RESEARCH ARTICLE

Comparison of Clinical Efficacy of Three Different Neoadjuvant Approaches (Chemotherapy Combined Vaginal Intracavitary Irradiation, Neoadjuvant Chemotherapy Alone or Radiotherapy) Combined with Surgery for Patients with Stage Ib2 and IIa2 Cervical Cancer

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Abstract

A total of 285 patients with stage Ib2 and IIa2 cervical cancer were categorized into three groups, and received preoperative neoadjuvant chemotherapy combined with vaginal intracavitary irradiation, neoadjuvant chemotherapy alone or radiotherapy, respectively. The effective rate of 70.6 % in group 1 was much higher than 41.4% in group 2 (*P*=0.000) and 46.9 % in group 3 (*P*=0.000); The percentage of patients receiving postoperative adjuvant therapy was 44.1% in group 1, much lower than 67.8% in group 2 (*P*=0.001) and 64.6% in group 3 (*P*=0.004); The percentage of patients with no postoperative risk factor in group 1 was 52.0%, much higher than 32.2% in group 2 (*P*=0.006) and 35.4% in group 3 (*P*=0.019); The occurrence rate of surgery-related complications in groups 1, 2 and 3 were 29.4%, 28.7%, and 33.3%, respectively, with no statistical differences among the groups (*P*=0.981). Regarding preoperative neoadjuvant complications, none were obvious in group 3, while occurrence rates of myelosuppression in groups 1 and 2 were 89.1% and 86.6%, of nausea and vomitting were 78.4% and 78.2%, but without significant differences (all *P*>0.05). Among 166 patients who received postoperative adjuvant therapy in the three groups, the occurrence rates were: 65.4%, 64.3% and 61.1% respectively for myelosuppression; 42.3%, 38.1%, and 38.9% for nausea and vomiting; 9.6%, 9.5% and 9.7% for urocystitis; and 63.5%, 69.0% and 65.3% enteritis and rectitis. There were no statistically significant differences among them (all *P*>0.05). The five-year disease-free survival rates (DFS) in groups 1, 2, 3 were 78.3%, 75.1%, 80.9%, respectively; the five-year overall survival rates (OS) were 81.4%, 78.2%, and 81.1%, respectively. The five-year OS of 166 patients receiving postoperative in the three groups were 72.4%, 69.5%, and 71.8%, respectively, with no significant variation (all *P*>0.05). Although there were no differences among three groups in DFS and OS, preoperative neoadjuvant chemotherapy combined with intracavitary radiotherapy may increase the effective rate and the percentage of patients with no postoperative risk factors and decrease the percentage of patients receiving postoperative adjuvant therapy, thereby decreasing complications indirectly and increasing quality of life.

Keywords: Cervical cancer - neoadjuvant chemotherapy - synchronous chemoradiation - intracavitary irradiation

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Introduction

Cervical cancer (CC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, and more than 85% of new cancer cases and deaths occur in developing countries, including in China (Jemal et al., 2011). As early stage tumor, stage Ib2 and IIa2 cervical cancer is a high-risk cancer with easy recurrence and metastasis, its 5-year survival rate is as low as about 50%, and is mainly treated with surgery combined neoadjuvant therapy (Zhao et al., 2012). This study aims to find the best neoadjuvant treatment strategy for patients with stage Ib2 and IIa2 cervical cancer by comparing the clinical efficacy of three different neoadjuvant therapy, preoperative chemotherapy combined radiotherapy, purely neoadjuvant chemotherapy or radiotherapy.

Materials and Methods

Study population

We retrospectively analyze 285 patients with stage Ib2 and IIa2 cervical cancer, who were treated with surgery combined preoperative neoadjuvant therapy in the fifth,

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the third, and the first hospital of Zhengzhou university between January 2002 and December 2011. According to the differences of the neoadjuvant therapy, they were categorized into three groups. In group 1, 102 patients received preoperative chemotherapy combined vaginal intracavitary irradiation, the mean age was 48.1±11.2 years old; In group 2, 87 patients received preoperative neoadjuvant chemotherapy only, the mean age was 48.2±11.3 years old; In group 3, 96 patients received preoperative neoadjuvant vaginal intracavitary irradiation only, the mean age was 47.8±11.0 years old, there were no statistical differences among them (P=0.967). In addition, there were no statistical differences among three groups in FIGO stage, Histological type, the degree of differentiation, periods of chemotherapy, chemotherapy plan, and dose of radiotherapy too (all P>0.05), as they were shown in Table 1.

Preoperative neoadjuvant therapy

Neoadjuvant chemotherapy: paclitaxel adds cisplatin, as it was called TP (Hosaka et al., 2012; Nagai et al., 2012), and every three weeks as a period of treatment; or paclitaxel adds carboplatin, as it was called TC (Kim et al., 2012; Sehouli et al., 2012), every three weeks as a period of treatment too; or bleomycin adds vincristine adds cisplatin, as it was called PVB (Singh et al., 2004; Ki et al., 2009), every ten days as a period of treatment, for 1 to 3 periods.

Vaginal intracavitary irradiation: patients were treated with 192Ir of afterloading vaginal brachytherapy, the dose was 10 to 30 Gy, 10 to 12 Gy/time, 1 time a week, for 1 to 3 times (Suzuki et al., 2008; Chen et al., 2010).

There were no statistical differences among three groups in chemotherapy, the number of treatment periods, and the doses of irradiation (all P>0.05), as they were shown in Table 1. Surgery (Ryu et al., 2007)

All 285 patients received extensive whole hysterectomy, pelvic and paraaortic lymphadenectomy after 2 to 3 weeks of neoadjuvant therapy. if it was needed, ovarian transposition operation was given at the same time (total of 56 cases, 19 cases in group 1, 18 cases in group 2, and 19 cases in group 3), there were no statistical differences among three groups (P>0.05).

Postoperative adjuvant therapy (Demirci et al., 2012)

Partial patients received external radiation therapy and/or synchronous chemotherapy including cisplatin if they supervened intravascular tumor emboli or tumor invasion depth was deeper than half of stroma. Partial patients received external radiation and synchronous chemotherapy including cisplatin if their pelvic lymph node, surgical margin or the parametrial tissue were positive, and received local radiation if they had been paraaortic lymph node tumor metastasis.

Therapeutic evaluation

Response evaluation criteria in solid tumors (RECIST) (Tsuchida et al., 2001) was adopted: disappearance of all target lesions as complete response (CR), at least a 30% decrease in the sum of the longest diametre (LD) of target lesions as partial response (PR), at least a 20% increase in the sum of the LD of target lesions as progressive disease (PD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD as stable disease (SD), and CR or PR were taken as effective.

Statistical analysis

SPSS 19.0 was applied for statistical analyses. The Kaplan-Meier estimator was used for disease-free survival rate (DFS) and overall survival rate (OS) calculation. The χ^2-test was used for the comparison of the curative effect, postoperative risk factors, postoperative adjuvant therapy, complications and survival situation, the t-test was used for comparison of mean age. A statistically significant difference was considered if P was <0.05.

Results

Curative effect

The effective (CR+PR) rate of 70.6% (71/102) in group 1 was much higher than 41.4% (36/87) in group 2 (P=0.000) and 46.9% (45/96) in group 3 (P=0.000). However, there were no statistical differences between group 2 and group 3 (P=0.455). Especially, the CR rate of 24.5% (25/102) in group 1 was much higher than 6.9% (6/87) in group 2 (P=0.001) and 6.3% (6/96) in group 3 (P=0.000) too, in the same way, there were no statistical differences between group 2 and group 3 (P=0.860). As they were presented in Table 2.

Postoperative risk factors and adjuvant therapy

The postoperative risk factors include tumor invasion depth was deeper than half of stroma, pelvic lymph node, surgical margin or the parametrial tissue positive, and intravascular tumor emboli.

The percentage of patients with no postoperative risk

Table 1. The Comparison of Clinical Stage, Histological Type, Differentiation Degree, and Chemoradiotherapy Among Three Groups

	Group 1 (n=102)	Group 2 (n=87)	Group 3 (n=96)	*P*
Mean age (yr)	48.1±11.2	48.2±11.3	47.8±11.0	0.967
FIGO stage n(%)				0.918
Ib2	85 (83.3)	73 (83.9)	82 (85.4)	
IIa2	17 (16.7)	14 (16.1)	14 (14.6)	
Histological type n(%)				0.793
SCCa	94 (92.2)	79 (90.8)	85 (88.5)	
AdenoCa	6 (5.9)	7 (8.0)	10 (10.4)	
AdenoSCCa	2 (2.0)	1 (1.1)	1 (1.0)	
The degree of differentiation n(%)				0.994
well	15 (14.7)	14 (16.1)	15 (15.6)	
moderately	49 (48.0)	40 (46.0)	47 (49.0)	
poorly	38 (37.2)	33 (37.9)	34 (35.4)	
Periods of chemotherapy n(%)				0.711
1	50 (49.0)	45 (51.7)	-	
2-3	52 (51.0)	42 (48.3)	-	
Chemotherapy plan n(%)				0.851
TP or TC	60 (58.8)	50 (57.5)	-	
PVB	42 (41.2)	37 (42.5)	-	
Dose (Gy) of radiotherapy n(%)				0.972
10-12	39 (38.2)	-	38 (40.0)	
20-24	58 (56.9)	-	53 (55.2)	
30	5 (4.9)	-	5 (5.2)	

FIGO, International Federation of Obstetrics and Gynecology; SCCa, squamous cell carcinoma; AdenoCa, adenocarcinoma; AdenoSCCa, adenosquamous carcinoma; "-" indicates that the column is absence

Table 2. The Comparison of Postoperative Risk Factors and Postoperative Adjuvant Therapy Among Three Groups

	Group 1 (n=102)	Group 2 (n=87)	Group 3 (n=96)
Effect n(%)			
CR	25 (70.6)	6 (6.9)[a]	6 (6.3)[b]
CR+PR	71 (70.6)	36 (41.4)[c]	45 (46.9)[d]
PD+SD	31 (29.4)	51 (58.6)	51 (53.1)
the number of risk factors n (%)			
0	53 (52.0)	28 (32.2)[e]	34 (35.4)[f]
1	33 (32.4)	35 (40.2)	37 (38.5)
≥2	16 (15.7)	24 (27.6)[g]	25 (26.1)[h]
postoperative adjuvant therapy n (%)			
with	45 (44.1)	59 (67.8)[i]	62 (64.6)[j]
without	57 (55.9)	28 (32.2)	34 (35.4)

P^{a}=0.000, group 1 VS. group 2; P^{b}=0.001, group 1 VS. group 3; P^{ab}=0.860, group 2 VS. group 3; P^{c}=0.000, group 1 VS. group 2; P^{d}=0.000, group 1 VS. group 3; P^{cd}=0.455, group 2 VS. group 3; P^{e}=0.006, group 1 VS. grop 2; P^{f}=0.019, group 1 VS. grop 3; P^{ef}=0.644, group 2 VS. grop 3; P^{g}=0.046, group 1 VS. grop 2; P^{h}=0.072, group 1 VS. grop 3; P^{gh}=0.814, group 2 VS. grop 3; P^{i}=0.001, group 1 VS. grop 2; P^{j}=0.004, group 1 VS. grop 3; P^{gh}=0.644, group 2 VS. grop 3

factors in group 1 was 52.0% (53/102), it was much higher than 32.2% (28/87) in group 2 (P=0.006) and 35.4% (34/96) in group 3 (P=0.019), however, there were no statistical differences between group 2 and 3 (P=0.644). On the contrary, the percentage of patients with two or more than two risk factors in group 1 was 15.7% (16/102), it was much lower than 27.6% (24/87) in group 2 (P=0.046), but there were no statistical differences between group 1 and group 3 of 26.1% (25/96) (P=0.072), similarly, between group 2 and group 3 (P=0.814).

On the postoperative adjuvant therapy, the percentage of patients receiving it was 44.1% (45/102), it was much lower than 67.8% (59/87) in group 2 (P=0.001) and 64.6% (62/96) in group 3 (P=0.004), but there were no statistical differences between group 2 and group 3 (P=0.644).

Complications

The complications include surgery-related complications, such as ureteral injury, poorly incisions healing, lymphocyst-related infections, urinary retention, and chemoradiation-related complications, such as myelosuppression, nausea and vomitting, urocystitis, enteritis and rectitis. All 285 patients went through neoadjuvant therapy and combined surgery smoothly, and there was no one died of treatment. The occurrence rate of surgery-related complications in the three groups were 29.4% (30/102), 28.7% (25/87), and 33.3% (32/96), respectively, there were no statistical differences among three groups (P=0.981). There had no obvious chemoradiation-related complications in group 3, the occurrence rate of myelosuppression in group 1 and group 2 were 89.1% and 86.6%, there were no statistical differences between them (P=0.973), of nausea and vomitting were 78.4% and 78.2%, there were no statistical differences between them too (P=0.994). Among 166 patients receiving postoperative adjuvant therapy in the three groups, the chemoradiation-related complications occurrence rate of myelosuppression were 65.4%, 64.3%, and 61.1%, respectively; of nausea and vomitting were 42.3%, 38.1%, and 38.9%, respectively; of urocystitis were 9.6%, 9.5% and 9.7%, respectively; of enteritis and rectitis were 63.5%, 69.0%, and 65.3%, respectively; there were no statitical differences among them (all P>0.05).

Survival situation

All patients were followed up except 7 patients were lost, the mean follow-up time was 46 months (range from 9 to 136 months). In group1, 2, and 3, the two-year DFS of them were 82.1%, 77.6%, and 87.5%, there were no statistical differences among them (P=0.832); in the same way, the five-year DFS were 78.3%, 75.1%, and 80.9% (P=0.762), the five-year OS were 81.4%, 78.2%, and 81.1% (P=0.951). The five-year OS of 166 patients receiving postoperative adjuvant therapy among three groups were 72.4%, 69.5%, and 71.8%, respectively, there were no statistical differences among them (P=0.698)

Discussion

Neoadjuvant chemotherapy is a research hot spot for locally advanced cervical cancer, its effect was reported for the first time by Sardi in 1993 (Sardi et al., 1993), their study showed that the five-year OS of 81% in 76 patients with Ib2 stage who were given three course of PVB preoperative chemotherapy, It was much higher than 63% in 75 patients who were given surgery directly. After that, there were more scholars proved that neoadjuvant chemotherapy may increase the survival rate than those who were treated with surgery directly (Namkoong et al., 1995; Sardi et al., 1997; Cai et al., 2006), but there had opposite opinions, for example, in Eddy's study (Eddy et al., 2007), the five-year DFS was 59.7% in patients who were given three course of vincristine and cisplatin preoperative chemotherapy, 56.2% in patients who were given surgery directly, their OS were 67.7% and 63.3%, respectively, there were no statistical differences in progression-free survival rate (PFS) and OS between them. In present study, we found that, five-year OS rate of 78.3% is much close to 81% in Sardi study (Sardi, et al. 1993).

To present day, preoperative radiotherapy include three methods, they are external radiation therapy, intracavitary radiation therapy, and external combined intracavitary radiation therapy. In Stehman study (Stehman et al., 2007), the tolerance was better, there was no notable increased side reaction, the five-year PFS was 62%, and recurernce rate was 15%, if the patients were given 40-45 Gy external radiation therapy, or 30 Gy brachytherapy at A point before given widely hysterectomy, and pelvic and paraaortic lymph node dissection. In Yao et al.' (2009) study, they found that, in the cervical cancer patients with Ib2 stage, the side reaction was less, there were no notable increased complications, and the OS was 83%, if they were given 20-30 Gy of preoperative afterloading intracavitary radiation therapy under vaginal mucosa 0.5 cm and beside the radioactive source 1cm, 10 to 12 Gy per time, 1 time a week, before the operation was performed for10 to 14 days, this indicates that afterloading intracavitary radiation therapy is a effective preoperative treatment for cervical cancer patients. Beskow considered that (Beskow et al.,

2002), preoperative brachytherapy may make 79% of the cervical cancer patients pathological examination to complete remission, and the later is the most important factor for the survival of lymph nodes negative cervical cancer patients. Wang thought that (Wang et al., 2010), preoperative radiotherapy may only increase the success rate of operation, but there was no influence on survival for cervical cancer patients with Ib2 stage who were treated with preoperative noeadjuvnat radiotherapy. Li study indicated that (Li et al., 2008), the effective rate was 94.7%, the five-year OS was 80.0% if the cervical cancer patients were given 20 to 30 Gy of preoperative intracavitary radiation therapy. To compare with the above studies, our study shows that, the effective rate of pure intracavitary radiation therapy was only 46.9%, it may be relation with the radiation dose, in this study, 41% patients were given 10-12 Gy radiation, only 58% patients were given 20-30 Gy radiation.

Preoperative neoadjuvant chemotherapy combined radiotherapy: At present, the research about the preoperative neoadjuvant chemotherapy combined radiotherapy includes external radiation therapy combined synchronous chemotherapy, external and intracavitary radiation therapy combined synchronous chemotherapy. In Huguet study (Huguet et al., 2008), all 92 cervical cancer patients with Ib2 to IIb stage were given preoperative external radiation therapy (the median dose was 40.5 Gy) combined fluorouracil added cisplatin synchronous chemotherapy, and 62 cases were given additional intracavitary radiation therapy (the median dose at A point was 20 Gy), the outcome showed that preoperative intracavitary radiation therapy may increased the rate of pathological complete remission, and the later was a independent risk factor for increasing DFS. Modarress though that (Modarress et al., 2005), 45-46 Gy preoperative external radiation therapy combined cisplatin synchronous chemotherapy may increase the rate of pathological complete remission, but compare to pure chemotherapy, there were no statistical differences in postoperative lymph node metastasis, parametrium tumor invasion and OS. Our study indicates that preoperative neoadjuvant chemotherapy combined intracavitary radiation therapy may decrease the percentage of patients with no postoperative risk factor, although it can not increase the five-year OS.

Postoperative adjuvant radiotherapy: In the Gynecologic Oncology Group (GOG) 92 study (Rotman et al., 2006), they found that postoperative adjuvant radiotherapy may decrease the recurrent risk (HR=0.54, *P*=0.007), prolong PFS (HR=0.58, *P*=0.009). In present study, 166 patients received adjuvant radiotherapy, 45 cases in group 1, and 59, 61 cases in group 2 and 3, respectively. The percentage of 44.1% who received postoperative adjuvant radiotherapy in group 1 is much lower than 67.8% in group 2 and 64.6% in group 3, but there is no statistical difference among them in five-year OS.

In summary, although there are no differences among three groups in DFS and OS, but preoperative neoadjuvant chemotherapy combined intracavitary radiotherapy may increase the effective rate and the percentage of patients with no postoperative risk factor, decrease the percentage of patients receiving postoperative adjuvant therapy, thereby, it may decrease complications indirectly, and increase the life quality. But it is necessary to launch large-scale perspective studies for whether take it as a effective treatment for Ib2 and IIa2 cervical cancer patients.

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