RESEARCH ARTICLE

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Phase II Study to Evaluate the Safety and Efficacy of Neoadjuvant Chemotherapy with Weekly Paclitaxel and Carboplatin Followed by Radical Chemoradiation in Locally Advanced Cervical Cancer in Egyptian Population

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Abstract

Background: Since 1999, platinum based chemoradiation (CRT) is the standard treatment for locally advanced cervical cancer patients, but the estimated increase in overall survival (OS) over a 5-year period was only 6% in patients treated with CRT versus radiotherapy alone.There have been no additional developments in the treatment of locally advanced cervical cancer(LACC) patients since CRT introduction and approximately 30-40% of those patients failed to achieve complete response to CRT. Therefore, alternative approaches are needed to improve the outcome for such patients. NACT with Weekly paclitaxel and carboplatin for 4 - 6 weeks as dose-dense chemotherapy prior to CRT could be one such potential approach. **Methods:** A phase II, prospective , non randomized study was conducted at the Clinical Oncology Department of Ain Shams University hospital. 42 patients diagnosed with locally advanced cervical cancer patients (FIGO 2018 stage IIB to IVA) and were treated by NACT carboplatin (AUC2) and paclitaxel (80 mg/m 2) for 4 - 6 week, then they proceeded to definitive CCRT (with a dose of 45-50.4 Gy) with weekly cisplatin followed by brachytherapy. Response rate and toxicity were the primary endpoints and Survival were the secondary endpoints. **Results:** Median age at diagnosis - 48 years ; 90% (38/42) of cases diagnosed with squamous cell carcinoma and 9% (4/42) diagnosed with other histologies; 38% (16/42) had FIGO stage IIB , 40% (17/42) with stage IIIC, 7% (3/42) stage IIIB, 7% (3/42) with stage IVA, 5% (2 /42) with stage 2A and only 1 case diagnosed with stage 3A. 42 patients were evaluated.The overall response rate post-NACT was 71% and 61% developed complete response rate (CR) at end of all treatment course. Grade 3and 4 adverse events during NACT were most common, with hematological toxicity occurring in 21% of patients. There were no treatment- related deaths. The 9-month and 12-month overall survival rates were 94% and 84% , respectively. **Conclusion:** NACT with dose dense protocol, followed by CCRT, is a treatment option for locally advanced cervical cancer with controllable adverse events and agood response rate.

Keywords: Cervical cancer- Dose-Dense Neoadjuvant Chemotherapy (NACT)- Paclitaxel/carboplatin

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Introduction

Cervical cancer is a significant global public health issue. It ranks as the fourth most common cancer in terms of both incidence and mortality in women with an estimated 660,000 new cases and 350,000 deaths worldwide in 2022 [1]. The situation is even worse in developing countries as regional morbidity is 3–10 times greater than that in developed countries [2]. It is considered the second most common female malignant tumor in developing countries, where 85% of cervical cancer deaths are documented [3]. The difference in prevalence between high- and low-income countries is also in part attributed to the difference in access to population screening, which has led to an increase in the risk of long-term untreated human papillomavirus (HPV) infection [4]. Persistent HPV infection is the most important predisposing factor for the development of cervical cancer [5]. Currently, the standard treatment for locally advanced cervical cancer (LACC) is definitive chemoradiation therapy (CRT) with concurrent cisplatin-based chemotherapy [6, 7]. However, the overall survival (OS) rates for patients with stage IIB and III-IV cancer are 60–65% and 25%-50%, respectively, which are considered low [7]. Therefore, it is important to investigate better treatment strategies. Numerous studies have investigated the role of neoadjuvant chemotherapy (NACT), and although a meta-analysis of 21 randomized trials revealed no increase in OS with

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NACT, there was an observed correlation between short cycle length and outcome [8]. Advanced cervical cancer is common in developing nations, and unfortunately, there is limited access to radiotherapy facilities [9]. The use of neoadjuvant chemotherapy before CRT is based on the principle that chemotherapy may shrink the primary tumor, increasing the sensitivity of malignant cells to subsequent radiotherapy (RT). Additionally, the uncompromised blood flow in radiation-naïve patients results in higher chemical drug concentrations at the tumor site than in patients pretreated with radiation,and micrometastatic disease can be eradicated by chemotherapy and prevents a significant proportion of relapses [10, 11].Moreover, particularly in developing countries, the incidence of cervical cancer is high, and access to radiotherapy facilities is limited .

Platinum and taxane together have been shown to be effective in treating advanced and recurrent cervical cancer, with 40–50% overall response rates [12].

A single-arm, phase II, prospective and nonrandomized study of 42 patients was conducted at the Clinical Oncology Department of Ain Shams University Hospital. Patients with a histologic diagnosis of cervical carcinoma staged according to the International Federation of Gynecology and Obstetrics (FIGO 2018) from IIB to IVA were included [13]. Patients planned to receive 4- 6 weeks of paclitaxel and carboplatin followed by CCRT (40 mg/m2 of cisplatin per week or carboplatin AUC 2; the EBRT dose was 45-50.4 Gy over 25- 28 fractions followed by image - guided adaptive brachytherapy, (IGAB). In this study, we assessed the effectiveness and tolerability of a dose-dense NACT regimen in patients with locally advanced cervical cancer (LACC) after standard treatment.

Materials and Methods

Eligibility requirements and study population

Patients who were at least 18 years old and had histological evidence of squamous and nonsequamous cervical carcinoma , or locally advanced disease with FIGO 2018 stages IIB to IVA were eligible for recruitment. All patients underwent a cervical biopsy, and examination under anesthesia (EUA) and imaging to finish their staging, which is explained below. For American Joint Committee on Cancer staging, chest radiography, abdominal CT scan, and pelvic magnetic resonance imaging (MRI or pelvic computed tomography scan if MRI was contraindicated), as well as abdominal CT scan, chest radiography, cystoscopy and sigmoidoscopy were performed when needed. All patients had an ECOG performance status of 0–2, adequate bone marrow function (neutrophils ≥1.5 × 109 per L), adequate hepatic function (ALT or AST < 2.5 ULN, and total bilirubin < 1.25 ULN), and adequate renal function (glomerular filtration rate, GFR ≥ 60 ml/min, as determined by creatinine clearance). The response assessment was performed via Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). The Institute's Ethics Committee approved to this study. Prior to starting treatment, written informed consent was acquired.

Inclusion criteria:

* Patients, aged 18 years or older with a histologically confirmed diagnosis of primary cervical carcinoma.

* Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

* All patients underwent biopsy, examination under anesthesia (EUA) and imaging to complete the staging.

* According to the 2018 International Federation of Cervical Cancer Obstetrics and Gynecology (FIGO) staging standard, the patient was diagnosed with FIGO stage IIB-IVA disease.

* Adequate organ (renal, liver and bone marrow) function .

Exclusion criteria

* Patients who are unfit for receiving chemotherapy (ECOG score ≥ 3).

* Patients who were not locally advanced at the time of presentation, or had distant metastases at initial diagnosis.

* Patients who were previously treated with pelvic radiotherapy, had a previous diagnosis of another type of cancer or who were suffering from decompensated (active) medical comorbidities .

Neoadjuvant chemotherapy

(schedules included paclitaxel (80 mg/m2) and carboplatin (AUC 2) was administered continuously for 4−6 weeks).

If the ANC was less than 1.0× 109/L or if the platelet count was <75×109/L on the day of the cycle, both medications were omitted in any given week. The paclitaxel dosage was adjusted to 85% of the full dose in all subsequent cycles, and the carboplatin dosage was set at an AUC of 1.6. If further hematological toxicity develops,NACT should not be continued. Paclitaxel should be omitted if patients experience Grade 3 persistent peripheral neuropathy. After discontinuation of the NACT regimen, CRT should be started when hematological toxicity recovers. If the weekly ANC is < 500/mm3 and the platelet count is < 50000/mm3, radiation should be withheld until the counts improve to above that level.

Chemo-radiation (CRT)

Patients are subsequently treated with CRT as soon as their hematological toxicity recovers,and it is better to begin on week 7 with concomitant cisplatin (40 mg/m2, maximum 70 mg) given weekly for 5− 6 weeks. The pelvic external beam radiotherapy dose was 50.4 Gy via 6 MV in 25–28 fractions over 5−5.5 weeks with IMRT or conformal radiotherapy. Patients with common iliac and/or para-aortic lymph node metastases were treated with extended fields, resulting in a total dose increase of 55–60 Gy. Regardless of the tumor response after NACT, radiotherapy was scheduled according to the pre-NACT stage without dose modification. The aim of IGBRT is to deliver a brachytherapy dose of 40–45 Gy (EQD2) (D90) to reach atotal EBRT + a brachytherapy dose of 85–90 Gy to the high-risk volume and 60 Gy (D98) to the intermediate-risk volume following the completion of external beam radiation therapy. We did our best to ensure that the total duration of radiotherapy should be

completed within 56 days.

Planned curative treatment was discontinued in cases of disease progression, withdrawal of consent, or unacceptable toxicity. Patients with a significant hypersensitivity reaction to paclitaxel or carboplatin were withdrawn from the study.

Response assessment

All patients were examined weekly before each cycle of NACT for toxicity evaluation. The responses were evaluated following the NACT regimen at week 7, at the end of CRT before IGBTs and at 12 weeks after the end of the entire treatment course. The RECIST v1.1 criteria [14] were used to evaluate the response, and the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 was used to grade the toxicity.

Follow-up

Patients were followed up at the outpatient clinic by symptom assessment and clinical examination every 3 months in the first 2 years, every 4–6 months for an additional 3 years and annually thereafter. Radiological evaluations, such as chest CT scans, were conducted as clinically indicated, and pelvic abdomen magnetic resonance imaging was performed every 3 months for the first 2 years every 4–6 months for an additional 3 years and then, annually.

Using the PASS 11 program for sample size calculation, a review of the results from a previous study revealed that neoadjuvant chemotherapy with doses of dense weekly paclitaxel and carboplatin for 6 weeks, followed by CCRT, is a feasible approach and is associated with a high response rate (response rate = 67.8%) in locally advanced cervical cancer patients compared with M. McCormack et al. [15] a phase II study.We calculated a sample size of 67, which produced a two-sided 90% confidence interval with a width equal to 0.2 when the sample proportion was 0.680. May 2022 marked the beginning of the recruitment process, which ended in October 2023. The trial was carried out in compliance with the International Council on Harmonization's guidelines (ICH) and the Islamic Organization for Medical Science (IOMS). All patients signed an informed consent form. An informed consent form was signed by every patient. The study protocol was approved by the Research Ethics Committee at the Faculty of Medicine, Ain Shams University Federal Wide Assurance No. FWA 000017585 (REC- FMASU@med-asu-edu.eg) MD 164 2022.

The response rates after NACT and 12 weeks after the end of the entire treatment course and toxicity were the primary endpoints. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) were used to evaluate the response [14]. For the purpose of the analysis, we evaluated complete and partial responders as one group and called them responders, and patients who showed stable and progressive disease, were considered one group, called nonresponders. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [16] was used to grade toxicity. Late toxicity was defined as adverse events that occurred six months after the end of treatment. Each patient was assigned the highest grade,for each type of adverse event. The secondary endpoint was survival. The calculation of overall survival (OS) was based on recruitment through the date of death or last follow-up, and progression-free survival (PFS) was calculated from the study date to the date of progression, and was detected according to RECIST v1.1. or death for any reason. At the time of the most recent follow-up, patients who did not experience progression or death were censored. January 2024 was the date of last follow-up. To estimate survival, the Kaplan–Meier method was used. A t test was used to compare quantitative variables. Both Fisher's exact test and the x2 test were used to compare qualitative variables. The threshold for statistical significance was $P < 0.05$. Analysis was performed via the Statistical Package for Social Science (SPSS 26).The analyses were conducted via the intention-to-treat (ITT) method.

Results

Between May 2022 and October 2023, 59 patients were eligible. Seventeen patients were excluded: 3 because of a diagnosis of distant metastasis at initial presentation, 2 because of their preference to be treated at another institute, 4 because they were confirmed to have endometrial adenocarcinoma rather than cervical adenocarcinoma, 4 because of their refusal to receive NACT, 2 because they died before starting treatment and the remaining 2 because they underwent upfront surgery. Additionally, our sample size was supposed to be 67 patients, but our study closed earlier for the sake of the patients and to avoid bias from an unavoidable delay between the end of NACT and the start of definitive radiotherapy because our therapy device was broken for a long period of time (Table 1).

Patient Demographics

A total of 42 patients, who were newly diagnosed with histologically confirmed invasive cervical carcinoma with FIGO 2018 stages IIB to IVA were recruited from the gynecological oncology outpatient unit of a single center in Egypt, at the Clinical Oncology and Nuclear Medicine, Department , at Ain Shams University Hospital. The patients' baseline characteristics are shown in Table 2. The median age was 48 years (range ,31− 70 years), and the percentage of patients diagnosed with stage 2A disease was 4.8% (2/42), that diagnosed with IIB disease was 38% (16/42), that diagnosed with IIIA disease was 2.4% (1/42), that diagnosed with IIIB disease was 7% (3/42), that diagnosed with IIIC disease was 40% (17/42), and that diagnosed with IVA was 7% (3/42).

Overall, 7% of the patients (3/42) had para-aortic lymph nodes with metastatic deposits. Squamous cell carcinoma was the most common histological type (90%, 38/42). All patients were investigated via MRI Pelvi-abdomen with contrast and CT chest on initial presentation, at the time of assessment response and during follow-up.

Treatment compliance

During NACT, 95% of the patients (40/42) received a four-week NACT regimen with a full chemotherapy dose,

and 85% of the patients (36/42) completed 6 weeks of NACT. Only 9% of the patients needed cycle delay, and 7% of the patients were treated with dose modification (Table 3).

Three patients could not complete the full course of NACT (1 patient received only 3 weeks due to repeated infections and renal impairment, and 2 patients received only 2 weeks as they experienced clinical progression). Eighty-eight percent (37/42) of patients underwent CCRT after NACT; only 1 patient underwent radical hysterectomy after NACT due to the presence of a pelvic kidney, and this patient was sacrificed by pelvic irradiation. The other four (4/42) patients received radical external beam radiotherapy alone without concomitant chemotherapy due to poor GFR or patient preference. Eighty-six percent of patients (32/37) received concomitant weekly cisplatin, and approximately 19% of patients (8/37) received concomitant carboplatin (AUC 2) (5 patients received carboplatin from the start of radiation, and 3 patients shifted from cisplatin to carboplatin to develop toxicities: creatinine clearance <60 ml/min).

With respect to the number of cycles of concomitant chemotherapy, only 91% (29/32) of the patients received 4–6 cycles of cisplatin; one patient received 3 cycles, then she shifted to weekly carboplatin, another patient received only 1 week of cisplatin, then shifted to carboplatin (AUC 2) because of the development of sensory neural hearing, and the last patient stopped concomitant chemotherapy after 2 weeks because of her preference.

Forty-one patients (97%, 41/42) received radical radiotherapy (Table 4). Thirty-four patients (92%, 34/37) completed their radiotherapy course (EBRT and brachytherapy), and the remaining 3 patients did not receive brachytherapy, due to local and systemic progression or death. Thirty-five percent (13/37 patients) received a pelvic sidewall boost. Two patients were diagnosed with para-aortic lymph node metastasis (PALN) and para-aortic lymph node boosting. The brachytherapy dose was 28 Gy in 4 fractions, HDR, over 2 weeks ,but only two patients received a brachytherapy dose of 35 Gy in 5 fractions because of their poor response after CCRT.

Clinical response to NACT

Table 5 displays the response rates. Neoadjuvant chemotherapy was administered to 42 patients, and thirty-five (85%) patients completed all six cycles of NACT, whereas six patients did not complete all weeks of the NACT regimen; of those six patients, three had five NACT cycles, two of which showed signs of disease progression after two cycles, and one of which ended after three cycles because of repeated urinary tract infections and deteriorated kidney function. Radiological evaluation was performed after NACT was completed for 7 to 10 days, and 71% (30/42) of the patients responded clinically ;19% (8/42) achieved a complete response (CR), and a partial response (PR) was observed in 22 (52%, 22/42) patients. Only 3 patients (7%, 3/42) progressed locally. The response of the remaining 9 patients (21%, 9/42) was stable disease.

Only 37 patients received CCRT, and the remaining 5 patients (5/42, 12%) did not receive concomitant chemotherapy, as one of them underwent radical hysterectomy after NACT because of presence of the pelvic kidney; these patients were sacrificed if pelvic irradiation was received, and the other 4 patients received radical radiotherapy alone because of poor kidney function.

Twenty-two patients (62%, 22/37) achieved a clinical response: 35% (13/37) achieved complete resolution of their disease, and 27% (10/37) achieved a partial response (PR). Stable disease (SD) and progressive disease (PD) were observed in 30% (11/37) and 8% (3/37) of the patients, respectively. Among the 4 patients who did not receive concomitant chemotherapy and who received radical radiotherapy alone, one developed local progression, two achieved a partial response, and the other achieved a complete response.

Thirty-seven patients (37/41) completed their course by receiving brachytherapy, and only 35 patients were evaluated, as two patients were not radiologically assessed; as one of them died before the time of assessment, and the other was lost to follow-up since she finished her radiotherapy. A total of 77% (27/35) of patients responded clinically 12 weeks after completing the radiotherapy course (Table 4); 20 patients (57%, 20/35) achieved a complete response (CR), and a partial response (PR) was observed in 7 patients (20%, 7/35). The proportion of patients with stable disease after the entire treatment course was 11.4% (4/35). Only four patients (4/35, 11.4%) experienced disease progression (3 patients developed local and distant progression systemically, and the last patient progressed systemically alone).

Among our study population, only thirty-one patients (31/35) were treated per the protocol and were assessed clinically and radiologically. The overall response rate was 81%, and the complete response (CR) rate after the entire treatment course was 61%.

Supplementary Table 1 shows the correlations between the response rate and clinicopathological parameters. We compared 12 patients who did not achieve a clinical response (SD+PD) following NACT with 30 patients who achieved a clinical response (CR+PR).

The Kaplan–Meier plots for OS are shown in Figure 1. The OS rates at 9 months and 12 months were 94.4% and 84.4%, respectively (Figure 2). A total of 29 (69%) patients remained after 1 year (52 weeks), 5 (11.9%) patients died within the year of follow-up, one patient died after 1 year, and 7/42 patients were lost to follow–up or the time of the study was <1– year (censored cases). The Kaplan–Meier plots for PFS are shown in Figure 3. The PFS rates at 9 months and 12 months were

Table 1. Demographic Data and Medical History of the Included Patients

	Mean ± SD N (%)	Median (IQR)	Range
Age	48.6 ± 9.2	48 (40.5 - 57)	(31 - 70)
DM	7 (16.6%)		
HTN	12 (28.6%)		
Other medical comorbidities	12 (28.6%)		

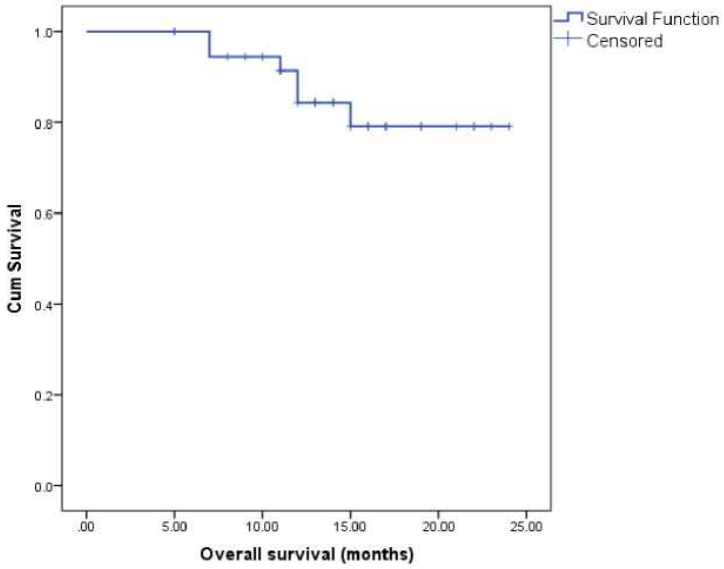

Figure 1. Kaplan-Meier Plots for Overall Survival (OS) for 38 Participants Included in the Study

Table 2. Baseline Characteristics

		N= 42 (%)
Staging	2A	2 (4.8%)
	2B	16 (38%)
	3A	1 (2.4%)
	3B	3 (7%)
	3C	17 (40.5%)
	4A	3 (7%)
Histology	Squamous	38 (90.5%)
	Adenocarcinoma	2 (4.8%)
	Others	2 (4.8%)
ECOG	1	36 (85.7%)
	2	6 (14.29%)
Tumor differentiation	1	2 (4.76%)
	2	24 (57%)
	3	16 (38%)

84% and 74.1%, respectively (Figure 4). There were 9 events associated with PFS (3 patients who were alive with disease progression and 6 who died). Six patients had passed away overall by the time of our analysis due to bleeding (1patient at 2 months after finishing all her treatment), cervical cancer disease burden (3 patients), AKI (1 patient at 2 weeks after finishing the CRT) and respiratory failure (1 patient at 2 months after finishing her entire treatment course as she developed lung and pleural metastasis) Supplementary Tables 2-6.

Safety

During NACT, G3/4 neutropenia and anemia occurred in 15% and 12% of the patients, respectively. Five patients (15%) needed blood transfusions, and another 5 patients (15%) were supported by granulocyte-colony stimulating factor.

The most frequent nonhematological toxicity was alopecia : 32 women (94%) had G2 alopecia. Conversely,

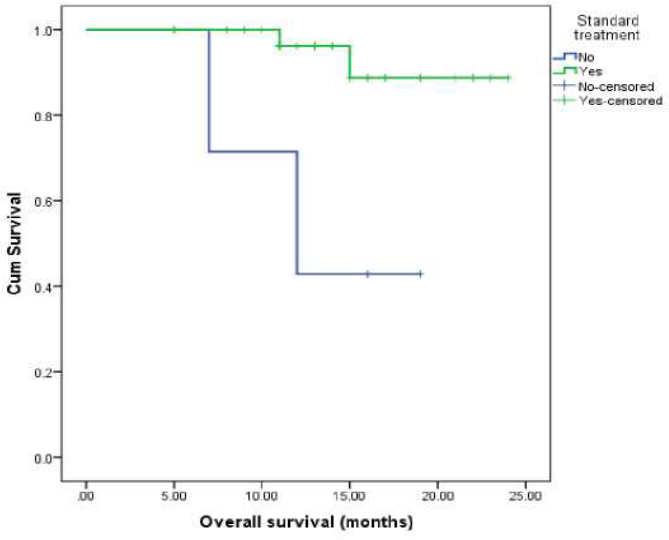

Figure 2. Relation of Treatment Per Protocol with Overall Survival of the Studied Patients by Kaplan-Meier Analysis

Table 3. Compliance with Neoadjuvant Chemotherapy (NACT)

	Number of patients (%) N = 42
Number of NACT weeks completed	
2	2 (4.7%)
3	1 (2.4%)
4	40 (5.2%)
5	3 (7.1%)
6	36 (85.7%)
Stopped before 6 weeks	6 (14.3%)
Reasons	
Hematological toxicity	2
Allergic reaction Toxicity	1
Disease progression	2
Poor GFR	1
Cycle (week) delay	4 (9.5%)
Reasons	
Hematological Toxicity	4 (9.5%)
Dose reduction	3 (7%)
Reasons	
Hematological Toxicity	3 (7%)

Table 4. Radiotherapy Details

Characteristics		No. of patients (41/42***)
1) Radiothearpy technique	3DCRT/IMRT	Nov-31
	Pelvic	29
2) Radiotherapy fields	Pelvic and para-aortic	12
	Parametrium*/Pelvic nodes	---/13
3) Radiation boost	Para-aortic nodes	2
	45-50.4 Gy/56-60 Gy	28/13
4) Dose of EBRT	Cisplatin/Carbopaltin	32/8
5) Concomitant chemotherapy	28 Gy/35 Gy	29/2
6) Brachytherapy(HDR)	< or =55 days/>55 days	19/22
7) OTT (From start of RT to the end of BT n**= 37)	Median	9(7 - 10.5)
	(range)	(4 - 18)

BT, brachytherapy; OTT, overall treatment time; No, number; HDR, high dose rate; 3DCRT, conformal radiotherapy; IMRT, intensity-modulated radiotherapy; EBRT, external beam radiotherapy;*, No one received a parametrium boost by EBRT owing to the availability of interstitial brachytherapy in our center; **, Four of 41 patients underwent only EBRT efficacy analysis; ***41/42, as the remaining patient (1) case had pelvic kidneys (congenital), which prevented her from receiving pelvic irradiation; thus, she underwent curative surgery after downsizing via NACT.

G1 vomiting and G1 hepatotoxicity were reported in 5.8% and 2.9% of the patients, respectively. No treatment -related deaths were reported.

During CCRT, G3/4 neutropenia, anemia and thrombocytopenia developed develop in 30%, 13% and 3% of patients, respectively. With respect to nonhematological toxicities, grade 3/4 diarrhea and peripheral neuropathy developed in 3% and 3%, respectively of the patients. Nine patients developed renal impairment, and 6 patients developed G2 renal impairment (the management of these patients was as follows: 3 patients received carboplatin instead of cisplatin, the other 3 patients received cisplatin with dose reduction, and the remaining 3 patients developed G3 or greater nephropathy, which needed to be avoided while receiving concomitant chemotherapy and continued only radical pelvic radiation).

Adverse events that occurred more than 6 months after the end of treatment were considered late. The late toxicities were mainly low grade and included dyspareunia and anal pain.

Discussion

CCRT significantly improved 5-year overall disease-free survival (HR=0.78, 95% CI=0.70 - 0.87), 5-year locoregional disease-free survival (HR=0.76, 95% CI=0.68 - 0.86), 5-year metastasis-free survival (HR=0.81, 95% CI=0.72- 0.91) and 5-year OS (HR=0.81, 95% CI=0.71- 0.91) [6]. However, approximately 30–40%

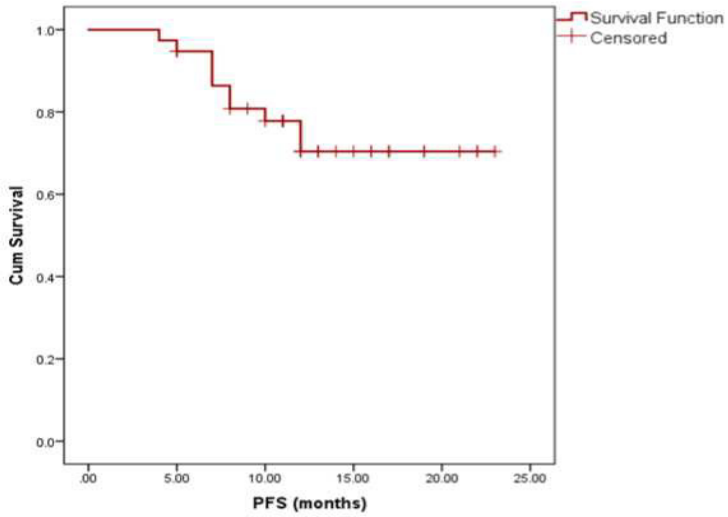

Figure 3. Kaplan-Meier Plots for Progression-Free Survival

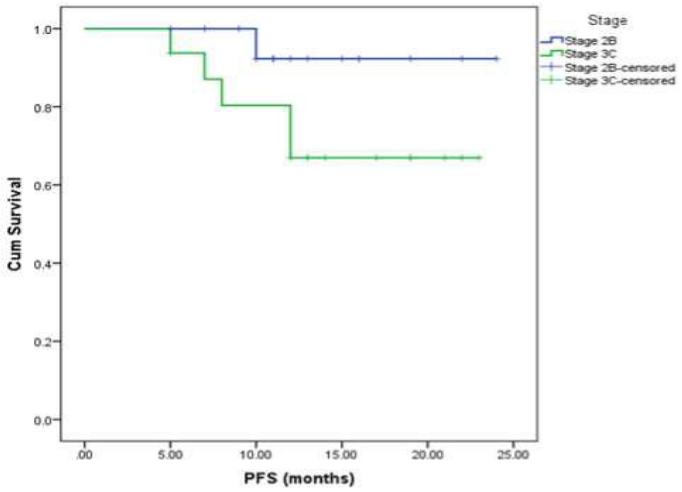

Figure 4. Relationships between Stage and Progression -Free Survival in the Studied Patients According to Kaplan-Meier Analysis

of LACC patients fail to achieve complete resolution following the standard of care [12]. Therefore, alternative approaches are needed to improve the outcome for such patients. NACT prior to definitive RT is considered ineffective because of increased toxicity, decreased PFS, and lower survival rates [12]. A meta-analysis revealed

Table 5. Tumor Response According to the RECIST 1.1 Criteria[14].

		Mean ± SD N (%)	Median (IQR)	Range
Response after NACT for 42 cases	CR	8 (19%)		
	PR	22 (52.38%)		
	SD	9 (21.43%)		
	PD	3 (7.14%)		
	RR	30 (71.38%)		
partial response %		60.7% ± 12.4%	60% (50% - 70%)	(40% - 90%)
Response after CCRT	CR	13 (35.1%)		
For 37 cases	PR	10 (27.1%)		
	SD	11 (29.7%)		
	PD	3 (8.1%)		
	RR (CR+PR)	23 (62.2%)		
	*not treated per protocol	5 (11.9%)		
Overall radiotherapy treatment (weeks)		9.25 ± 3.24	9 (7 - 10.5)	(4 - 18)
Overall treatment duration		22.17 ± 6.35	20 (17.5 - 26.5)	(13 - 40)
Time from neoadjuvant chemotherapy till end of brachytherapy (weeks)				
Overall Response	CR	20 (57.14%)		
For 35 cases	PR	7 (20%)		
	SD	4 (11.43%)		
	PD	4 (11.43%)		
	RR (CR+PR)	27 (77.4%)		
	Not received brachy or not evaluated	6		
Overall Response for 31 cases **	CR	19 (61.3%)		
	PR	6 (19.35%)		
	SD	3 (9.68%)		
	PD	3 (9.68%)		
	RR (CR+PR)	25 (80.6%)		

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CCRT, concomitant chemoradiotherapy; RT, radiotherapy; * not received radiotherapy or concomitant chemotherapy; **treated per protocol (11 patients not treated per protocol; 4, not received concomitant chemotherapy; another 4, did not receive brachytherapy; 1, operated after NACT; 1, lost to follow-up after completing all the treatment; and finally, died before the assessment.

a 7% improvement in 5− year overall survival (OS) in studies that used a NACT regimen with short cycle intervals < 14 days; thus, the use of NACT at shorter intervals (dense doses) may result in improved outcomes in patients receiving induction chemotherapy [8].

The combination of taxane and platinum has been shown to effectively treat advanced and recurrent cervical cancer, with response rates ranging from 40 to 50% [12].

We tested a dose-dense weekly protocol of paclitaxel and carboplatin for four to six weeks before standard chemoradiation treatment for locally advanced cervical cancer. The treatment was generally well tolerated. Grade 3 and 4 adverse events during NACT were most common, with hematological toxicity occurring in 21% (9/42) of patients. The percentage of patients with G3/4 neutropenia was 11.9% in our study. Toxicity was managed by the use of G-CSF, and only one patient developed neutropenic fever. This result was higher than the 9% rate reported by McCormack et al. 2013, but it was lower than the 32%, 56% and 36% reported by Singh et al. [17], Salihi et al. [18] and Li et al. [19], respectively.

Our study confirmed the findings of Li et al. [19], who reported that the most common adverse event during NACT was, that the 76% rate (32/42) in our study was higher than the 90% (45/50) reported by Li et al. [19].

During CCRT, 19% of patients developed grade 3 or 4 hematological toxicities, and grade 3and 4 nonhematological adverse events (AEs) were reported in 12% of our study. This result was lower than that reported by Li et al. [19], who reported that 52% of patients experienced grade 3 and 4 hematological toxicity, and only 32 patients experienced grade 3 and 4 nonhematological adverse events. Additionally, our results were lower than those reported by McCormack et al. 2013 [15], as 41% of patients developed any grade 3/4 hematological toxicity. The grade 3/4 neutropenia rate in our trial was 7%, which is considerably lower than the 33% reported by McCormack et al. 2013[15], the 29% reported by Singh et al. 2013 [17] and the 36% reported by Li et al. 2023 [19]. Therefore, this trial revealed that neoadjuvant chemotherapy with concurrent chemoradiation is a feasible and tolerable regimen for patients with LACC.

Our response rate was evaluated according to RECIST 1.1[14]. In accordance with this trial design, after the fourth to sixth weeks of neoadjuvant chemotherapy were completed, radiological assessment was conducted within days. The optimal response rate (CR+PR) to this short course of neoadjuvant chemotherapy, was 71%, and the overall response rate was 81% 12 weeks after the end of the entire treatment course. This result was similar to that reported by McCormack et al. [15], as 73% was the overall response rate (ORR) reported post - NACT, but the ORR 12 weeks after all treatment was greater (91%) than that in our study. Li et al. [19] reported higher response rates of 79% after NACT, and 90% reported 12 weeks after all treatment courses in 50 LACC patients, treated with 4 weeks of the cisplatin and paclitaxel NACT regimen prior to CCRT.

Sixty-eight percent of the overall response rate reported by Singh et al. [17] post − NACT, in 28 patients with FIGO stages IIB-IVA disease received NACT using paclitaxel (60 mg/m2) and carboplatin (AUC-2) weekly for 6 weeks, but the ORR 12 weeks post-CCRT was 93%, which is higher than our findings.

Our reported overall response rate at the end of all treatment courses was lower than that reported in most comparative studies, as most of the patients did not start radiotherapy at the ideal time after the end of NACT, and as previously mentioned (Table 5), not all sample sizes were treated per protocol. Others have identified stable disease after NACT as a poor prognostic sign [20]. Twenty-one percent of patients (9/42) had stable disease at the end of NACT (5 patients achieved complete resolution of their disease after the end of the entire treatment course), and only 1 patient still achieved a stable response at 12 - weeks at the end of treatment; and subsequently, she underwent curative radical salvage surgery, and the remaining 3 patients developed distant metastases 3 months post-CCRT. Three patients experienced local disease progression after NACT, and by tracking these patients at the end of our study, 2 patients achieved a partial response at12– weeks at the entire treatment course; the last patient developed distant metastasis 3- months after CCRT , after which she started palliative systemic treatment.

Compared with the Li et al. [17] study, in which 10(21%) patients had stable disease at the end of NACT, four patients developed disease progression 3 months after CCRT, and two had progressive disease during follow-up. Four patients died as a result of the disease.

In our study, after one year of follow-up, 36% (15/42) of patients were alive without disease. The 9-month and 12-month OS rates were 94% and 84.4%, respectively, and the 9-month and 12-month PFS rates were 84% and 74%, respectively.

After one year of follow-up, 78% (22/28) of patients from Singh et al. were alive without disease, and the 3-year OS rate reported by McCormack et al. was 68% [15,10]. In the Li et al. 2023 trial, after a median follow-up of 28 months, the 3-year OS rate was 83.9%, whereas the 3-year PFS rate was 73.6% [9].

The post-NACT response was associated with superior progression-free survival, but the difference was not statistically significant (the 6-month and 12-month progression-free survival rates for responders were 89% and 78.6%, respectively, whereas the 6-month and 12-month progression-free survival rates for nonresponders were 71.6% and 61.4%, P=0.2), and (the 6-month and 12-month overall survival rates for responders were 100% and 95.7%, respectively. The 6-month and 12 - month overall survival rates for nonresponders were 80% and 70%, respectively).

We will follow patients who are still alive for at least 5 years to, determine whether NACT can provide a survival benefit. Additionally, we aimed to include patients who were diagnosed with FIGO 2018 stage III C disease in another trial, in which those patients could safely receive NACT, and to determine if we could safely de-escalate the radiotherapy dose to boost regional lymph nodes with metastasis deposits if they achieved a complete response after the NACT regimen, we will compare their outcomes with those in that study, in which we did not perform

any radiotherapy dose modification, regardless of their response to NACT, in stage IIIC cervical cancer patients.

Strengths and weaknesses (removed)

• NACT is considered an alternative and feasible approach to minimize the associated morbidity of pelvic malignancies,such as pain and bleeding, which may occur, while waiting for definitive CCRT, and it has the advantages of being low cost and readily available, as radiotherapy is a scarce resource in low-income countries, leading to a long waiting list.

• Poor recruitment led to a small sample size, as many cases were excluded from recruitment after starting our study (for example, stage III C, owing to a higher incidence of developing complete resolution of previously documented regional lymph nodes with metastatic deposits), which led to a debate of the increase in the radiotherapy dose to those lymph nodes, patients with established fistulas or impending fistulas, as their rationale was to prevent delays from starting the definitive treatment, and patients with bilateral hydronephrosis, even after double j or nephrostomies, to be able to reserve their renal functions for concomitant cisplatin.

• Unfortunately, most patients are delayed from the beginning of their concurrent chemoradiation for approximately 6 weeks, mainly due to a long waiting list for radiotherapy, a shortage of radiotherapy devices and many instances of radiation device malfunctions with a long time to fix that malfunction; thus, most patients have radiotherapy durations that are longer than what can be considered ideal.

Nonhomogeneity of the stages

• There is no control arm for determining whether NACT followed by CCRT is more effective than CCRT alone.

• Owing to the short follow-up duration, we do not know whether NACT can provide a survival benefit.

Conclusion

NACT with a dense - dose protocol, followed by CCRT, is a treatment option for locally advanced cervical cancer patients with controllable adverse events and good response. The clinical response rate was 81%, but none of the variables were able to predict the response to NACT.

Author Contribution Statement

All authors contributed equally in this study.

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Abbreviations

ANC: absolute neutrophil count
AEs: adverse events
CCRT: Concurrent chemoradiation
NACT: Neoadjuvant chemotherapy
LACC: Locally advanced cervical cancer
OS: overall survival
PFS: Progression-free survival
MRI: Magnetic resonance imaging
CT: Computed tomography
GFR: Glomerular filtration rate
G-CSF: granulocyte colony-stimulating factor
ECOG: Eastern Cooperative Oncology Group
RECIST: Response evaluation criteria for solid tumors
IGBRT: Image-guided adaptive brachytherapy
HRCTV: High-risk clinical target volume
HPV: Human papillomavirus
AEs: adverse events
CTCAE: Common Terminology Criteria for Adverse Events
AUC: Area under the curve
CR: Complete response
PR: partial remission
PD: Progressive disease
PALN: Para-aortic lymph node
SD: Stable disease
RT: Radiotherapy
TRAE: Treatment related adverse events

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660.
2. Hu Y, Han Y, Shen Y, Chen J, Chen Y, Chen Y, et al. Neoadjuvant chemotherapy for patients with international federation of gynecology and obstetrics stages ib3 and iia2 cervical cancer: A multicenter prospective trial. BMC Cancer. 2022;22(1):1270. https://doi.org/10.1186/s12885-022-10355-3.
3. Emam m, elsayed as. # 210 obligatory subtotal hysterectomy: Novel strategy for prevention of cervical stump carcinoma. Int J Gynecol Cancer. 2023;33:A343. Https://doi.Org/10.1136/ijgc-2023-esgo.723.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. https://doi.org/10.3322/caac.21492.
5. Kjær SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: Role of persistence. J Natl Cancer Inst. 2010;102(19):1478-88. https://doi.org/10.1093/jnci/djq356.
6. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 2010;2010(1):CD008285. https://doi.org/10.1002/14651858.Cd008285.
7. Tharavichitkul E, Lorvidhaya V, Kamnerdsupaphon P, Sukthomya V, Chakrabandhu S, Klunklin P, et al. Combined chemoradiation of cisplatin versus carboplatin in cervical carcinoma: A single institution experience from thailand.

BMC Cancer. 2016;16:501. https://doi.org/10.1186/s12885-016-2558-9.
8. Tierney J, Rydzewska L, Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration (NACCCMA) Collaboration. Neoadjuvant chemotherapy for locally advanced cervix cancer. Cochrane Database Syst Rev. 2004(2). https://doi.org/10.1002/14651858.CD001774.pub2.
9. Mumba JM, Kasonka L, Owiti OB, Andrew J, Lubeya MK, Lukama L, et al. Cervical cancer diagnosis and treatment delays in the developing world: Evidence from a hospital-based study in zambia. Gynecol Oncol Rep. 2021;37:100784. https://doi.org/10.1016/j.gore.2021.100784.
10. González-Martín A, González-Cortijo L, Carballo N, Garcia JF, Lapuente F, Rojo A, et al. The current role of neoadjuvant chemotherapy in the management of cervical carcinoma. Gynecol Oncol. 2008;110(3 Suppl 2):S36-40. https://doi.org/10.1016/j.ygyno.2008.05.012.
11. Reed N, Balega J, Barwick T, Buckley L, Burton K, Eminowicz G, et al. British gynaecological cancer society (bgcs) cervical cancer guidelines: Recommendations for practice. Eur J Obstet Gynecol Reprod Biol. 2021;256:433-65. https://doi.org/10.1016/j.ejogrb.2020.08.020.
12. Kumar L, Gupta S. Integrating chemotherapy in the management of cervical cancer: A critical appraisal. Oncology. 2016;91 Suppl 1:8-17. https://doi.org/10.1159/000447576.
13. Salib MY, Russell JHB, Stewart VR, Sudderuddin SA, Barwick TD, Rockall AG, et al. 2018 figo staging classification for cervical cancer: Added benefits of imaging. Radiographics. 2020;40(6):1807-22. https://doi.org/10.1148/rg.2020200013.
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised recist guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. https://doi.org/10.1016/j.ejca.2008.10.026.
15. McCormack M, Kadalayil L, Hackshaw A, Hall-Craggs MA, Symonds RP, Warwick V, et al. A phase ii study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. Br J Cancer. 2013;108(12):2464-9. https://doi.org/10.1038/bjc.2013.230.
16. U.S. Department of health and human services, "common terminology criteria for adverse events (ctcae) v.5.0," cancer ther. Eval. Progr., p. 155, 2017.
17. Singh RB, Chander S, Mohanti BK, Pathy S, Kumar S, Bhatla N, et al. Neoadjuvant chemotherapy with weekly paclitaxel and carboplatin followed by chemoradiation in locally advanced cervical carcinoma: A pilot study. Gynecol Oncol. 2013;129(1):124-8. https://doi.org/10.1016/j.ygyno.2013.01.011.
18. Salihi R, Leunen K, Moerman P, Amant F, Neven P, Vergote I. Neoadjuvant weekly paclitaxel-carboplatin is effective in stage i-ii cervical cancer. Int J Gynecol Cancer. 2017;27(6):1256-60. https://doi.org/10.1097/igc.0000000000001021.
19. Li J, Li Y, Wang H, Shen L, Wang Q, Shao S, et al. Neoadjuvant chemotherapy with weekly cisplatin and paclitaxel followed by chemoradiation for locally advanced cervical cancer. BMC Cancer. 2023;23(1):51. https://doi.org/10.1186/s12885-023-10517-x.
20. Park DC, Suh MJ, Yeo SG. Neoadjuvant paclitaxel and cisplatin in uterine cervical cancer: Long-term results. Int J Gynecol Cancer. 2009;19(5):943-7. https://doi.org/10.1111/IGC.0b013e3181a23c2e.