RESEARCH ARTICLE

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The Feasibility and Safety of Induction Chemotherapy Followed by Definitive Chemoradiation in Patients with Locally Advanced Cervical Cancer: A Single-Arm Phase II Clinical Trial

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Abstract

Background: The present study aimed at investigating the feasibility and safety of induction chemotherapy followed by definitive chemoradiation (dCRT) in patients with locally advanced cervical cancer. **Materials and Methods:** In this single-arm clinical trial, patients with cervical cancer (stages IB3-IVA) received a median four cycles of induction chemotherapy (paclitaxel and carboplatin, every three weeks) followed by dCRT (which consisted of the whole pelvis at the dose of 45-50 Gy along with weekly cisplatin (40 mg/m^2) followed by intracavitary brachytherapy at the total dose of 80-90 Gy). Primary end point was local control at three months, which was assessed by gynecologic examination and pelvic MRI. The secondary outcome of the study was treatment-related toxicity. **Results:** Seventy-four patients with the mean age of 51.6 ± 9.5 years were included. The most frequent (51.4%) disease stage was IIB. Complete and partial clinical responses were observed in 60.8% and 14.9% of patients, respectively. The frequency of progressive disease and stable disease were 14.9% and 9.5%, respectively. Grade II and III neutropenia (during neoadjuvant chemotherapy were 13.5% and 2.7%, respectively; these figures during chemoradiation were 29.7% and 13.5%, respectively. A treatment interruption was observed for 60.8% (45 cases) of patients during chemoradiation and 31.1% during induction chemotherapy. **Discussion and conclusion:** Induction chemotherapy followed by chemoradiation is feasible in patients with locally advanced cervical cancer; however, the toxicity should be managed properly to avoid delayed e treatment. More than three quarters of the patients achieved complete or partial clinical response within a three-month follow-up.

Keywords: Locally advanced cervical cancer- induction chemotherapy- definitive chemoradiation

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Introduction

Cervical cancer is one of the most common cancers of the female reproductive system, and is the leading cause of cancer-related deaths in women, especially in developing countries. The frequency of cervical cancer is varying in different parts of the world. While cervical cancer is the second most common cancer in developing countries, this cancer ranks the tenth place in developed countries (Jemal et al., 2011). Overall, the survival of patients with cervical cancer is dismal and even in the early-stage of disease, only 80% of patients will survive up to five years. At higher stages, the 5-year survival drops to 50-60 % when it is confined to the pelvis (Balasubramaniam et al., 2021).

There are three main treatment modalities for cervical cancer, which include surgery, radiotherapy, and chemotherapy. The choice of surgical treatment in patients with cervical cancer and its type depend on the cancer stage specified by the International Federation of Gynecology and Obstetrics (FIGO) staging system. The standard treatment for patients with bulky cervical cancer in stages IB2–IVA has been chemoradiation over the

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past decade. The results of five published clinical trials (three of them exclusively addressed locally advanced patients) revealed a significant improvement in the overall survival and disease-free survival as a result of using chemoradiation treatment. This finding changed the direction of treating this group of patients worldwide (Keys et al., 1999; Morris et al., 1999; Peters et al., 2000; Rose et al., 1999; Whitney et al., 1999).

Recently, more intense treatments have been of interest. A relatively large randomized phase III clinical trial by Dueñas-González et al. investigated the concurrent chemoradiation with the gemcitabine/cisplatin regimen. This approach was followed by surgery, after the completion of which two additional cycles of this regimen was prescribed as an adjuvant treatment (Duenas-Gonzalez et al., 2011). Although their study showed a 9% improvement in the three-year progression-free survival, this approach is still not considered as a standard approach due to its considerable toxicity. Currently, some studies have been conducted regarding the usefulness of adding chemotherapy before (ongoing INTERLACE trial) or after (OUTBACK) chemoradiation. However, none of the proposed approaches have been associated with positive results (Marth et al., 2017).

The rationale for using the neoadjuvant chemotherapy approach in patients with cervical cancer has been to reduce the size of the primary tumor, increase the probability of complete resection, eradicate micrometastases, potentially increase blood supply to tumors, and reduce hypoxic cells. The findings of a meta-analysis showed that neoadjuvant chemotherapy followed by surgery, as compared to radiotherapy, was associated with a 35% reduction in the risk of death (p=0.00004 and HR=0.65), and improved patient survival by 14% (from 52% to 64%) (Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration, 2003). In that study, 872 patients with locally advanced cervical cancer enrolled in five different clinical trials were evaluated. In this study, 441 patients with FIGO stage IB2-III cervical cancer were subjected to a secondary meta-analysis, and neoadjuvant chemotherapy based on cisplatin followed by radical surgery was compared to conventional radiotherapy. The most important problem of the studies included in this meta-analysis was their insufficient radiotherapy dose such that brachytherapy was not performed in 27% of the patients, and the prescribed dose to point A was less than 60 gray (Gy) in 11% of the patients. Moreover, in all the evaluated studies, the control group included patients treated with radiotherapy alone, which is currently not the standard treatment for patients with advanced cervical cancer; presently, concurrent chemoradiation is the standard treatment for this group of patients. Therefore, the present study was designed to investigate the treatment response to induction chemotherapy followed by chemoradiation in patients with locally advanced cervical cancer.

Materials and Methods

This single arm non-randomized phase II clinical trial included patients with cervical cancer admitted to the radio-oncology department of Namazi Hospital in Shiraz, Iran in 2020. According to a 2016 study by Narayan and colleagues (Narayan et al., 2016), considering alpha equal to 5% and the formula n=(Z_(1-α⁄2)^2 pq)/d^2 (p = 84%, d = 0.10 , Z= 1.96), the sample size was calculated to be 74 patients by considering the 10% drop of the initial 81 patients. Non-random and consecutive sampling was done among patients with cervical cancer that met the inclusion criteria of the present study. Inclusion criteria consisted of all women providing the signed written consent with newly diagnosed cervical cancer, the age of more than or equal to 18 to 75 years, the functional status of less than two based on the Eastern Cooperative Oncology Group (ECOG), the confirmed diagnosis of squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma by histology, the early clinical stage IB3, IIA with the size of larger than 4 cm, IIB-IVA in gynecologic examinations based on FIGO staging system, the adequate bone marrow function (neutrophil count of more than 1,500, hemoglobin level of higher than g 10/dL, and platelet count of more than 100 x 10^3), the appropriate liver function (liver enzyme level of less than 5 times normal, bilirubin level of less than 1.5 times normal, and alkaline phosphatase level of less than 5 times normal), and adequate renal function (mL/ min60< glomerular filtration rate (GFR)). The exclusion criteria included pregnancy, previous pelvic radiotherapy, presence of grade two or higher neuropathy, history of hypersensitivity reactions to paclitaxel or cisplatin, serious medical illness (severe heart, liver, or renal failure), presence of other concurrent malignancies, distant metastasis, hearing impairment, and presence of contraindications for magnetic resonance imaging (MRI) with injectable contrast. Moreover, the exclusion criteria during the study encompassed the neoadjuvant treatment discontinuation, lack of response and disease progression, failure to refer for gynecologic examinations, and failure to refer for brachytherapy. The study protocol was approved by the Research Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1400.173). The study was then registered in the Iranian Registry of Clinical Trials (IRCT) (IRCT20210808052110N1).

First, the eligible patients' demographic and clinical information such as age, sex, medical and surgical history, and physical examination along with the clinical stage based on the 2018 FIGO staging system were recorded using the data collection form. Patients' height and weight were measured before treatment. Moreover, body mass index (BMI), body surface area (BSA), and glomerular filtration rate (GFR) were calculated for each patient. All patients were examined by the gynecologic oncology fellowship who checked the position, characteristics, and stage of the tumor.

The diagnosis of squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma of the cervix was confirmed by pathological evaluation on the sample obtained from the biopsy of the cervix. Then, the patients were visited by the gynecologic oncology fellowship surgeon, and if the cancer was considered locally advanced, they were referred to the radio-oncology clinic to receive definitive chemoradiation (dCRT)

treatment. Before starting the treatment, all patients underwent a gynecologic examination, pelvic MRI with and without injection, computerized tomography (CT) scan of abdomen and pelvis, chest CT scan, or chest X-ray (CXR). Moreover, the clinical staging of the tumor was performed using the 2018 FIGO staging system. The patients' functional status was evaluated based on the ECOG performance status scale. Moreover, laboratory parameters such as complete blood count (CBC), liver function test (LFT), renal function test (RFT), and electrolytes were measured for all patients prior to the initiation of the treatment. After obtaining written informed consent, the induction chemotherapy was prescribed every three weeks for four cycles with the carboplatin (area under the curve: 5) and paclitaxel (175 per square meter) regimen before chemoradiation and brachytherapy. Before each cycle of chemotherapy, patients were visited and examined every time. In addition to controlling the treatment complications, CBC, LFT, and RFT were checked as well.

After completing the induction chemotherapy cycles and controlling CBC, LFT, and RFT, the patients underwent chemoradiation of the whole pelvis. To do so, at first, patients were subjected to CT scan with SOMATOM Definition AS Siemens scanner (Siemens Healthcare GmbH, Erlangen, Germany), and the obtained images were transferred to the treatment planning system through a DICOM network (INFINITT). Then, treatment volumes including gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were drawn on the prepared images. The information obtained from the gynecologic examination and MRI before radiotherapy was used to determine the GTV. Next, tumor CTV or CTV1 was defined as covering the entire uterus, cervix, and gross tumor (excluding muscles, small intestine, and bones). In order to draw PTV1, a margin of 15 mm was added to CTV1. Subsequently, CTV2 was added to cover the parameters and one-third to the upper half of the vagina. Moreover, a margin of 10 mm was added to CTV2 to draw PTV2. Finally, to cover the pelvic lymph nodes, CTV3 was drawn by covering internal iliac, external iliac, common iliac, and pre-sacral lymph nodes, and PTV3 was obtained by adding 7 mm margin to CTV3.

The radiotherapy complications including diarrhea, proctitis, non-infectious cystitis, and hematological disorders were graded (grades 1 to 5) based on the radiotherapy oncology group (RTOG) criteria and the 5th version of the common terminology criteria for adverse events (CTCAE). Severe complications equal to RTOG grades three/four were defined as the patient required hospitalization during induction chemotherapy or chemoradiation. Just after completion of chemoradiation, the volume-based 3D planning for each tandem and ovoid insertion of HDR brachytherapy were used to keep the whole treatment time less than nine weeks. Although most patients in our study suffered from locally advanced tumors, all patients underwent brachytherapy using tandem and ovoid because of lack of access to interstitial brachytherapy.

Evaluation of treatment response was performed by the gynecologic examination, Pap smear, and pelvic MRI three months after the completion of all treatments. If there was a suspicious result in any of the examinations (feeling a cervical mass in the gynecologic examination, abnormal Pap smear results, or abnormal signal of cervix in pelvic MRI), consultation with gynecological oncology fellowship was done to obtain a biopsy.

The primary and secondary outcomes of the study were the response rate in the three-month follow-up and complications, respectively. Response evaluation criteria in solid tumours (RECIST) criteria were used to evaluate the primary outcome. According to the mentioned criteria, the patients were divided into four categories: complete response (i.e., the absence of all malignant lesions with less than 10 mm lymph node size), partial response (i.e., at least 30% reduction in the size of the malignant lesion), progressive disease (i.e., an increase of at least 20% in the size of the malignant lesion), and stable disease (i.e., not having enough characteristics to be included in the progressive and relative disease criteria). Patients were then followed up during induction chemotherapy every three weeks (before each cycle of chemotherapy) and weekly during chemoradiation in terms of acute toxicity and acceptance of the treatment protocol. Finally, the effectiveness and safety of the treatment protocol were evaluated.

The collected data were analyzed using Statistical Package for Social Sciences (SPSS) v. 24. Statistical indicators such as frequency, percentage, mean, and standard deviation were used to describe the data. Graphs and tables were drawn to graphically represent and tabulate the data. Inferential statistics including Chi-square and Fisher's Exact Test were used to compare qualitative data. In order to compare patients' age and duration of treatment regarding the treatment response in the three-month follow-up, normal distribution of data was checked using the Kolmogorov-Smirnov test, which showed the normal distribution of this variable in the studied population. Then, one-way analysis of variance (ANOVA) was used. Considering the significance of the ANOVA test results regarding the duration of treatment, Tukey's post hoc test was used to compare the two groups. The significance level for the tests was considered 0.05.

Results

In the present study, 74 patients with cervical cancer with the mean age of 51.6 ± 9.5 years (median 52.0 and range 30-70 years) were subjected to induction chemotherapy, chemoradiation, and brachytherapy during the study period, and their response rate was addressed by evaluating pelvic MRI images after treatment, Pap smear results, and gynecologic examinations three months after treatment. The patients' entrance into the study is shown in Figure 1.

Majority of the patients were in stage IIB based on the 2018 FIGO staging system (51.4%, 38 cases). Moreover, most patients had squamous cell carcinoma (85.1%, 63 cases). Regarding the external radiotherapy, 59 patients (79.7%) only underwent whole pelvic treatment without para-aortic region (Table 1).

In terms of treatment response, the results of the

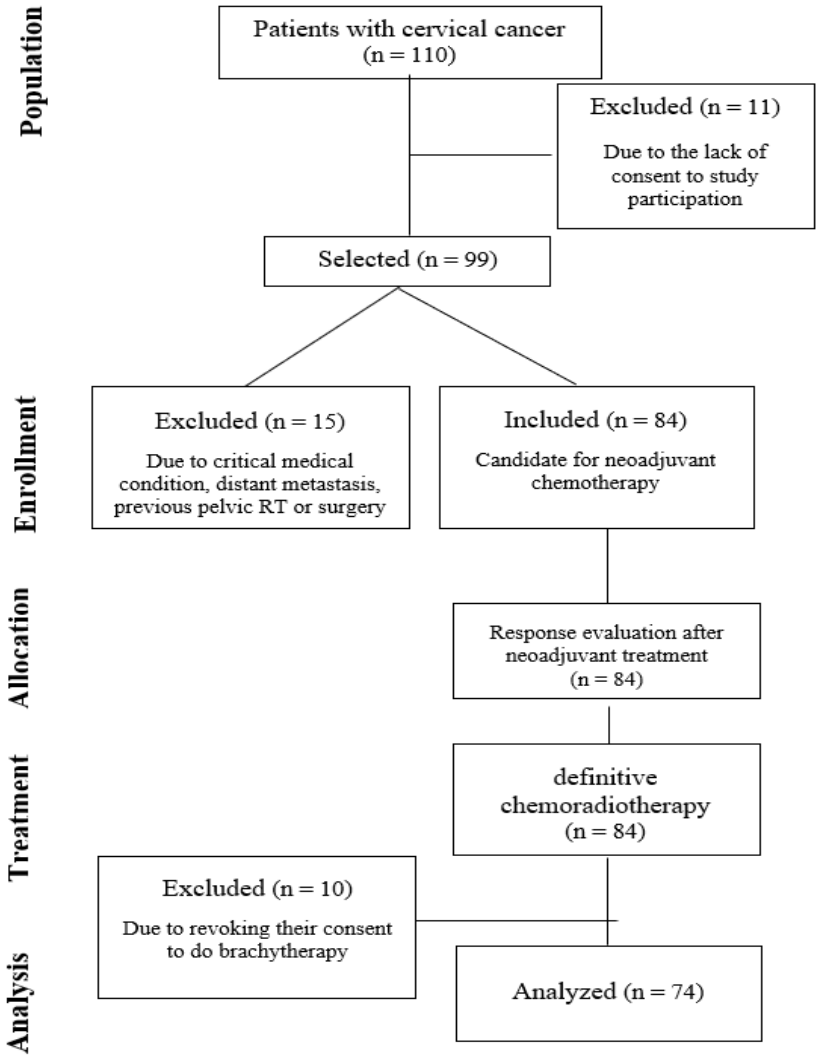

Figure 1. Flowchart of Patients Entering the Study

three-month follow-up of patients with cervical cancer undergoing induction chemotherapy followed by chemoradiation and brachytherapy based on RECIST criteria revealed that 60.8% of patients (45 cases) had a complete response to treatment while 14.9% of them (11 cases) had partial response. The frequency of progressive and stable diseases were 14.9% (11 cases) and 9.5% (7 cases), respectively.

Table 1. Patients' Demographic Characteristics

	Frequency	Percentage
FIGO stage		
IB3	3	1.4
IIA2	4	4.5
IIB	38	51.4
IIIA	4	4.5
IIIB	6	8.1
IIIC1	4	4.5
IIIC2	15	20.3
Histology		
SCC	63	85.1
Adenocarcinoma	6	8.1
Adenosquamous carcinoma	5	6.8
Treatment field		
Whole pelvis	59	79.7
Whole pelvis and para-aorta	15	20.3

The most severe hematological complication were grade two and three neutropenia (during induction chemotherapy: 13.5% and 2.7%, respectively; during chemoradiation: 29.7% and 13.5%, respectively). In total, the occurrence of complications was associated with the temporary treatment discontinuation in 60.8% of patients (45 cases). Temporary treatment discontinuation was reported in 31.1% of patients (23 cases) under induction chemotherapy and in 56.8% of patients (42 cases) under chemoradiation (Table 2 and Figure 2).

The mean age of patients with complete response, partial response, progressive disease, and stable disease were 51.6 ± 10.3 years, 50.9 ± 10.6 years, 52.6 ± 7.5 years, and 51.2 ± 6.6 years, respectively (p=0.980). Complete pathological response was reported in 66.7% of stage IB3 patients, 75% of stage IIA2 patients, 73.7% of stage IIB patients, 25% of stage IIIA patients, 50% of stage IIIB patients, 50% of stage IIIC1 patients, and 40% of stage IIIC2 patients (p=0.179). Complete pathological response

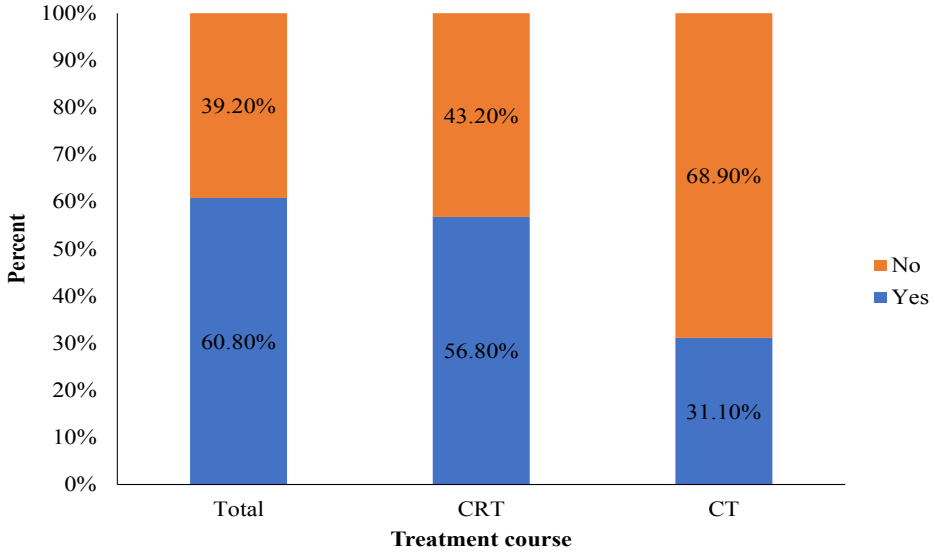

Figure 2. Distribution of the Temporary Treatment Discontinuation due to the Occurrence of Complications in the Treatment of Patients with Cervical Cancer Undergoing Induction Chemotherapy Followed by Chemoradiation and Brachytherapy

in patients with and without delay in chemotherapy were reported to be 47.8% and 66.7%, respectively (p=0.369). Complete pathological response was similar in patients with and without delay in chemoradiation (59.4% vs. 61.9%, respectively, p=0.910). Complete pathological response in patients with squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma were reported to be 60.3% (38 cases), 66.7% (4 cases), and 60% (5 cases), respectively (p=0.444). Examining the response rate in patients with cervical cancer undergoing induction chemotherapy followed by chemoradiation and brachytherapy indicated no significant association in terms of treatment delay regardless of its type (p=0.857). Complete pathological response was similar in patients with and without treatment delay (57.8% vs. 65.5%, respectively, p=0.857).

The comparison of the mean duration of treatment according to treatment response in patients with cervical cancer undergoing induction chemotherapy followed by chemoradiation and brachytherapy is presented in Figure 3. The mean duration of treatment in patients with complete response, partial response, progressive disease, and stable disease were 151.1 ± 6.9 days, 159.6 ± 9.1 days, 157.4 ± 9.8 days, and 154.2 ± 6.5 days, respectively. The result of ANOVA test showed a significant difference between the compared groups (p=0.008). Furthermore, the result of Tukey's post hoc test showed that only the mean duration of treatment in patients with complete response was significantly less than the mean duration of treatment in patients with partial response (p=0.014), and no association was observed between the other subgroups compared.

Discussion

Cervical malignancies are among the most common malignancies of women. Timely treatment is very significant in their management such that according to the available scientific literature, the interval between the start and the end of dCRT and brachytherapy should be

Table 2. Treatment Complications

Characteristics	0 N (%)	1 N (%)	2 N (%)	3 N (%)	4 N (%)
Dermatitis	12 (16.2)	56 (75.7)	3 (4.1)	3 (4.1)	0
GI toxicity	7 (9.5)	41 (55.4)	22 (29.7)	2 (2.7)	2 (2.7)
GU toxicity	9 (12.5)	47 (63.5)	17 (23)	1 (1.4)	0
During induction chemotherapy					
Neutropenia		4 (4.5)	10 (13.5)	2 (2.7)	0
Thrombocytopenia		2 (2.7)	2 (2.7)	3 (4)	0
Anemia		40 (54)	12 (16.2)	4 (4.5)	0
During chemoradiation					
Neutropenia		4 (4.5)	22 (29.7)	10 (13.5)	
Thrombocytopenia		0	4 (4.5)	4 (4.5)	0
Anemia		32 (43.2)	12 (16.2)	0	0

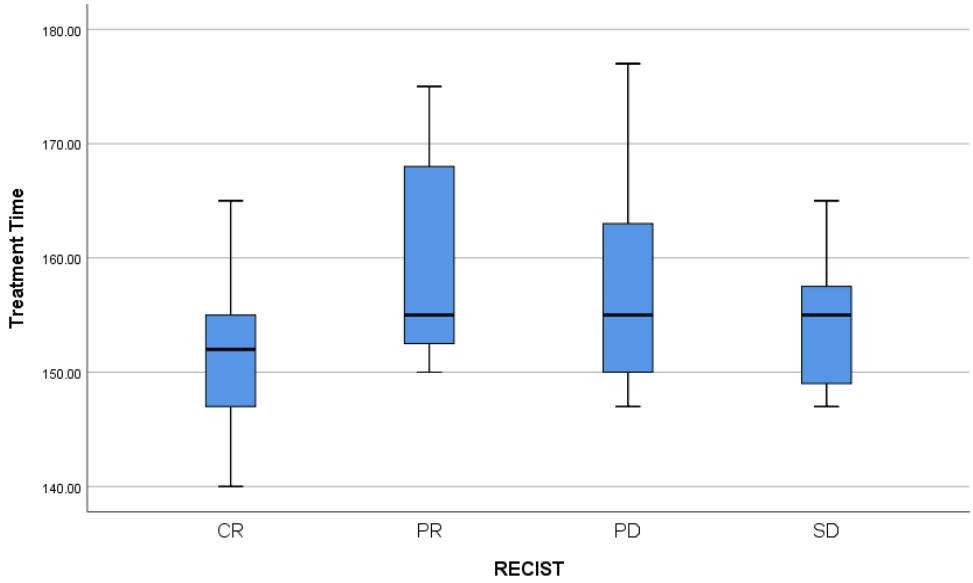

Figure 3. Comparison of the duration of Treatment in Patients with Cervical Cancer Undergoing Induction Chemotherapy Followed by Chemoradiation and Brachytherapy According to the Pathological Response

kept less than eight weeks (Hong et al., 2017). However, the start of treatment may be delayed in some clinical scenarios, especially in developing countries such as Iran due to their limited access to radiotherapy facilities (Mayadev et al., 2022). In such situations, it is suggested to use chemotherapy as an auxiliary approach with the aim of reducing the load of the accelerator device and create an opportunity to plan the treatment while inducing a significant oncologic effects (Ahmed et al., 2021; Ouabdelmoumen et al., 2018). Such an approach may be associated with a significant reduction in tumor size, a reduction in the risk of distant metastasis, and an increase in the probability of clinical response. Of course, it should be noted that the use of multi-drug regimens may be associated with bone marrow or non-blood complications, which often cause delays in the patients' treatment (Benson et al., 2019; da Costa et al., 2019; de Azevedo et al., 2017; McCormack et al., 2013; Narayan et al., 2016; Singh et al., 2013). Unfortunately, until now, there has not been a randomized phase III clinical trial investigating different approaches in the non-surgical treatment of cervical malignancy, and the findings are mainly obtained from single-group and phase II or cohort trials. The present single arm non-randomized clinical trial aimed at investigating the treatment response to induction chemotherapy followed by chemoradiation in patients with locally advanced cervical cancer, during which the patients underwent four cycles of induction chemotherapy every three weeks with carboplatin and paclitaxel regimen before dCRT. In terms of treatment response, the results showed that 60.8% of patients (45 cases) had complete response to treatment while 14.9% of them (11 cases) had partial response. The frequency of progressive and stable diseases were 14.9% (11 cases) and 9.5% (7 cases), respectively. Moreover, the most common non-hematological complications were grade one dermatitis (75.7%, 56 cases), grade one gastrointestinal complications (41 cases, 55.4%), and grade one genitourinary complications (63.5%, 47 cases). The study of hematological complications in patients with cervical cancer undergoing induction chemotherapy followed by chemoradiation and brachytherapy showed that the most severe hematological complication were grade two and three neutropenia (during induction chemotherapy: 13.5% and 2.7%, respectively; during chemoradiation: 29.7% and 13.5%, respectively). Of course, no cases of fever and neutropenia were observed in the examined patients. Grade three and two thrombocytopenia were observed during induction chemotherapy in 4% of patients (3 cases) and 2.7% (2 cases) of patients, respectively. The frequency of grade three and two thrombocytopenia during chemoradiation were 4.5% (4 cases) and 4.5% (4 cases), respectively. Grade three anemia was reported only in 4.5% of patients (4 cases) during induction chemotherapy, and none was observed during chemoradiation. Furthermore, the occurrence of complications during chemoradiation led to the removal of one simultaneous cycle of chemotherapy in 18 patients (24.3%). Overall, the occurrence of complications was associated with the temporary treatment discontinuation in 45 patients (60.8%). Temporary treatment discontinuation was reported in 31.1% of patients (23 cases) under induction chemotherapy and in 56.8% of patients (42 cases) under chemoradiation. None of the studied variables including age, treatment delay, tumor histology, and disease stage had a significant association with the pathological response.

In the present study, treatment response was observed in three quarters of patients after treatment with induction chemotherapy and dCRT, and most of the patients indicated a complete response. Lack of a response indicating a stable or progressive disease was also observed in a quarter of patients. In Tian et al.'s study (2021), 120 women with stage IB2 and IIB-IVA cervical cancer were retrospectively examined after induction chemotherapy and dCRT. The complete/partial response rates were 81.7% and 99.2%

after the completion of induction chemotherapy and chemoradiation, respectively (Tian et al., 2021). In a phase II clinical trial conducted by Benson et al., (2019), 27 patients with advanced cervical malignancies underwent induction chemotherapy followed by chemoradiation; the results of their follow-up examinations revealed the complete response observed in 76% and 87.5% of patients after induction chemotherapy and chemoradiation, respectively. The treatment regimen used in the study by Tian et al., (2021) for induction treatment was paclitaxel with cisplatin or loplatin every three weeks for two to four cycles while the regimen in Benson et al., (2019)'s study, it consisted of six cycles of weekly chemotherapy with paclitaxel and carboplatin regimen (Benson et al., 2019; Tian et al., 2021). Both of the aforementioned studies were different from the present study in terms of the duration of treatment and regimen. It should also be noted that the follow-up approach and the tools used for determining the tumor response rate to induction treatment in these two studies were different from the approach used in the present study. In addition, Tian et al. did not describe the protocol they used for evaluating the treatment response in their study. Furthermore, Benson et al., (2019)'s study used abdominal and pelvic CT scans along with clinical examinations and Pap smear results to follow up patients and evaluate the response to induction treatment. Therefore, if the findings of clinical examinations and Pap smear are based on inaccurate tools such as CT scan , the results of such studies cannot be considered as a reliable criterion for data comparison (Benson et al., 2019; Tian et al., 2021). However, in addition to the gynecologic examination and Pap smear results, the results of MRI were used in the present study three months after the treatment to evaluate the treatment response.

In the randomized phase II clinical trial conducted by da Costa et al., (2019), patients with cervical cancer in stage IIB-IVA were randomly assigned to one of the induction chemotherapies and chemoradiation group (n=55) or chemoradiation alone group (n=52). After the completion of the treatment, the complete response rate was significantly higher in the chemoradiation alone group as compared to the induction chemotherapy group (80.3% vs. 56.3%, P = 0.008), which was associated with better survival in the chemoradiation alone group.

However, approximately 60% and 15% of the patients in the current study had a complete and partial treatment response, respectively. It should be considered that the regimen used for chemotherapy by da Costa et al., (2019) included three cycles of gemcitabine and cisplatin, which was associated with significant treatment discontinuation in the patients receiving induction treatment (20% vs. 6.8 %). Therefore, in their study, one of the most important reasons for the weaker results of induction chemotherapy as compared to chemoradiation alone can be the higher rate of treatment discontinuation in patients undergoing induction chemotherapy as well as the delay in starting chemoradiation due to the prescription of induction chemotherapy. The mentioned delay in starting definitive treatment can have adverse effects on the survival of patients with cervical malignancy such that the prescription of three cycles of treatment every three weeks in the best case and in the absence of treatment toxicity is associated with a 9-week delay in the initiation of chemoradiation. The meta-analysis conducted in this respect showed that an interval of 14 days or less in induction chemotherapy cycles was associated with clinical benefits in patients with cervical malignancy although caution should be exercised in interpreting the results of this study (Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration, 2003).

The phase II study conducted by de Azevedo et al., (2017) regarding the effectiveness of induction chemotherapy and then chemoradiation in the treatment of stage Ib2-IVa cervical cancer showed that the use of induction chemotherapy regimen including cisplatin and gemcitabine was associated with an 81% response rate, which is relatively similar to the findings of the present study. In the present study, treatment response, most of which were complete responses, was observed in three quarters of patients after treatment with induction chemotherapy and dCRT. The regimen used by de Azevedo et al., (2017) was gemcitabine and cisplatin, which was also similar to the regimen used by da Costa et al., (2019) although de Azevedo et al., (2017)'s study was different from da Costa et al., (2019)'s study in terms of the dose of cisplatin (35mg/m^2) and the number of treatment cycles (two cycles). Considering the results of the present study and those of de Azevedo et al., (2017)'s study, it seems that prescribing two cycles of gemcitabine and cisplatin chemotherapy every three weeks or four cycles of paclitaxel and carboplatin chemotherapy every three weeks were associated with similar clinical responses (da Costa et al., 2019; de Azevedo et al., 2017).

In the present study, the highest complete pathologic response rates were recorded in patients with stage IIA2 (75%) and IIB (73.7%). To compare our findings with the findings of other studies addressing standard treatment (chemoradiation and then brachytherapy), the results of the study by Pereira et al., (2017) can be taken into consideration. They examined the data of 75 patients with stage IB2-IIIB cervical cancer under chemoradiation and revealed that the complete clinical response rate in this group of patients was 33.3%. It is worth noting that the complete clinical response rate was 80% in the subgroup of patients who used cisplatin as a sensitizing drug to radiotherapy, while the complete clinical response rate was 31% in other patients who used other chemotherapy drugs for this purpose. In our study, the highest complete clinical response rates were observed in patients with stage IB2 (100%,), IIA (50%), and IIB (22%). In another study, Duenas-Gonzalez et al., (2002) investigated the response to chemoradiation and then brachytherapy in 41 patients with stage IB2-IIIB cervical cancer and reported a clinical response of 87% in those patients. Moreover, while interpreting the results reported by Pereira et al., (2017) and Duenas-Gonzalez et al., (2011) it should be taken into account that the evaluation of the treatment response in these two studies was performed only by considering the findings of the clinical examinations with or without the reported cytology evaluation, which is less sensitive than the pelvic MRI (Nawapun et al., 2021). In

another study by Lee et al., (2017), 225 patients with FIGO stage Ib2-IVa cervical cancer (based on pre-treatment MRI) were subjected to pelvic MRI examination between cisplatin-based chemoradiotherapy and brachytherapy. Their results showed response rates of 49.7% (Lee et al., 2017). But the results regarding the response rate are not presented according to the clinical stage; rather, the evaluation of the response between chemoradiotherapy and brachytherapy instead of the end of the treatment, is different from the present study. In a study by Schernberg et al., (2018), 260 patients with cervical cancer were evaluated in terms of tumor size reduction in MRI before brachytherapy. A volume reduction of more than 90% was reported in 54.6% of patients. The highest rate of response was reported in stage IIB patients (50%) and subsequently in stage IB2 patients (31%). In the study by Schernberg et al., (2018) MRI was performed between the completion of chemoradiotherapy and brachytherapy. In another study by Beriwal et al., (2018), the complete metabolic response was investigated in 155 patients with stage IB1-IV4 cervical cancer after chemoradiotherapy and brachytherapy. In their study, the metabolic response was evaluated by FDG-PET/CT scan and pelvic MRI 10-16 weeks after the completion of treatment. Complete metabolic response was reported in 72% of patients, partial response in 18.7% of patients, and progressive disease in 9% of patients. The results were not presented by stage, but most of the patients were in stage IIB. In the present study, a complete response to treatment was reported in 60.8% of patients and a partial response in 14.9% of them, which was similar to the results of the study by Beriwal et al., (2012) It seems that using the neoadjuvant chemotherapy approach followed by standard treatment or starting treatment with the standard approach without neoadjuvant chemotherapy (definitive chemoradiotherapy and then brachytherapy) has the same short-term results; therefore, radio-oncology specialists can consider obtaining the clinical conditions of the patient (for example, the need to observe a quick response in a patient with urinary tract obstruction) and the radiotherapy center (for example, a long waiting list in the field of high load of patients) should use each of these two approaches. In a study by Javadinia et al., (2020) author suggested that the 6-, 12-, 18-, and 24-month overall survival of patients with cervical cancer was 98%, 86%, 75%, and 50%, respectively.

Investigating the hematological complications in patients with cervical cancer undergoing induction chemotherapy followed by chemoradiation and brachytherapy showed that grade two and three neutropenia during induction chemotherapy occurred in 13.5% of patients (10 cases) and 2.7% of patients (3 cases), respectively, while grade two and three neutropenia during chemoradiation occurred in 29.7% of patients (22 cases) and 13.5% of patients (10 cases), respectively. Of course, no cases of fever and neutropenia were reported in the examined patients. Grade three and two thrombocytopenia were observed in 4% of patients (3 cases) and 2.7% of patients (2 cases) during induction chemotherapy. The frequency of grade three and two thrombocytopenia during chemoradiation were 4.5% (4 cases) and 4.5% (4 cases), respectively. Grade three anemia was reported only in 4.5% of patients (4 cases) during induction chemotherapy, and no cases were reported during chemoradiation. Moreover, the occurrence of complications during chemoradiation led to the removal of one cycle of concurrent chemotherapy in 24.3% of patients (18 cases). Among the non-hematological complications, the most common complications were grade one dermatitis, grade one gastrointestinal complications, and grade one genitourinary complications. Overall, the occurrence of complications was associated with the temporary treatment discontinuation in 60.8% of patients (45 cases). Temporary treatment discontinuation was reported in 31.1% of patients (23 cases) under induction chemotherapy and in 56.8% of patients (42 cases) under chemoradiation. In Tian et al., (2021)'s study, the use of induction chemotherapy before dCRT was associated with grade three, four, or higher gastrointestinal toxicity, as well as leukopenia, neutropenia, and thrombocytopenia. The treatment regimen used in Tian et al., (2021)'s study for induction treatment was paclitaxel with cisplatin and or loplatin every three weeks for a minimum of two to a maximum of four cycles and weekly cisplatin chemotherapy regimen. Unfortunately, Tian et al.did not provide a detailed description of the number of treatment cycles. In the randomized phase II clinical trial conducted by da Costa et al., (2019), induction chemotherapy and dCRT were compared to chemoradiation alone in patients with cervical cancer in stage IIB-IVA. Their results showed that grade three neutropenia, grade three nausea/vomiting, and neuropathy were significantly higher in patients undergoing induction treatment. In their study, induction chemotherapy included three cycles of gemcitabine (1,000 mg/m^2 on day 1 and day 8) and cisplatin (50 mg/m^2 on day 1), and complications in 20% of patients were associated with the treatment discontinuation. The phase II study conducted by de Azevedo et al., (2017) showed that using an induction chemotherapy regimen including cisplatin and gemcitabine was associated with significant complications, and hematological and gastrointestinal toxicity were the most common toxicities. Grade three/four toxicity was observed during induction chemotherapy and chemoradiation in 20% and 44% of patients, respectively. In the study of Narayan et al., (2016), the use of chemotherapy before the standard chemoradiation treatment with one of Platin/5-FU or Taxol/Platin/5-FU regimes were associated with a significant treatment toxicity such that grade three/four hematological toxicities were higher in the induction chemotherapy group as compared to chemoradiation alone. However, the occurrence of non-hematological toxicity was not significantly different between the two groups. The use of TPF triple chemotherapy regimen was associated with higher complications. Baruah et al., (2022) reported similar results in patients with cervical cancer receiving chemoradiation. Besides, the psychological effects of suffering from cancer and its treatments should be taken into consideration (Moezian et al., 2022; Salek et al., 2021; Shirzadeh et al., 2016; Shomoossi et al., 2013).

Despite the fact that the use of induction chemotherapy is associated with good therapeutic effects on the treatment of patients with cervical malignancy, caution should be

exercised regarding the type of regimen selected as well as the number and dose of drugs used so that the treatment approach adopted does not decrease the patient's tolerance leading to a delay in definitive chemoradiation.

The present study suffers from some limitations as well, which includes the dissatisfaction of some patients that met the criteria for entering the study to complete the treatment protocol as well as their unwillingness to perform brachytherapy after the completion of induction chemotherapy and chemoradiation, which reduced the sample size. In order to manage this limitation, not only the objectives and benefits of the study were explained to the patients but also the time of data collection and sampling was expanded. Furthermore, since conducting the study as a single arm trial precluded the possibility of comparing the obtained results with the findings of the peer group, the generalizability of the results of the present study was at risk. Moreover, a significant number of the studied patients were suffering from large cervical masses so that the use of tandem ovoid as the only brachytherapy tool cannot be a breakthrough in delivering the appropriate dose and creating optimal local control. In addition, the use of 45 Gy dose in the treatment of para-aortic lymph nodes due to lack of access to IMRT was also associated with underdosing of these lesions.

It is proposed to conduct, in future, two-group randomized controlled clinical trials with a larger sample size by controlling the confounding factors to confirm the findings of this study. Moreover, it is essential to follow up the patients in terms of their overall survival and disease-free survival for 12 to 60 months and compare the results with other patients treated in the same center. In addition, considering that the use of induction chemotherapy may be associated with a delay in the prescription of definitive treatment (chemoradiation and brachytherapy) in patients with cervical malignancy, comparing the findings obtained from patients treated with induction and adjuvant chemotherapy approaches seems to be illuminative. Furthermore, since targeted treatments and immunotherapy are an integral part in the treatment of patients with malignancy nowadays, it is necessary to examine the role of simultaneous administration of this group of treatments during neoadjuvant/adjuvant chemotherapy or in combination with chemoradiation in future studies and clinical trials. Additionally, other brachytherapy approaches such as interstitial brachytherapy and new external radiotherapy techniques such as IMRT should also be attended to in future studies to address the limitations of the present study. The presentation of the results of this study in scientific conferences and its publication in reliable scientific and research journals can effectively help other researchers in designing upcoming studies.

In conclusion, the results of the present study revealed the appropriate clinical response of patients with cervical cancer malignancy to the approach of induction chemotherapy followed by chemoradiation such that more than three quarters of patients had a complete/partial response in the three-month follow-up. Of course, it should be noted that the use of induction chemotherapy was associated with the treatment discontinuation in a significant number of patients. Although the treatment discontinuation during induction chemotherapy was less frequent than the treatment discontinuation during chemoradiation, it is worth considering that the main treatment of patients with locally advanced cervical cancer is the chemoradiation, and that the administration of induction chemotherapy reduces the patients' tolerance of chemoradiation.

Author Contribution Statement

Study concept and design: N.A. and F.S.N.; acquisition of data: Z. Sh. and Sh. O.; analysis and interpretation of data: M.H. and A.M.; drafting the manuscript: M.M, M. A., and H.N.; critical revision of the manuscript for important intellectual content: N. Kh., B. K., and S.H.H.; statistical analysis: biostatical expert.

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Ethical approval statement

The study protocol was approved by the Research Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1400.173), and a written informed consent form was obtained from the patients or their legal guardian.

Clinical trial registration number

The study was registered in the National Clinical Trials System (IRCT20210808052110N1).

Data availability statement

All data generated and analyzed during this study can be accessed through direct communication with the corresponding author upon the agreement of all research team members.

Conflict of interest statement

The authors report no conflicts of interest.

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