Four-year overall survival comparison between Radical Hysterectomy after Neoadjuvant chemotherapy and concurrent chemo-Radiation in stage IB2-IIB in cervical cancer patients

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Abstract

Background: In this study, the response of the patients with stage IB2-IIB cervical cancer to the treatment using radical hysterectomy (RH) and neoadjuvant chemotherapy (NACT) was compared with the patients who received only chemoradiotherapy.

Material and Methods: In this retrospective study, we compared 59 and 23 patients with stage IB2-IIB cervical cancer receiving CRT and NACT + RH, respectively, between 2014 and 2019. The disease recurrence, mortality, and survival rate were analyzed in these patients.

Results: In the RH group, 7 (30.4%), 2 (8.7%), and 14 (60.9%) patients were stage IB2, IIA, and IIB, respectively. In the control group, the patients were distributed in the stages IB2, IIA, and IIB as 28 (47.5%), 2 (3.4%), and 29 (49.2%), respectively. The disease recurrence was 11 (18.6%) and 0 patients for the control and study group. The mortality was reduced in the study

group; 11 (18.6%) vs. 2 (8.7%) patients. The survival rate was increased when the patients underwent NACT+RH; 91.3% compared with 81.4% of the patients ($p< 0.0001$)

Conclusion: Neoadjuvant therapy followed by radical hysterectomy for patients with cervical cancer increases the patients' survival, improves the disease prognosis, lowers the risk of disease relapse, and enhances the benefits of the treatment for patients.

Keywords: Neoadjuvant chemoradiotherapy, Radical hysterectomy, Cervical cancer, Neoadjuvant chemotherapy.

Introduction

Since 2018 cervical cancer has become an important issue to be eliminated due to its high prevalence among women.[1,2] Despite its treatable nature, it burdens a very high cost and mortality rate in low- and middle-income countries (LMIC) due to the underdeveloped hygiene standards where most of death (80-90%) occurs.[3,4] According to the global strategy of the World health organization (WHO), three main objectives should be followed to reduce cervical cancer-related mortality, including the screening of women twice during their lifetime, vaccination of girls under the age of 15, and the treatment of the women diagnosed with early-stage cervical cancer by 2030.[1] Cervical cancer has been staged in 4 groups according to the Federation of Obstetrics and Gynecology (FIGO) 2009 criteria. The detection of the disease at earlier stages could be lifesaving; however the large size, rapid spreading to the lymph nodes and high rate of metastasis, high proliferative characteristic of the cells, and great tendency to recurrence reduces the survival rate in late-stage diagnosed patients.[5]

Choosing the appropriate method in locally advanced cervical cancer (LACC) treatment is controversial,[6] nonetheless, concurrent chemo-radiotherapy (CRT) remains a preferred approach. However, in LMIC, the frequently applied method is neoadjuvant therapy followed by surgery and then complementary radiotherapy if necessary.[7,8] Radical hysterectomy followed by adjuvant therapy is the selective treatment for early-stage cervical cancer or for patients requesting to preserve ovarian function.[9,10] Definitive CRT is the suggestive method for patients with bulky tumors or non-operable patients and those with higher risk factors for morbidity after surgery.[11] Despite all these efforts, the recurrence and distal metastasis of the disease are still seen in 25-40 % of the patients.[12]

Recent studies suggested a neoadjuvant therapy combined with the radical hysterectomy for stage IB2 to IIB patients with cervical cancer. Still, there is no confirmed document approving the results of these investigations. In this retrospective study, we will compare the 4-year survival rate of the patients undergoing radical surgery following neoadjuvant chemotherapy (NACT) compared with patients receiving only CRT.

Materials and methods

Patients' information

Patients diagnosed with stage IB2-IIB cervical squamous cell carcinoma referred to Alzahra Hospital, Tabriz, Iran, voluntarily participated in this full-scale retrospective cohort study from March 2014 to March 2019. The clinical data of the patients were collected and analyzed. According to the recorded data sheets, patients were divided into two groups; the control group included patients who received standard CRT, and the study group consisted of patients undergoing radical hysterectomy and neoadjuvant therapy. The study was carried out with the approval of the ethics committee of the Tabriz University of medical sciences (code: IR.TBZMED.REC.1401.1074) and by obtaining an informed consent form from the patients.

Inclusion and exclusion criteria

To participate in the study, patients must be of reproductive age and be diagnosed with cervical squamous cell carcinoma (stage IB2-IIB) according to FIGO staging criteria. Also, the clinical information of the patients must be complete. The time interval between diagnosis and treatment should not be more than 3 weeks. For the study group, the size of the tumor after 3 cycles of neoadjuvant therapy should be reduced by at least 50%. Patients of both groups will be matched in terms of age and time interval between disease diagnosis and treatment initiation.

Exclusion criteria include receiving targeted therapy before this treatment, previous chemo- or radiotherapy, the presence of other types of malignancies, resistant or progressive tumors, menopause, and pregnancy.

Treatment regimen

Control group (group 1): During the standard CRT, the patient undergoes 25 sessions of pelvic radiotherapy with chemotherapy (weekly cisplatin) and then brachytherapy.

Study group (group 2): The patients who received 3 cycles of NACT and in response, the tumor size was reduced at least to half (>50%), followed by a radical hysterectomy and pelvic lymphadenectomy and, if necessary, para-aortic lymphadenectomy. The dosage of chemotherapy agents was determined as Cisplatin in 50mg/m2 and Taxel in 175mg/m^2 every 3 weeks for 3 cycles.

Clinical data collection

Patient information was extracted from the hospital files or the patients themselves. The variables include age, place of birth, gravidity, parity, abortion history, type of surgical and non-surgical treatments performed, type of adjuvant treatment, number of chemotherapy cycles, sexual function, digestive, urinary, and Peripheral neuropathy, the time interval between diagnosis and start of the treatment, recurrency, cause of death and four-year survival.

Pathological data collection

The clinical data specified to the tumor condition was collected from the pathological reports for each patient, including the stage of the tumor, involvement of the lymph nodes, pathological

type of the tumor, metastasis to the distal organs, the frequency of disease recurrence, and the place of recurrence.

Statistical analysis

Frequency (percentage) and mean (standard deviation) was used to describe quantitative data using SPSS version 26 statistical software. Quantitative data were analyzed using the Kolmogorov-Smirnov test to check the normality of the data. In order to compare the qualitative data in 2 groups, a chi-square test, and for quantitative data, if normal, an independent t-test, and if non-normal, the Mann-Whitney U test were used. *P-value* < 0.05 was considered significant for all tests.

Results

Patients' characteristics

Patient characteristics are provided in (Table 1). 59 patients receiving CRT were compared with 23 patients receiving NACT before undergoing radical hysterectomy. The patients' age distribution was similar and was 54.81 ± 12.34 for group 1 and 51.09 ± 9.91 for group 2, on average. The patients on average experienced 3 pregnancies with no abortion history. 78% of the patients were related to urban populations, while only 4% lived in rural societies.

Table 1. Baseline patients' characteristics.

Variables	Control group (n = 59)	Study group (n = 23)	P-value
Age (year)			
Mean ± SD	54.81 ± 12.34	51.09 ± 9.91	*0.09*
Gravidity			
Median (min-max)	4 (0-11)	3 (1-11)	*0.07*

Live children			
Median (min-max)	3 (0-8)	2 (1-7)	*0.27*
Abortion			
Median (min-max)	0 (0-4)	0 (0-4)	*0.22*
Place of birth			
Urban	56 (94.9)	22 (95.7)	*0.88*

Pathological information

The patients in both groups were recognized with cervical squamous cell carcinoma, 59 patients received only CRT, and 23 underwent a radical hysterectomy after NACT. Time intervals from the start of the disease symptoms to diagnosis in both groups were 1-3 months. In the control group, 29 (49.2%) patients were diagnosed with stage IB2, 2 (3.4%), and 28 (47.5%), were diagnosed with the stages IIA and IIB, respectively. In the second group, the majority of the patients were categorized as stage IB2 (14 patients; 60.2%), and the remaining (2 and 7 patients; 8.7% and 30.4%) were diagnosed with stages IIA and IIB, respectively (Table 2).

Table 2. Patients' pathogenic data.

Variables	**Control group (n = 59)**	**Study group (n = 23)**	**P-value**
Time interval between diagnostics and treatment median (min-max)	1 (1-3)	1 (1-3)	0.78
Tumor stage n (%)			
IIB	28 (47.5)	7 (30.4)	
IIA	2 (3.4)	2 (8.7)	0.28
IB2	29 (49.2)	14 (60.9)	

Treatment complications

Sixteen patients (27.1%) in group 1 and 3 patients (13%) in group 2 experienced gastrointestinal complications ($P < 0.0001$). Cramp was the most common complication in group 1. Urinary complications were in the 7 patients (11.8%) in the control group; however, patients who underwent radical hysterectomy showed no urinary symptoms.

Urinary incontinence was the most complication. The most common side effect due to CRT was sexual dysfunction which occurred in 94.9% of patients; however, 11 patients (47.8%) in group two complained of sexual dysfunction. The peripheral neuropathy in the control and study group were 42.4% and 52.2%, respectively ($P < 0.0001$, Table 3).

Table 3. Treatment complication.

Variables	**Control group (n = 59) n (%)**	**Study group (n = 23) n (%)**	**P-value**
Sexual			
Decreased libido	5 (8.5)	5 (21.7)	
vaginal dryness	20 (33.9)	1 (4.3)	*< 0.0001*
Decreased libido+ vaginal dryness	31 (52.5)	5 (21.7)	
Gastrointestinal			
Diarrhea	1 (1.7)	0 (0)	
Constipation	7 (11.9)	1 (4.3)	*< 0.0001*
Cramp	8 (13.6)	2 (8.7)	
Urinary			
Incontinence	1 (1.7)	0 (0)	
Incontinence+retention	41 (69.5)	21 (91.3)	*< 0.0001*
Peripheral neuropathy	25 (42.4)	12 (52.2)	*< 0.0001*

Clinical outcome

The results were analyzed with four important aspects: recurrence, death, cause of death, and 4-year survival. Data demonstrated that radical hysterectomy has significantly reduced the recurrence of the disease i.e., 11 patients (18.6%) were recognized with disease recurrence in the control group. In contrast, no recurrence was reported in the study group ($P < 0.0001$).

Moreover, the mortality rate was significantly decreased in the patients undergoing radical hysterectomy, where 8.7% of patients died in patients who underwent operation compared with 18.6% of patients in the control group ($P < 0.0001$).

The data demonstrate the most common case death in the main group was disease recurrence (54.6%), which was significantly less than the study group. In the control group, 6 patients (54.5%) died from disease recurrence. In contrast, the remaining had different reasons, including myocardial infarction (MI) in 27.3%, uncontrolled diabetes in 9.1%, and pulmonary embolism in 9.1% of the patients. Furthermore, the cause of all deaths in the study group has disease recurrence.

The data demonstrated that 91.3 % of the patients (n=21) and 81.4% (n=48) in study and control group, respectively, survived for at least 4 years.

Table 4. Clinical outcome compression between the control and the study group.

Variables	**Control group (n = 59)** **n (%)**	**Study group (n = 23)** **n (%)**	**P-value**
Recurrence	11 (18.6)	0 (0)	*< 0.0001*
Death	11 (18.6)	2 (8.7)	*< 0.0001*
Cause Of Death			
Recurrency	6 (54.5)	2 (100)	
Pulmonary embolism	1 (9.1)	0 (0)	
MI	3 (27.3)	0 (0)	
Uncontrolled diabetes	1 (9.1)	0 (0)	
4-year survival	48 (81.4)	21 (91.3)	*< 0.0001*

MI: myocardial infarction.

Discussion

Cervical cancer is the fourth leading diagnosed malignancy worldwide. A global study about the prevalence of 36 cancers in 186 countries revealed that cervical cancer accounts for approximately 750,000 newly diagnosed cases (6.6% of all new cases of malignancies in women) and 310,000 annual deaths (7.5%).[13,14] Despite many efforts that have been made to increase the clinical outcome of these patients, 30% of women with cervical cancer fail to benefit from the favorable results and show a poor prognosis.[15]

This study compared the clinical outcome of the patients with cervical squamous cell carcinoma receiving CRT or NACT+RH. NACT is a beneficial method in the treatment of many types of cancer due to: a) the bed of the vascular tissue before radiation therapy is intact and the effectiveness of the chemo-agents in this site is much higher; b) NACT eliminates the hypoxic

cells, thus expands the efficiency of the radiation therapy; c) it reduces the tumor size and infiltration, improves the tumor environment for surgery by reducing the possibility of tumor recurrence after hysterectomy; d) neoadjuvant chemo agents improves the management of the subclinical lesions thus reduces the possibility of disease recurrence and metastasis.[16,17]

This study demonstrated that the patients receiving CRT alone suffered more gastrointestinal, urinary, and sexual symptoms due to the CRT side effects. Gastrointestinal and sexual symptoms were two main side effects of the drugs for these patients. Radical hysterectomy reduced the need for the repeat of the chemotherapy cycles, thus leading to less suffering from the severe side effects of these agents. The history of medical treatments for cervical cancer is mainly known with chemotherapy. Still, nowadays, in many countries, it has widely accepted that the NACT, besides the radical hysterectomy, is more beneficial for patients.[18] Our results were in concordance with these reports showing improved management of the disease with reduced symptoms induced by high dosage of the chemo agents. Despite these favorable results, a study performed in 2018, reported that the NACT followed by a radical surgery shows a similar outcome to the radical hysterectomy alone, and even the repetition of the radiotherapy cycles simultaneously with chemotherapy showed no significant difference in the result.[19,20]

In this study, in the control group 43 patients didn't need to receive any neodjuvant treatment after CRT while in the study group only 16 of 23 patients did not receive NACT. moreover, in the control group, 16 patients out of 59 underwent NACT (27.11 %) however, in the study group, only 7 patients of all 26 patients underwent NACT (30.4%) where in 5 of 7 patients (71.4%) NACT was continued and 2 of 7 (28.5%) underwent radiotherapy. The results of the current study claimed that the disease recurrence was significantly reduced in the patients undergoing radical hysterectomy + NACT. In a study on 91 patients with stage IB2 cervical cancer who

received CRT, radical hysterectomy with/without NACT, or NACT reported no significant difference in clinical outcome.[21] Another study showed that 18.3% of patients were recognized with positive lymph nodes in their pelvis and the disease relapsed in 17.2% of them.[22] Our data showed that 18.6% of the patients who received CRT treatment and none who received NACT+RH experienced disease recurrence. Moreover, our results showed a significantly reduced mortality rate in the patients receiving RH followed by NACT (8.7%) compared to the control group (18.6%). 6 patients (54%) in the control group died due to disease recurrence and multiple metastases. The cause of death for the two dead patients in the study group was the multiple metastases of the cancer cells. Furthermore, our results showed a significant increase in the 4-year survival of the patients treated with NACT+RH. Mousavi et al[23] reported an increased survival rate in 79% of the cervical cancer patients after the NACT followed by RH, which was in accordance with our data. We showed that the survival rate might be higher and reaches 91.3%.

NACT before radical surgery significantly reduces the tumor volume and progression and improves the patient's prognosis leading to a decreased recurrence rate. It also helps to reduce surgical complications, including bowel and bladder injury due to extensive surgery.[15] The current study has the following limitations: 1) non-uniformity of the patient population, 2) Lack of completeness of patients' medical records, and lack of access to complete information of patients who died.

Conclusion

Neoadjuvant therapy accompanied by radical hysterectomy for patients with cervical cancer increases the patients' survival, improves the disease prognosis, lowers the risk of disease

relapse, and enhances the benefits of the treatment for patients. The shortened cycles of chemotherapy reduce the complications induced by chemo-agents.

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Conflict of Interests

The authors declare that they have no conflict of interest.

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