

# Comparative study of the effect of neoadjuvant chemotherapy followed by radical hysterectomy versus chemoradiotherapy in locally advanced cervical cancer (stage Ib2\_Ilb): a retrospective cohort study

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## ABSTRACT

**Background:** Despite many advances, locally advanced cervical carcinoma (LACC) is one of the most important and challenging stage in treatment of cervical cancer.

**Material and methods:** The present study is a retrospective cohort study that was conducted on 67 patients between 2012 and 2019. Inclusion criteria were patients with LACC( stage Ib2\_Ilb )that treated with NACT followed by RS (group 2) and chemo radiotherapy (group1). We evaluate staging of the disease, pathological indicators, indication of radiotherapy after surgery, duration of follow-up, the patient's condition at the last follow-up period and complications by studying patient's record. Data was analyzed using SPSS 20 and P<0.05 considered to be significant.

**Result:** In term of recurrence, 13(36.1%) cases in group 1 were shown a recurrence in two years after treatment and in group 2,2patiente (10.5%) have recurrences in two years. In terms of recurrence, significant differences was shown between the two groups (P = 0.04). There was no significant difference in mortality rate between two groups using Chi-square test. One and two -year-disease free survival were observed in 27 (75% )and in 21 (58.3% )in group1 and in 19 ( 100%) and in 17 ( 89.5% ) in group 2 respectively.The differences between two groups were significant (p=0.02 & p=0.03 ).Three- year- disease free- survival was observed in 13 (36.1%) and 10(52%) patients of group 1 and 2 respectively (p=.103) that was not significant.

**Conclusion:** This research has shown that NACT followed RS is superior to chemo radiotherapy in term of relapse and DFS in one and two years in LACC.

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## INTRODUCTION

Cervical cancer is increasingly recognized as a serious, worldwide public health concern. It is the second most common cancer in the world and the most common female cancer in developing countries(1, 2). International Federation of Gynecology and Obstetrics (FIGO) classified cervical cancer into three broad types: early stage (stage IA–IB1), locally advanced cervical cancer (stage IB2–IIB) , and advanced (stageIIIA- IVB )(3).The term locally advanced cervical carcinoma (LACC) is used to describe cervical carcinoma >4cm and stage IB2 or IIA2 (4). The treatment for cervical cancer is surgery or chemo radiotherapy. Surgical application is limited for Stage 1 to IIA and the 5-years survival prognosis is good. But LACC has a worse prognosis and mainly treated with chemoradiotherapy (5-7). Most studies in the field of cervical cancer have focused on neoadjuvant chemotherapy (NACT) followed by radical surgery (RS) in stage IB2/IIA2 despite that the primary treatment is concurrent chemo radiotherapy (CCRT) (8). However, there is still no general agreement on treatment of LACC because the result of NACT was inconsistent. Most study support this treatment due to advantages of it, such as cancer reduction and reducing the surgical problem which may improve patients' quality of life and other effects(9, 10).on the other hand, some researchers believe that

NACT followed by RS didn't improve overall survival(OS)(11).

The aim of this study to evaluate NACT followed RS versus chemoradiotherapy because there is no consensus on which treatment is optimal in LACC and radiotherapy may be have serious consequences in patients.

## MATERIAL AND METHODS

The present study is a retrospective cohort study that was conducted between 2012 and 2019 on 67 patients in oncologic center of Imam Khomeini Hospital after obtaining permission from the Ethics Committee of Tehran University of Medical Sciences (ethical code:43533). Inclusion criteria were patients with locally advanced cervical cancer that treated with NACT followed by RS and chemo radiotherapy. Exclusion criteria included other therapeutic options and insufficient registration of cases information. The data was collected by studying and reviewing patients' records and recording them in an information form. The researcher-made checklist included age of patient at the diagnosis time ,staging of the disease, pathological indicators, indication of radiotherapy or chemoradiotherapy after surgery, duration of follow-up ,the patient's condition at the last follow-up period , early onset complications( Hematologic complications and Toxicity due to

chemotherapy) and late bladder complications (vesicovaginal fistula), Intestinal complications included rectovaginal fistula, intestinal stenosis after radiotherapy; Vaginal atrophy; Hematologic complications due to chemotherapy such as Grade 3-4 Myelo suppression. Data was analyzed using SPSS 20 and  $P < 0.05$  considered to be significant.

**Treatment protocol:** Chemo radiotherapy (group 1): In this group patients received whole pelvic external radiotherapy and brachytherapy plus 5 cycle of cisplatin 40 mg/m<sup>2</sup> once weekly at the same time of external radiotherapy.

NACT followed by RS (group2): In this group, patients treated with paclitaxel 175 mg/m<sup>2</sup> and cisplatin (50mg/m<sup>2</sup>) once every three weeks. After the second and third chemotherapy cycle patients were evaluated in terms of response to treatment and if they had appropriate response after 3 cycles of treatment, they became candidate for radical surgery. After than they were undergoing radical hysterectomy type C and bilateral lymphadenectomy according Querleu-Morrow classification system. Patients in this group based on Postoperative histopathological results, may be treated with adjuvant radiotherapy alone or concomitant chemo radiotherapy.

#### Criteria for chemo radiotherapy after surgery:

Existence of worse prognostic factors including Positive surgery margins; Positive lymph nodes in postoperative pathology specimens and positive parameters.

Criteria for radiotherapy after surgery :

Tumor invasion more than a third of cervical stroma ; Presence of lymphovascular space invasion and tumor size more than 4 centimeter.

**Follow up:** Patients were evaluated once every 3 months and then once a year after treatment. Complications of radiotherapy ,chemotherapy and the presence or absence of recurrence ,time and place of recurrence are extracted from the files and also disease free survival after 1, 2 and 3 years was evaluated.

## RESULTS

In this present study 67 patients with stage 1B2-IIB cervical cancer were assessed. 45 individuals were treated by chemo radiotherapy and 22 cases with NACT followed by RS. The missing data was 12 patients due to lack of complete information. We used Mann-Whitney test to compare quantitative variables between the two groups. The mean age variable is also significantly higher in group 1, so that the mean age in The first group was  $49.42 \pm 10/10$  years and the mean age of the second group was  $42.77 \pm 8.21$  years ( $P = 0.012$ ). In our study there was also a significant difference in size of tumor between the two groups. In group 1, the average tumor size was 6 Cm with

the standard deviation 1.43 cm, and in group 2 average tumor size was 5.13 cm with the standard deviation 0.63 cm ( $P = 0.004$ )(table 1).

According to the Chi-square test, there wasn't a significant difference between the two groups in terms of tumor type ( $P=0.218$ ). The pathology of the tumor in 38 cases from group 1(84.4%) and in 20 cases from group 2 (90.9%) was squamous cell carcinoma.

In terms of stage of tumor, Chi-square test has shown a significant difference between the two groups. 5 cases (11.1%) in group 1 and 11 cases (50%) in group 2 were in Stage1b2. So that the highest rate in group 2 (50%) was in Stage1b2, but 89% of patients in group 1 were in Stage IIB ( $P = 0.001$ )

Out of 55 patients, 13 cases( 36.1% )in groups 1 and 2 cases (10.5% )in group 2 showed a recurrence and according Chi-square test this difference was significant( $P = 0.04$ ).

There was no significant difference in mortality rate between two groups using Chi-square test and death was happened in 3 patients(8.3%) in group 1 and one patient (5.3%) in group 2 ( $P=0.57$ ).

According Chi-square test, one year disease free survival was reported in 27 patients (75%) in group1 and 19 patients (100%) in group 2. This difference was statistically significant ( $p=0.02$ ).

Two years disease- free survival was reported in 21 patients (58.3%) in groups 1 and 17 (89.5%) cases group 2. Chi-square test has shown that difference was significant ( $p=0.003$ ).

Three year disease-free survival was observed in 13 (36.1%) and 10(52%) patients of group 1 and 2 respectively. According Chi-square test this difference was not significant ( $p=0.103$ )(table2)

Changes in complications were compared using Chi-square test and this difference was not statistically significant ( $P=0.749$ ). 10 patients (27.8%) in groups 1 and 4 Patients (21.1%) in group 2 had complications after treatment (table 3).

In group 2, four patients received radiotherapy after surgery (21.1%) and 10cases (52.6%) received chemoradiotherapy after surgery .5 patients (26.3 %) did not need any additional postoperative treatment (table 4).

Of the four patients who received radiotherapy after surgery, two cases (50%) were candidate due to deep invasion to cervical stroma and two cases (50%) due to deep stromal invasion plus Lymph vascular space invasion . Out of a total of 10 Patients who received complementary chemo radiation after surgery, 7 cases (70%) had positive pelvic lymph nodes, 1 case (10%) positive surgical margin, and two Cases (20%) the positive parameters.

Table1: Comparison between qualitative and quantitative variabilities.

	Group1	Group2	P-value
Age(year)* mean±sd	49.10±10.10	42.77±8.21	0.012
Stage(Frequency/Percent)**			0.0001
IB	5(11.1%)	11(50%)	
IIA	0	5(22.7%)	
IIB	40(88.9%)	6(27.3%)	
Pathology(Frequency/Percent)**			0.218
Squamous cell carcinoma	38(84.4%)	20(90.9%)	

Adwncarcinoma	2(4.4%)	2(9.1%)	
Others	5(11.7%)	0	
Size(cm)* mean±sd	6.00±1.43	5.13±0.63	0.004

\*Mann-Whitney test

\*\*Fischer-Exact test

Table2: Treatment outcomes between two groups / Fischer-Exact test

	Group 1	Group 2	P-value
DFS(1 year):			
no	9(25%)	0	
yes	27(75%)	19(100%)	
			0.02
DFS(2 years):			
no	15(41.7%)	2(10.5%)	
yes	21(58.3%)	17(89.5%)	
			0.030
DFS(3 years):			
no	16(44.44%)	3(15.78%)	
yes	13(36.11%)	10(52.63%)	
missing	7(19.44%)	6(31.57%)	
			0.103
Recurrence:			
no	23(63.9%)	17(89.5%)	
yes	13(36.1%)	2(10.5%)	
			0.040
Death:			
no	33(91.75)	18(94.7%)	
yes	3(8.3%)	1(5.3%)	
			0.570

Table3: Complications in two groups / Fischer-exact test

	Group1	Group2	P-value
Complications:			
no	26(72.2%)	15(78.9%)	
yes	10(27.8%)	4(21.1%)	
			0.749
Complication Type:			
Fistula	3(30%)	0	
G I	4(40%)	0	
Urinary	2(20%)	2(50%)	
Neurologic	1(10%)	0	
Vaginal Atrophy	0	2(50%)	

Table 4: Adjuvant treatment in group2

	Group2
Treatment after surgery:	
none	5(26.3%)
Radiotherapy	4(21.1%)
Chemoradiotherapy	10(52.6%)
Cause of Radiotherapy:	
Deep stromal invasion	2(50%)
Deep stromal invasion+LVSI	2(50%)
Cause of Chemoradiotherapy:	
Positive lymph nodes	7(70%)
Positive surgical margins	1(10%)
Positive parameters	2(20%)

## DISCUSSION

In Iran cervical cancer with a prevalence of 4.4 percent and a mortality rate of 50 percent has a special importance. According FIGO classification, treatment of early stages of cervical cancer is just, surgery but primary choice treatment option is chemo radiotherapy at the LACC stage (12-14). But relapse occurs in 25 to 40% of patients despite treatment(15). However, the observed difference between two groups in term of recurrence rate in this study was

significant. So that the recurrence rate was lower in group2. The cause may be explained by the larger tumor size, older age and the higher stage in group 1. On the other hand this finding did not confirmed by other study, So that they believed that recurrence and mortality rate were similar in two groups (16). In another study NACT could not improve prognosis and lymph node metastasis (17).

Current study found that one-and two- years- disease-free survival was higher in the NACT group but three-year-

disease free survival was not difference between two groups. The most interesting finding was that one –year-disease- free survival in NACT group was 100%. This finding supported by other study that disease- free- short interval increases in NACT (18, 19). In meta analysis that conducted by kim ,NACT did not improve long term survival(20). In the study by Gupta in term of DFS(disease-free survival) and OS(overall survival) ,chemo radiotherapy was superior than NACT followed RS.

The results of this study did not show statistically significant difference between the two groups in terms of complications following treatment. The reason is the small number of samples and the retrospective nature of the study. In the study by Guta the delayed toxicities at 24 months ,rectal, bladder and vaginal complication was higher in chemo radiotherapy group (21).

The most important clinically relevant finding was the not need for radiotherapy in five (26.3% ) Patients after surgery. Because radiotherapy is related with early and long-term toxicity so that it seems that NACT followed by RS and it is a promising therapeutic option(22). It seems that neoadjuvant chemo therapy can improve the patient's quality of life by reducing the need for radiotherapy. NACT can shrinkage tumor, decrease problem of surgery and improve outcome(23).

## CONCLUSION

The present study was designed to determine the comparative effect of NACT followed RS versus chemo radiotherapy. This research has shown that NACT followed RS is superior to chemo radiotherapy in term of relapse and DFS in 1 and 2 year in LACC.

**Limitation:** The retrospective nature of the study, the small number of subjects included in the study and the inability to long term follow up were the limitations of the present study.

**Strength:** In this study, all patients were evaluated at intervals, first every three months and then at least up to 3years.

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