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COMPARATIVE STUDY OF CHEMORADIATION AND NEOADJUVANT CHEMOTHERAPY BEFORE RADICAL HYSTERECTOMY IN STAGE IB - IIB BULKY CERVICAL CANCER AND WITH TUMOR DIAMETER GREATER THAN 4 CM

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ABSTRACT

Tumor size seems to be a determinant in the prognosis of early cervical cancer. Patients with tumor size greater than 4 cm (bulky) in diameter have worse outcome.[1] The purpose of this study was to compare the efficacy of preoperative combined chemoradiation and neoadjuvant chemotherapy (NAIC) programs followed by radical hysterectomy in stage Ib – IIb bulky cervical cancer.

From September 1999 to April 2002, 60 patients with stage Ib – IIb bulky cervical cancer were treated with preoperative external beam radiotherapy to 45Gy plus weekly cisplatin 50 mg/m² or preoperative neoadjuvant chemotherapy by cisplatin 50 mg/m² and vincristin 1 mg/m² every 7-10 days, for three courses. Surgery was performed 4-6 weeks after completion of the preoperative treatment.

There was no significant difference between age, stage, tumor size and histopathological type in the two groups ($p>0.05$).Toxicity associated with the two treatment methods was usually mild. In the chemoradiation group, two patients developed vesicovaginal fistula, and four patients developed long term hydronephrosis that needed ureteral stenting. Before surgery, complete and partial clinical response had no significant difference between the two groups ($p>0.05$). After surgery, lymph node and parametrial involvement had no significant difference between the two groups ($p>0.05$). In the NAIC group more patients had significant residual tumor ($p=0.012$) but residual tumor size had no significant difference between the two groups ($p>0.05$). Pathological complete response was significant-ly higher in the chemoradiation group ($p= 0.004$).

According to the results of this study it seems that NAIC and chemoradiation have similar effects on survival prognostic factors.

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INTRODUCTION

The uterine cervix is of major interest and importance to almost every gynecologist. To the gynecologic oncologist it represents a common focus for the development of malignant tissues. [1]

In developing countries, screening not only has decreased the incidence and mortality rate of cervical cancer, but also has identified many women with preinvasive neoplasia, which can be treated easily. [2]

In contrast to industrialized countries, cancer of the cervix remains the primary killer cancer in women in third-world countries. [2]

In most institutions, the initial method of treatment for locally advanced disease is radiotherapy, both intracavitary (cesium or radium) and external x-ray therapy. [1,2] Although the controversy between surgery and radiotherapy has existed for decades, [1] whereas radiation therapy can be used in all stages of disease, surgery is limited to patients in stages I & II of the disease. [3]

Radiation was until recently the key and only modality for the routine treatment of locally advanced cervical carcinoma. However after years of studying multimodality treatments as an alternative to radiation alone in randomized phase III trials, the standard treatment has changed to chemo-radiation based on cisplatin. [3] Three recent meta-analyses have confirmed that cisplatin-based chemo-radiation adds an absolute 12% benefit in five-year survival over radiation therapy alone. Neoadjuvant chemotherapy followed by radiation has not been of proven benefit, but when neoadjuvant chemotherapy is followed by surgery, an absolute increase of 15% in five-year survival over radiation alone is seen. This benefit in survival is comparable to that obtained with the current chemoradiation schedules based on cisplatin. Despite these encouraging results there remains room for improvement as the five-year survival of patients treated with chemoradiation ranges from nearly 80% in bulky IB tumors to only 25% in stage IVA disease. [4]

In the radiation plus chemotherapy method, a variety of agents have been used in an attempt to increase the effectiveness of radiation therapy in patients with large primary tumors. In the neoadjuvant chemotherapy method, chemotherapy is used to shrink the tumor before radical hysterectomy or radiotherapy. [3]

Consecutive low dose cisplatin-based chemotherapy is a key drug for treatment of gynecologic malignancies. [5] Platinum compounds accumulation is at the highest level in the cervix and then in the myometrium, in both cervical and endometrial cancers. Platinum accumulation in the ovary and lymph nodes is only 0.58 and 0.57 times that in the myometrium, respectively. In patients with cervical cancer platinum accumulation in the myometrium and cervix are significantly higher than in the ovary and lymph nodes. Platinum accumulation in cervical cancer tissue is lower than in the myometrium and cervix. Cisplatin is easily distributed to the myometrium and cervix, but not to the ovary, lymph nodes, and cancer tissues. [6]

Despite remarkable improvement in clinical management, the survival of cervical cancer patients has shown only minor progress in the last decade, particularly in patients with advanced and high-risk disease. Multimodal treatment options have been investigated, such as the concurrent use of chemotherapy and radiation, neoadjuvant chemotherapy and radical hysterectomy, or neoadjuvant chemotherapy followed by radiotherapy. Recently, a flow of randomized clinical trials have demonstrated a benefit from concurrent chemoradiation for the treatment of cancer of the cervix. [7]

Tumor size is an important prognostic factor in patients with stage IB cervical cancer. The patient with stage IB2 (bulky) cervical cancer represents a therapeutic challenge. Neither radical hysterectomy nor primary radiation therapy are sufficiently effective and are associated with significant treatment-related complications including ovarian failure and psychosexual deficits. A number of phase III studies have explored alternative management approaches in this patient population. It appears that extrafacial hysterectomy following radiation therapy does not improve overall survival relative to radiation therapy alone. Consistent with results seen in locally advanced cervical carcinoma, chemoradiation therapy is superior to radiation therapy alone as primary treatment for stage IB2 cervical cancer and as adjuvant therapy for surgically treated patients with high-risk factors for recurrence. Neoadjuvant chemotherapy has resulted in high clinical response rates and operability rates. There are two phase III trials suggesting an improvement in survival with neoadjuvant chemotherapy followed by radical hysterectomy versus either surgery (and selected postoperative radiation) or radiation therapy alone. These emerging treatments should be scrutinized in prospective controlled trials. [8]

Multicentric randomized studies showed that chemotherapy with cisplatin, bleomycin, mitomycin C, and vincristin before radiation, has the same disease-free actual survival rate: 3 years. [9] But five landmark papers

have reported significant improved survival for patients with cervical cancer when neoadjuvant chemotherapy is used in combination with radiation. [10]

Neoadjuvant intraarterial infusion chemotherapy is able to effectively eliminate the pathologic risk factors in the pelvic cavity, to improve the operability in patients in stage IIb cervical cancer, considered inoperable, and to improve the prognosis of patients with locally advanced cervical cancer. [11]

None of the current surgical or radiation treatment strategies for cervical cancer satisfactorily leads to a high disease-free survival and a low risk for treatment-related complications in patients with bulky or locally-advanced disease. Neoadjuvant chemotherapy (NACT) prior to surgery or radiation therapy has been studied as a means to reduce tumor bulk thereby rendering subsequent therapy more effective. Impressive clinical response rates to cisplatin-based NACT have been achieved with acceptable toxicity and survival. Of the patients treated, approximately 20% will achieve a complete clinical response and many of these patients will prove to have a complete pathological response. There are too few randomized controlled studies to determine the effectiveness of NACT approaches, relative to standard treatments. [12]

The combination of cisplatin-vinorelbin is an active regimen in the treatment of patients in early stages and advanced carcinoma of the cervix. In the study of activity and toxicity of this regimen, hematological toxicity was mild, with neutropenia being the most frequent side effect. Non-hematological toxicity was frequent but never severe; one patient had grade 3 peripheral neurotoxicity. [13]

Ten years follow up of 80 patients with locally advanced stage Ib-IIb cervical cancer with tumor diameter of greater than or equal to 4 cm, after neoadjuvant chemotherapy by cisplatin, bleomycin and vincristin, and radical hysterectomy showed a reduction in tumor size after neoadjuvant chemotherapy in 75 cases. Overall 5 year and 10 year disease-free actual survival rates were 82% and 79.4%, respectively. Clinical stage, initial tumor size, clinical response and residual tumor size were not risk factors for recurrence after this therapy. However, pelvic lymph node metastasis was a significant risk factor for recurrence. [14]

In a study to investigate pretreatment variables related to prognosis and to evaluate long-term outcome in patients with bulky early-stage cervical carcinoma who were enrolled into a protocol treatment of neoadjuvant chemotherapy (NAC) followed by radical surgery, age (p=0.043) and histological type (adeno-adenosquamous vs. squamous carcinoma: p=0.010) were independent variables associated with RFS, and age (p=0.010) and pre-NAC tumor size (p=0.027) were significantly related to OS. [15]

In a single institution, a prospective randomized study was performed in which 295 patients in stage IIb were randomly allocated to three groups: only surgery, only radiation, and both combined with neoadjuvant chemotherapy, After 84 months follow up (mean) the survival rate for surgery and neoadjuvant chemotherapy was 65%, for radiation and chemotherapy 54%, for radiation alone 48% and for surgery alone 41%. The best survival rate was in patients who received chemotherapy followed by surgery and radiation. Resectability was significantly better in the neoadjuvant chemotherapy plus surgery group (80%) compared with the surgery alone group (56%), (p<0.001). Neoadjuvant chemotherapy plus surgery and radiation had a greater survival rate in tumors (both >5cm and <5cm) compared with surgery and radiation. [1]

The purpose of this study was to compare the efficacy of preoperative combined chemoradiation and neoadjuvant chemotherapy programs followed by radical surgery in stages Ib-IIb bulky cervical cancer.

MATERIAL AND METHODS

From September 1999 to April 2002, 60 consented patients who had been admitted in Vali-Asr Hospital, affiliated to Tehran University of Medical Sciences, in stages Ib-IIb bulky cervical cancer were randomly allocated to two intervention groups. The inclusion criteria were normal chest x-ray and normal intravenous pyelourethrography (IVP). The exclusion criteria consisted of pregnancy, history of previous cancer, cervical stump, diabetes mellitus, renal diseases, liver diseases and bone marrow disorders.

In the neoadjuvant chemotherapy group, cisplatin (50mg/m^2) plus vincristin (1mg/m^2) were infused intravenously every 7-10 days for three courses. After each course, patients were examined and probable complications were registered. The chemoradiotherapy group received extrabeam radiotherapy (5 days every week with 1.5-2Gy per day) up to 4500-4600 Gy to complete the treatment course, also cisplatin (50mg/m^2 per week) was administered intravenously. Type III radical hysterectomy plus pelvic and para-aortic lymphadenectomy were done for each case 4-6 weeks after the preoperative treatment.

Table I. The characteristics of patients in neoadjuvant chemotherapy and chemoradiotherapy groups

Patients characteristics \ Treatment group		Chemoradiotherapy	Neoadjuvant chemotherapy	P value
Mean age (year)		53 ± 12.1	48 ± 10.09	0.33 (t = 1.64)
Stage *	Ib1	1 (3.3%)	3 (10%)	0.76 (χ^2 =1.36)
	Ib2	12 (40%)	13 (43.3%)	
	IIa	7 (23.4%)	5 (16.7%)	
	IIb	10 (33.3%)	9 (30%)	
Pathological diagnosis	SCC**	29 (96.7%)	27 (90%)	0.61 (χ^2 =1.22)
	Adenocarcinoma	1 (3.3%)	3 (10%)	
Mean tumor size (cm)		4.53 ± 1.26	4.46 ± 1.05	0.42 t = 0.004

* FIGO staging, ** Squamous cell carcinoma

Table II. The frequency of clinical responses in neoadjuvant chemotherapy and chemoradiotherapy groups.

Clinical response \ Treatment group	Chemoradiotherapy	Neoadjuvant chemotherapy	P value
Complete	7(23.3%)	5(16.7%)	0.51 (χ^2=0.41)
Partial	23(76.7%)	25(83.3%)	
Total	30(100%)	30(100%)	

Table III. The frequency of lymph node involvement in neoadjuvant chemotherapy and chemoradiotherapy groups.

Treatment group \ Number	0	I	2	3	Sum	P value
Chemoradiotherapy	23 (76.7%)	4 (13.4%)	1 (3.3%)	2 (6.6%)	30 (100%)	0.98 t = 1.5
Neoadjuvant chemotherapy	23 (76.7%)	3 (10%)	3 (10%)	1 (3.3%)	30 (100%)	

After operation, specimens were checked pathologically in order to find lymph nodes and parametrial involvement, and the size of residual tumor mass, if present. Patients were checked and examined every three months for postoperative complications. Complete clinical response was defined as complete tumor omission, and partial clinical response was omission of more than 50 percent of tumor mass. Complete pathological response was the microscopic omission of tumoral cells with no lymph nodes and parametrial involvement.

The data were analyzed with SPSS10. Significance of statistical differences were examined by t-student and chi-square tests.

RESULTS

In this study 60 patients have been divided to two groups, 30 in the neoadjuvant chemotherapy group and 30 in the chemoradiotherapy group. There was no statistical difference between the two groups in demographic information (p>0.05) (Table I).

Complete clinical response in the neoadjuvant chemotherapy group was seen in 5 patients (16.7%). In the chemoradiotherapy group it was seen in 7 patients (23.3%). Partial clinical response to treatment in neoadjuvant chemotherapy and chemoradiotherapy groups was detected in 25(83.3%) and 23(67.7%) patients respectively. There was no statistically significant difference in rate of response between the two groups (p=0.514) (Table II).

Lymph node involvement was detected in 7 patients (23.4%) in both groups (Table III). Parametrial involvement was seen in 8(26.7%) patients of the chemoradiotherapy group and 6(20%) patients of the neoadjuvant chemotherapy group. Difference between groups is not statistically significant (p=0.54) (Table IV).

Residual tumor in neoadjuvant chemotherapy and chemoradiotherapy groups was detected in 14 (46.7%) patients and 25 (83.3%) patients, respectively. This difference in residual tumor mass detection was statistically significant (Table IV). The residual tumor size had no

Table IV. The frequency of parametrial involvement and residual tumor mass in neoadjuvant chemotherapy and chemoradiotherapy groups.

		Chemoradiotherapy	Neoadjuvant chemotherapy	P value
Parametrial involvement	Yes	8 (26.7%)	6 (20%)	0.54 (χ^2 =0.37)
	No	22 (73.3%)	24 (80%)	
Total		30 (100%)	30 (100%)	
Residual tumor mass	Yes	16 (53.4%)	25 (83.4%)	0.012 (χ^2 = 5.39)
	No	14 (46.6%)	5 (16.6%)	
Total		30 (100%)	30 (100%)	

Table V. The comparison of residual tumor size in neoadjuvant chemotherapy and chemoradiotherapy groups.

Treatment group / Tumor size	Chemoradiotherapy	Neoadjuvant chemotherapy	P value
<1 cm	5	8	0.91 (χ^2 =0.28)
1 – 2 cm	8	14	
>2 cm	3	3	
Total	16	25	

Table VI. The frequency of pathological responses in neoadju-vant chemotherapy and chemoradiotherapy groups.

Treatment group / Pathological response	Chemoradiotherapy	Neoadjuvant chemotherapy	P value
Complete	13(43.3%)	3(10%)	0.004 (χ^2=8.52)
Partial	17(56.7%)	27(90%)	
Total	30(100%)	30(100%)	

significant difference between groups (p>0.05). The residual tumor size in our cases is shown in Table V.

Complete pathologic response was significantly higher in the chemoradiotherapy group (p=0.004) (Table VI).

The frequency of complications in neoadjuvant chemotherapy and chemoradiotherapy groups in both pre-hysterectomy and post-hysterectomy situations are shown in Tables VII and VIII.

Table VII. The frequency of complications before radical hysterectomy in neoadjuvant chemotherapy and chemoradiotherapy groups.

Treatment group / Complication	Chemoradiotherapy	Neoadjuvant chemotherapy
Nausea & vomiting (grade 2)	16	20
Diarrhea	3	3
Constipation	0	1
Dermatitis	1	0
Urinary tract infection	1	0
Creatinine rise	0	3
Liver enzyme rise	0	1
Stomatitis	0	1

Table VIII. The frequency of complications after radical hysterectomy in neoadjuvant chemotherapy and chemoradiotherapy groups.

Treatment group / Complication	Chemoradiotherapy	Neoadjuvant chemotherapy
Fever*	2	2
Wound infection	2	2
Mild ileus	1	1
Vesicovaginal fistula	2	0
Hydronephrosis	4**	1***
Edema (foot)	1	0
Rectal prolapse	1	0
Intestinal obstruction	1	0

* For two days more than 38°C
** hydronephrosis grade 3 & 4
*** hydronephrosis grade 2

DISCUSSION

In this study clinical response was detected in all of the cases. In the chemoradiotherapy group 23.7 percent of patients had complete clinical response. In a study with the aim of finding the feasibility of a combined preoperative chemoradiation program (cisplatin plus 5-fluorouracil plus

external beam radiotherapy and intraoperative radiotherapy), followed by radical hysterectomy, complete clinical response was observed in 55% of patients. Also, complete pathological response was detected in 67.5%. [10] Comparison with our findings reveals that 5-fluorouracil and intracavitary radiotherapy induce a higher rate of clinical and pathological responses.

In our neoadjuvant chemotherapy group, complete and partial clinical responses were detected in 16.7% and 83.3% of cases, respectively. In the survey of Hwang et al. on survival of patients with locally advanced stage Ib-IIb cervical cancer after neoadjuvant chemotherapy (cisplatin, vinblastine and bleomycin) followed by radical hysterictomy, complete response was seen in 50 percent. [7] In the survey of Duenas-Gonzalez et al, clinical responses were seen in 41 patients (95%) [95% confidence interval (CI) 89.2% to 100%] with four (9%) complete and 37 (86%) partial. [16] In the study of Kodama et al, twenty-five patients with advanced cervical
treated with neoadjuvant chemotherapy followed by radical hysterectomy or radiotherapy. According to the evaluation by MRI, complete response was achieved in 2 (8%) cases and partial response in 17 (68%) cases. Eventually the response rate was 76%. The response rate was higher in squamous cell carcinomas (85%) than adenocarcinomas or adenosquamous carcino-mas (67%).[17] These results are near the results of our study.

In our study, tumor residual mass was detected in 83.3% of patients and lymph node involvement was reported in 23.4% of patients in the neoadjuvant chemotherapy group. In Hwang et al.'s study, residual tumor mass and lymph node involvement was detected in 25% and 21.3% of patients, respectively. [14] It can be related to bleomycin effectiveness in this study.

In the study of Kim et al. which cisplatin, vinblastine and bleomycin were used before radical hysterectomy in stage I and IIa tumors larger than 4cm, a complete response rate was reported in 44% and partial response rate in 50% of patients. In our study complete response rate was lower (10%), but partial response was detected in 90%. [2]

Relatively similar to our study, following the therapy of 151 patients, who had stage IIb and III tumors, with the combination of cisplatin, vinblastine and bleomycin before surgery, plus radiation or radiation alone, 25 patients (22%) revealed complete response to radiation. [2] Lymph node involvement was not reported in that study, [2] but it was 23.3% in our study.

In a study to evaluate the efficacy and safety of neoadjuvant chemotherapy followed by radical hysterectomy and adjuvant radiation concurrent with weekly cisplatin for locally advanced cervical carcinoma, forty-three patients staged as IB2-IIIB were treated with three 21-day courses of carboplatin (area under the time-concentration curve 6 mg.min/mL) and paclitaxel at 175 mg/m^2 by 3-h infusion both on day 1 followed by radical type III hysterectomy and adjuvant radiation concurrent with 6-weekly doses of cisplatin at 40 mg/m^2. All of the patients were evaluated for response and toxicity to neoadjuvant chemotherapy. A total of 129 courses were administered. Forty-one patients underwent surgery (resectability 95%); pathologically complete or near-complete responses were seen in seven (17%) and eight (20%), respectively, positive surgical margins in five (12%), and positive pelvic lymph nodes in eight (20%). Twenty-six patients were scheduled for adjuvant chemoradiation. External radiation was delivered for 42.8 days (range 33-61), with a mean dose of 49.3 Gy (range 46-56), and a median of five cisplatin courses (two to six). The mean dose of brachytherapy was 32 Gy (range 25.5-35.6). Neoadjuvant therapy was well-tolerated with neutropenia grade 3 and 4 in 12% and 3% of the courses, respectively. Toxicity to adjuvant chemoradiation was mainly hematological and gastrointestinal, mostly grades 1/2. A total of 39 patients completed all scheduled treatment. At a median follow-up of 21 months (range 3-26), the projected overall survival in the intention-to-treat analysis was 79% (95% CI 62% to 88%). The triple modality of neoadjuvant chemotherapy followed by radical hysterectomy and adjuvant radiation concurrent with cisplatin is a highly active treatment for locally advanced cervical carcinoma with acceptable toxicity. [16] Results of this study are comparable to results of our study.

According to our findings, there is no significant difference between neoadjuvant chemotherapy and chemoradiotherapy, in treatment efficacy and survival prognostic factors. In the chemoradiotherapy group, complications such as vesicovaginal fistula, rectal prolapse, intestinal obstruction, and grade 3 and 4 hydronephrosis which needed ureteral stenting were seen.

These results suggest that both neoadjuvant chemotherapy and chemoradiotherapy methods are responsible for improvement of operability in patients with stage Ib-IIb bulky cervical cancer, by decreasing the size of tumor. Neoadjuvant chemotherapy is a good modality which can decrease the size of tumors. In large tumors, central hypoxia decreases the effect of radiotherapy, so neoadjuvant chemotherapy can increase the effect of radiotherapy by decreasing the size of tumors. When there is not any

access to intracavitary radiotherapy, surgery will be the second choice after neoadjuvant chemotherapy.

Randomized clinical trials are needed to investigate the effect of neoadjuvant chemotherapy and chemoradiotherapy in patients with higher stages.

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