records of patients with early stage CC admitted to Beijing Gynecology and Obstetrics Hospital were retrospectively reviewed. Patients were eligible for the study if they (1) were diagnosed with stage IB2 or IIA2 CC according to the International Federation of Obstetrics and Gynecology (FIGO) staging system [9]; (2) had a tumor more than 4 cm in diameter; (3) had normal liver and kidney function; (4) had karnofsky score [10] of over 90 points. Patients who were diagnosed with non-squamous cell cancer or during pregnancy were excluded.

Patients were divided into two groups according to the treatment techniques: preoperative radiotherapy group and immediate radical surgery group. The study protocol was approved by the ethics committee of this hospital, and informed consents were obtained from all of these patients.

2.2. Treatment procedures

Patients in preoperative radiotherapy group received preoperative intracavitary brachytherapy at a dose of 2000–3000 cGy (centigray) (radioactive source at 1 cm distance) using sources ^{192}Ir once a week (2–3 times in total). After 2–3 weeks of rest, radical hysterectomy and lymphadenectomy was performed. Patients in the surgery alone group received radical surgery directly.

After radical surgery, patients with vascular space invasion and cervical stromal invasion $\geq 1/2$ received subsequent therapy: external radiotherapy \pm concurrent cisplatin-containing chemotherapy, patients with lymph node metastasis and a positive margin received external radiotherapy plus concurrent cisplatin-containing chemotherapy, while those with para-aortic lymph node metastasis received nodal radiotherapy plus pelvic radiation.

2.3. Curative effect evaluation

The efficacy of radiotherapy for early stage CC was assessed by tumor response, including complete response (CR, clinical disappearance of all target lesions and no new lesions), partial response (PR, $>50\%$ tumor shrinking and no new lesions), stable disease (SD, $<50\%$ tumor shrinking and no new lesions) and progressive disease

(PD, no change in tumor size or the appearance of new lesions). CR and PR were considered effective, while SD and PD were considered ineffective.

Intraoperative blood loss, surgery duration, postoperative complications, and postoperative prognosis (such as the lymph node metastasis, the deep cervical stromal invasion, the vascular space invasion and the number of unfavorable prognostic factors) were recorded.

2.4. Statistical analysis

The data collected were analyzed using SPSS for Windows (version 17.0, SPSS Inc., Chicago, IL, USA). The χ^2 test and student *t*-test were used in univariate analysis of quantitative data and qualitative data respectively. The locoregional control rate and the survival rate at 1 year, 3 years and 5 years were observed and evaluated. $P < 0.05$ was regarded as significant difference.

3. Results

3.1. Characteristics of patients

Finally, a total of 171 patients with median age of 43 years (range, 21–75 years) were included in our study. Total 80 patients received preoperative intracavitary radiotherapy followed by radical surgery, and 91 underwent radical surgery alone. Basic characteristics of the patients were shown in Table 1. There were no significant differences in age, FIGO stage, tumor size and tumor grade between the two groups ($P > 0.05$).

3.2. Duration of surgery and surgical bleeding

Both surgery duration and bleeding volume of the two groups were found to conform to normal distributions. Compared with the surgery alone group, the operation duration ($P = 0.061$) and intraoperative blood loss ($P = 0.405$) in preoperative radiotherapy group were all decreased, but the differences did not reach statistical significance ($P > 0.05$). Detailed results were shown in Table 2.

3.3. Postoperative complication

All patients completed treatment and no treatment-related deaths occurred. The common postoperative complications of two group patients were lymphocystitis virus infection, the impaired wound healing, postoperative urinary retention and urinary tract infection. There were no significant differences between the preoperative radiotherapy group and the surgery alone group in the incidence of postoperative complications ($P > 0.05$, Table 3). These results indicated that preoperative radiotherapy did not increase the risk of postoperative complications.

3.4. Postoperative prognosis

Postoperative pathologic examination showed that 67 (83.75%) patients in preoperative radiotherapy group had poor prognosis: 22 cases had lymph node metastasis; 55 cases had deep cervical stromal invasion; 40 cases had vascular space invasion. In surgery alone group, 82 of them (90.11%) had poor prognosis, including 29 cases had lymph node metastasis, 72 cases had deep cervical stromal invasion and 50 cases had vascular space invasion. However, there were no significant differences between the two groups in lymph node metastasis, deep cervical stromal invasion, vascular space invasion, and other invasion or metastasis ($P > 0.05$, Table 4). These results indicated that preoperative radiotherapy did not improve the postoperative prognosis.

Table 1

Basic characteristics of patients in two groups.

Groups	Median age (years)	FIGO staging (cases)		Tumor size (cm)	Tumor grade (cases)		
		IB2	IIA2		G1	G2	G3
Preoperative radiotherapy group	40.40 ± 7.4	43	37	5.85 ± 0.7	14	46	20
Surgery alone group	43.39 ± 7.1	55	36	5.64 ± 0.6	12	53	26
<i>P</i>	0.201	0.378		0.867	0.695		

FIGO: International Federation of Gynecology and Obstetrics.

Table 2

Comparison of the surgery duration and intraoperative blood loss between two groups.

Groups	Preoperative radiotherapy group	Surgery alone group	<i>P</i>
Blood loss (ml)	658 ± 239	691 ± 319	0.405
Surgery duration (min)	171 ± 39	192 ± 64	0.061

Table 3

Postoperative complications of patients in two groups.

	Lymphocystis virus infection (case)	The impaired wound healing (case)	Postoperative urinary retention (case)	Urinary tract infection (case)
Preoperative radiotherapy group (n = 80)	9	5	9	4
Surgery alone group (n = 91)	11	3	12	5
χ^2	0.029	0.833	0.148	0.021
<i>P</i>	0.865	0.362	0.700	0.885

Table 4

The postoperative prognosis of patients in two groups.

Postoperative prognosis	Preoperative radiotherapy group (n = 80)	Surgery alone group (n = 91)	χ^2	<i>P</i>
Lymph node metastasis (cases, %)				
Positive	22 (27.50%)	29 (31.87%)	0.388	0.533
Negative	58 (72.5%)	62 (68.13%)		
The deep cervical stromal invasion (cases, %)				
No	25 (31.25%)	19 (20.88%)	2.396	0.122
Yes	55 (68.75%)	72 (79.12%)		
The vascular space invasion (cases, %)				
Positive	40 (50.00%)	50 (54.94%)	0.418	0.518
Negative	40 (50.00%)	41 (45.06%)		
The number of unfavorable prognostic factors ^a (cases, %)				
G0	13 (16.25%)	9 (9.90%)	6.867	0.076
G1	24 (30.00%)	34 (37.40%)		
G2	32 (40.00%)	25 (27.5%)		
G3	11 (13.75%)	23 (25.2%)		

^a Indicates the number of other unfavorable prognostic factors in addition to the tumor size and tumor grade.

3.5. Response and survival

Effective responses (CR, n = 26; PR, n = 50) were observed in 76 (95.00%) of the 80 patients in preoperative radiotherapy group, while the tumor response of the other 4 patients was SD.

The median follow-up time of the two groups was 30 months. In the preoperative radiotherapy group, 3 cases (3/80, 3.75%) lost to follow-up. Four cases (4.40%, 4/91) lost to follow-up in the surgery alone group. In preoperative radiotherapy group, the 1-, 3- and 5-year locoregional control rates were 88.75%, 82.50% and 77.50%, while that of surgery alone group were 79.12%, 61.54% and 52.75%, respectively. Significant differences in the 3- and 5-year locoregional control rates were found between the two groups ($P < 0.05$), which meant that preoperative radiotherapy combined with radical surgery achieved higher locoregional control rate. However, there was no significant difference in the 1-, 3- and 5-year survival rates between the two groups: 92.50% vs. 84.62% ($P = 0.109$), 85.00% vs. 81.32% ($P = 0.522$) and 80.00% vs. 74.72% ($P = 0.412$), respectively,

which meant that preoperative radiotherapy combined with radical surgery did not improve the long-term survival rate in patients with stage IB2, IIA2 CC (Table 5).

4. Discussion

Currently, the locoregional control rate of patients with locally advanced CC (stage IB2 and IIA2) underwent immediate radical surgery or radiotherapy is low. This is partly due to the high incidence of adverse prognosis [11]. Therefore, it is of great importance to improve the prognosis of the locally advanced CC in clinical practice. Our study showed that, compared with the surgery alone group, primary preoperative radiotherapy combined with surgery did not improve the long-term survival rate and postoperative prognosis in patients with stage IB2 and IIA2 CC. However, patients treated with primary preoperative radiotherapy plus radical surgery had higher locoregional control rate. Besides, preoperative radiotherapy did not increase the risk of postoperative

Table 5
Locoregional control rate and survival rate of two groups.

Groups	Locoregional control rate			Survival rate		
	1 year	3 year	5 year	1 year	3 year	5 year
Preoperative radiotherapy group (cases, %)	71 (88.75%)	66 (82.50%)	62 (77.50%)	74 (92.50%)	68 (85.00%)	64 (80.00%)
Surgery alone group (cases, %)	72 (79.12%)	56 (61.54%)	48 (52.75%)	77 (84.62%)	74 (81.32%)	68 (74.72%)
P	0.090	0.002	0.001	0.109	0.522	0.412

complications. Therefore, preoperative radiotherapy combined with surgery could be a feasible treatment mode for locally advanced CC carcinoma.

According to the recommendation proposed by National Comprehensive Cancer Network in 2015 [12], patients with stage IB2 and IIA2 CC could be treated as following: definitive pelvic radiotherapy + concurrent cisplatin-containing chemotherapy + brachytherapy (total dose to point A \geq 85 Gy) (category 1 or primary chemoradiation), radical hysterectomy + pelvic lymph node dissection \pm para-aortic lymph node sampling (category 2B), or pelvic radiotherapy + concurrent cisplatin-containing chemotherapy + brachytherapy (total dose to point A 75–80Gy) + adjuvant hysterectomy (category 3). The above-mentioned concurrent chemoradiotherapy was used as the first-line treatment in recent years, but preoperative radiotherapy combined with radical hysterectomy and lymphadenectomy was usually carried out in Chinese hospitals, as well as in our hospital. However, with regard to the controversy about the efficacy of this therapy in the treatment of early stage CC, the outcomes about preoperative radiotherapy combined with radical hysterectomy and lymphadenectomy need to be further validated.

Early studies have evaluated the connection between preoperative radiotherapy and morbidity as well as response rate. For example, Beskow et al. reported that preoperative radiotherapy could increase the 3 year survival rate in patients with stage IB and IIA CC to 87% and 75% respectively [13]. The report from Mayer et al. showed that the 5-year locoregional control rate of stage IB CC patients who received preoperative radiotherapy was significantly reduced to 83% [14]. Ordeanu et al. reported that the 3-year survival rate of patients with stage IIA and IIB CC who received preoperative radiotherapy was 92%, which was significantly higher than those who received radical radiotherapy (68%) [15]. A Chinese study by Wang et al. reported that there were no significant differences in the 5-year response rate or the overall survival rate between preoperative radiotherapy group and surgery alone group [16]. A study by Zivanovic et al. examined the outcomes in women with stage IB2 CC, and also demonstrated no significant difference in the 3-year overall survival rate between the two treatment groups [17]. In our study, the 1-, 3- and 5-year survival rates in the preoperative radiotherapy group were slightly increased, although the changes were not significantly different. However, the 3- and 5-year locoregional control rates were 82.50% and 77.50%, respectively, in preoperative radiotherapy group, which were much higher than 61.54% and 52.75% in surgery alone group. Our results were consistent with previous studies. These results indicated that patients undergoing preoperative radiotherapy showed much better control effect than those undergoing immediate radical surgery.

The result of our study showed that there was no significant difference in the incidence of unfavorable prognostic factors between the two groups, which meant that preoperative radiotherapy did not improve postoperative prognosis. Factors associated with the increased risk of surgical procedure include intraoperative and postoperative complications, such as lymphocystis virus infection and the impaired wound healing. The common radiation-associated complications includes postoperative urinary retention

and urinary tract infection [18,19]. In our study, there were no significant differences in surgery duration and intraoperative blood loss between the preoperative radiotherapy group and the surgery alone group. Besides, the incidence of postoperative complications in two groups was separately 33.75% vs. 34.06%, which suggested that the preoperative radiotherapy did not increase the risk of postoperative complications. In clinical practice, it is difficult to carry out the immediate surgery for the treatment of stage IB2 and IIA2 CC because of the large tumor size. Preoperative radiotherapy was helpful in removing the tumor completely and easily by shrinking the tumor and reducing the activity of tumor cells, which could reduce local recurrence and do not increase risk of post-operative complication. It was reported that most postoperative complications were related to radiation therapy per se [7]. The complication rates of CC patients undergoing radiation therapy and surgery were similar, but the it seems difficult to compare the chronicity and severity [6]. Therefore, the long term side effect of radiotherapy should be evaluated in a long-term follow-up of a randomized controlled trial.

5. Conclusion

In summary, compared with the surgery alone group, preoperative radiotherapy combined with radical surgery can improve the overall survival rate and postoperative prognosis in patients of the preoperative radiotherapy group. However, the preoperative radiotherapy group had a higher locoregional control rate, which may reduce the difficulty of radical surgery and not increase the risk of postoperative complications. Therefore, preoperative radiotherapy combined with radical surgery may be a feasible treatment mode in treating locally advanced CC. However, a larger sample size and additional prospective, randomized controlled research are necessary to confirm the feasibility of this treatment approach.

Ethical approval

All studies have been approved by Beijing Obstetrics and Gynecology Hospital Ethics Committee and performed in accordance with the ethical standards.

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Author contribution

Conceive and design the experiments: Tongqing Zhang, Dan Song, Jiao Chen.

Acquire and analyze the data: Weimin Kong, Tingting Liu, Simeng Jiao.

Draft and revise the manuscript: Fengshuang Li, Chao Han.

Conflict of interest

All authors declare that they have no conflict of interests to state.

Guarantor

Weimin Kong.

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