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Neoadjuvant Chemotherapy Followed by Chemoradiation: Is it Tolerable and Efficient in Management of Locally Advanced Cervical Cancer?

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Abstract

Background: Chemoradiation is the standard of care for management of locally advanced cervical cancer, but failure to control systemic disease occurs in one third of patients. Neoadjuvant chemotherapy (NACT) has been investigated in management of locally advanced cervical cancer in order to improve its prognosis. We assessed the tolerability and response rate of weekly NACT with paclitaxel and carboplatin before radical concurrent chemoradiation (CRT).

Methods: Single arm phase II trial of 50 patients with locally advanced cervical cancer (stage IB2-IVA). Patients received weekly paclitaxel (80 mg/m^2) and carboplatin AUC2 for six cycles followed by CRT (weekly cisplatin 40 mg/m^2, 50.4 Gray over 28 fractions plus brachytherapy).

Results: A total of 50 patients were recruited. Baseline characteristics were: median age at diagnosis 56 years, 92% squamous, 8% adenocarcinoma, FIGO stage IB2 (4%), II (28%), IIIA (28%), IIIB (12%), IVA (28%). Complete or partial response rate was 88.3% post NACT and 72.1% post CCRT. The median follow up was 12 months. Grade 3 toxicities were 14.8% during NACT and 13.8% during CCRT.

Conclusion: Dose-dense weekly NACT with paclitaxel and carboplatin followed by CRT achieved a good response rate. It is feasible with acceptable toxicity of NACT and high compliance to radiotherapy.

Keywords: Cervical cancer • Neoadjuvant chemotherapy • Chemoradiation

Introduction

Impact of using Neoadjuvant chemotherapy (NACT) in locally advanced cervical cancer patients has been investigated in many studies aiming to allow radical operability by decreasing the primary tumor size. It also will enhance the tumor vascularization with reduction hypoxic cells number, which will improve the tumor radiosensitivity and annihilate micrometastasis [1].

It was firstly used since 80s in locally advanced cervical cancer patients prior to radical surgery. Friedlander et al. [2] investigated the use of cisplatin, vinblastine and bleomycin (PVB) chemotherapy every 3 weeks and achieved 66% response rate.

This is followed by many trials with variable treatment schedules and promising results even with more aggressive chemotherapy protocols and short intervals [3,4].

In this study we evaluated the role of NACT using weekly paclitaxel and carboplatin for 6 weeks prior to chemoradiation (CRT) in patients with locally advanced cervical cancer.

Patients and Methods

This prospective study done on patients with locally advanced cervical cancer who attended to Clinical Oncology and Nuclear Medicine Department at Mansoura University Hospital in the period from May 2015 to January 2017 inclusive.

Eligibility criteria

a. Age is not less than 18 and not more than 70 years.
b. ECOG performance status 0-1.
c. Stage IB2–IIIB according to FIGO and histologically confirmed squamous, adenocarcinoma or adeno squamous carcinoma of the cervix.
d. Adequate complete blood count, hepatic and renal functions.
e. No prior anti-cancer treatment.
f. No other malignancy.

Exclusion criteria

I. Pregnancy.
II. Breast-feeding.
III. Severe systemic disease that is contraindicated with the use of chemotherapy.
IV. Cardiac disease.
V. History of cancer except basal cell carcinoma.
VI. Pre-existing neuropathy more than grade 1 due to any cause.

Pretreatment evaluation

i. Full personal, present, and past history.
ii. Full clinical examination including evaluation of performance status, general, local examination including examination under anaesthesia (EUA).
iii. Complete blood picture, renal and hepatic function.

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iv. Cystoscopy and sigmoidoscopy

v. Radiological investigations:

a) Base line CT abdomen and MRI pelvis.

b) Radiological investigations to exclude metastasis if there is suggestive symptoms

c) Chest X- ray or CT chest if there is suspicious lesion.

d) Bone scan if there is bony symptoms.

Treatment protocol

All patients planned to receive the following regimen:

A. NACT: Weekly paclitaxel (80 mg/m^2) in 250 ml of normal saline 0.9% intravenous (IV) over 1 hour followed by IV carboplatin AUC in 250 ml dextrose 5% over 60 min for 6 weeks.

B. CRT: External beam irradiation concurrent with weekly cisplatin(40 mg/m^2), with a one week gap between it and NACT aiming to deliver 45 Gray (Gy) in 25 fractions over 5 weeks, 5 days per week, using 3D conformal radiotherapy (8-15 MV photons).

C. Intra cavitary brachytherapy: High Dose Rate (HDR) brachytherapy of 21 Gy given to point A (7 Gy, once a week, for 3 weeks) following completion of CRT at Ayadi Almost akbal hospital in Alexandria.

D. Full blood counts: Performed and all patients examined weekly for toxicity during NACT and CRT. Evaluation of response done at week 7, 15, and at week 24.

Set-up and simulation procedures for 3D conformal radiotherapy

- The patients generally placed supine in a reproducible, immobilized position.
- CT simulation (5 mm slices) with IV contrast.

Target delineation

The gross tumor volume (GTV) included the whole macroscopic disease, clinical treatment volume (CTV) included (GTV + 1 cm) and planning target volume (PTV) included (CTV+0.5 cm).

Delineation of organs at risks (OARs)

OARs include bowel bag, bladder, rectum, left femoral head and right femoral head.

Optimization of 3 DCRT plan

I. A dose volume histogram (DVH).

II. PTV covered by 95% of isodose curves.

III. In homogeneity ranged from 95% to 105% as possible.

IV. Doses to organs at risk limited to their tolerances

a) **Bladder:** Received less than 50 Gy.

b) **Rectum:** Received less than 60 Gy.

c) **Femoral head:** Received less than 40 Gy.

d) **Bowel bag:** Restrict the dose to less than 45 Gy.

e) **Spinal cord:** Received less than 45 Gy.

3D Precise Treatment Planning System version 2.12 used for planning (Figures 1 and 2).

Machine

3D CRT delivered by linear accelerator (Elekta, Precise Treatment System™), Version 5, with 6 MV photon energy.

Post treatment evaluation

I. Assessment of response by MRI pelvis.

II. Estimation of response rate and calculation of progression free survival (PFS) and overall survival (OAS).

III. RECIST criteria used to classify according to as follow:

a) **Complete Response (CR):** Disappearance of all lesions.

b) **Partial Response (PR):** At least a 30% decrease in the sum of the Longest Diameter (LD) of lesions.

c) **Stable Disease (SD):** Neither PR nor Progressive Disease (PD).

d) **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of lesions, or the appearance of one or more new lesions.

I. Drug related and radiotherapy related toxicity evaluated every week according to NCI common toxicity criteria (Version 3).

Statistical analysis

PFS calculated as the interval between the start of treatment and disease progression. Overall survival (OAS) calculated as the interval between the diagnosis and last follow up or patient's death. The Kaplan-Meier product limit method used to estimate PFS and OAS. Statistical analyses performed using SPSS 2004 (version 16).

Follow up

Patients followed in Out Patient Clinic every 2 months during the first year then every 3 months during the second year. The median follow up is 12 months (range 9-18 months). This time calculated from the end of CRT. Tumor recurrence defined as pathologically confirmed cancer 3 months after CRT.

Results

From May 2015 to January 2017, 62 patients with cervical cancer presented to Clinical Oncology and Nuclear Medicine Department at Mansoura University Hospital. Fifty-three patients (85.4%) of them diagnosed as locally advanced in-operable non-metastatic disease. The diagnosis of those patients confirmed histologically and radiologically by CT or MRI. Three patients (5.6%) excluded due to poor performance status so we did not include them in the study. Fifty patients started NACT (Table 1).

Of those 50 patients, one patient (2%) died after first cycle of NACT, 1 patient (2%) died after fifth cycle of NACT and 1 patient (2%) developed hypersensitivity to paclitaxel so excluded from our study. Only 47 patients ended NACT and all of them reassessed by MRI.

Of those 47 patients, one patient did not receive CRT due to progressive disease, one patient did not complete CRT due to social troubles after achieving partial response following NACT and two patients did not receive brachytherapy due to shortage of the radioactive material.

Forty-three patients assessed for the toxicity and response and they followed up to assess the PFS and OAS. Two patients presented with moderate hydronephrosis for whom nephrostomy done before starting NACT.

Patient characteristics

Patient characteristics summarized in Table 1. Fifty patients were eligible to start the study, forty-five patients (90%) were presented with ECOG 0, 5 patients (10%) with ECOG 1. Nearly 92% of the histologically assessed cases were proved to be squamous cell carcinoma and 54% of them were grade II.

Toxicity: The NACT was well tolerated for most of patients, only 3 patients out of 50 patients (6%) were excluded from the study, 2 of them were died after receiving first and fifth cycles of NACT respectively and 1 patient developed hypersensitivity to paclitaxel.

Toxicities to NACT were vomiting in two patients (4.2%), alopecia in twenty patients (42.5%) and haematological toxicities in the form of grade 1 anemia in ten patients (21.2%), grade 1neutropenia in six patients (13.9%), grade 1 thrombocytopenia in five patients (10.6%), grade 3 neutropenia in three patients (6.3%), grade 3 anemia in 4 patients (8.5%) and grade 1 neuropathy in four patients (8.5%). All of them received supportive treatment and then

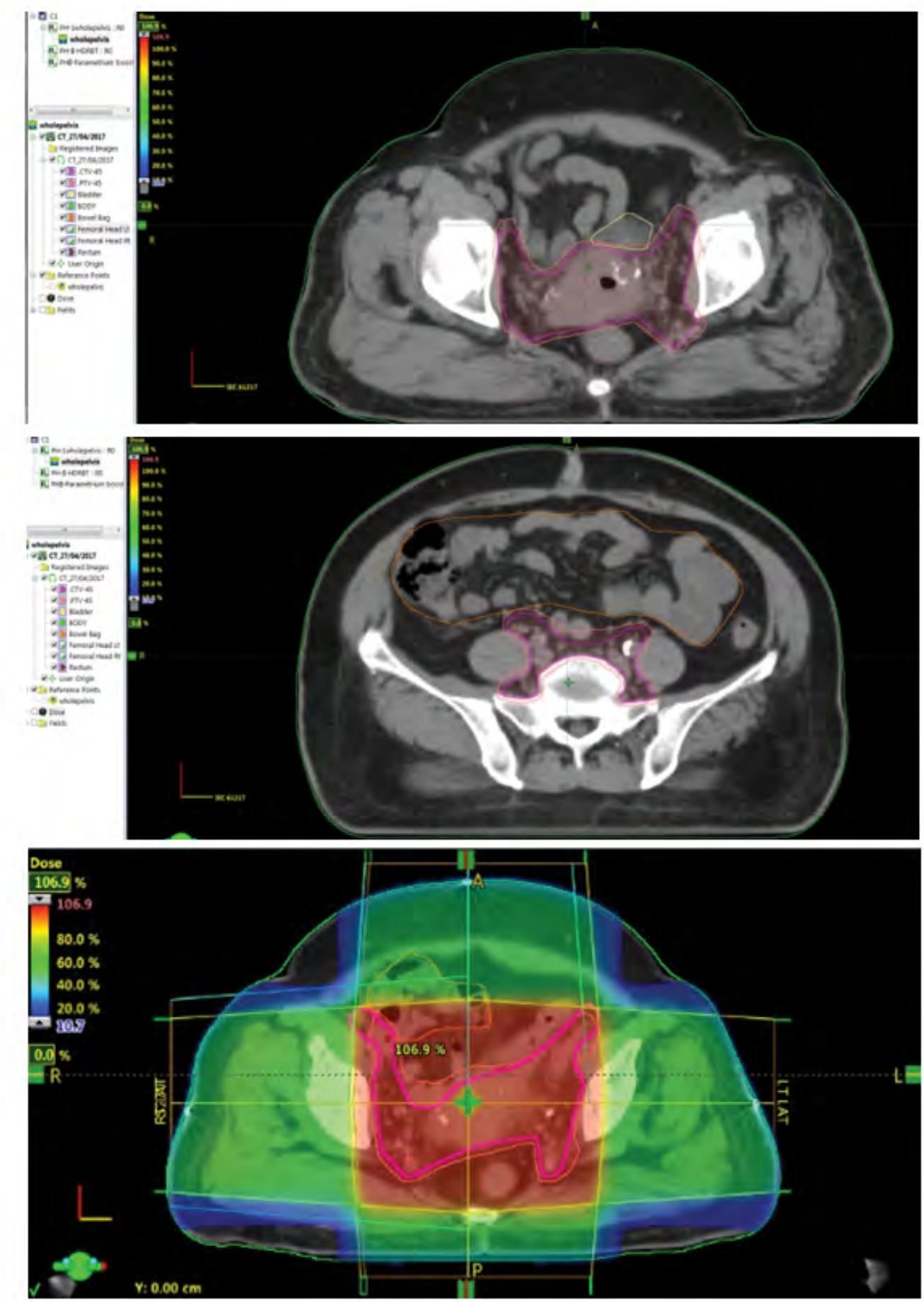

Figure 1. Optimization of 3 DCRT plan.

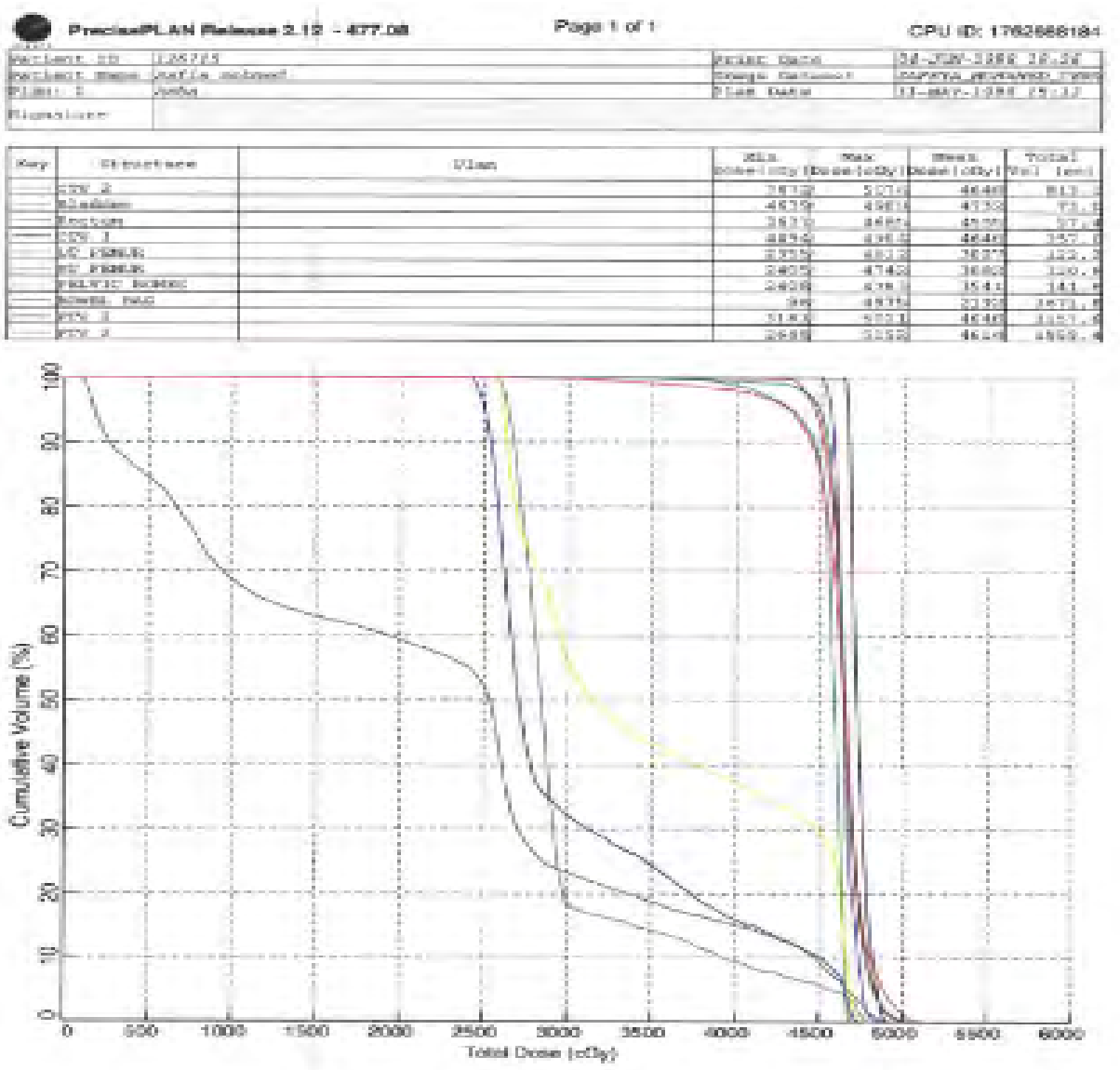

Figure 2. Dose volume histogram.

Table 1. Patient characteristics.

Characteristics		Number (Total)	Percentage
Age Median 59 y Range (41-82)	≤45	7 (50)	14
	>45	43 (50)	86
ECOG P.S	0	45 (50)	90
	1	5 (50)	10
Pathology	SCC	46 (50)	92
	Adenocarcinoma	4 (50)	8
Grade	I	7 (50)	14
	II	27 (50)	54
	III	16 (50)	32
FIGO Stage	IB2	2 (50)	4
	IIA	1 (50)	2
	IIB	13 (50)	26
	IIIA	14 (50)	28
	IIIB	6 (50)	12
	IVA	14 (50)	28
Comorbidities	DM	4 (50)	8
	HTN	2 (50)	4

continued their therapy. Most of these toxicities started to appear after the 3rd week of therapy (Table 2).

Response rate: 88.3% of patients (38/43) achieved a complete/partial response at the end of NACT, and 72.1% of patients (31/43) achieved a complete/partial response 12 weeks after completing CRT (Table 3 and Figure 3). A complete response seen in 18 patients after NACT and in 29 patients 12 weeks after finishing CRT (Figures 4 and 5). The percentage of patients with stable disease after NACT and CRT was 11.6% (5/43) and 18.6% (8/43), respectively. Four patients rapidly progressed after NACT, and four patients progressed after CRT (Table 3).

Survival: A total of 24 patients were alive after a median follow up period of about 20 months (ranged from 10 to 27 months) and at the time of analysis. The median PFS time for patients in this study was 15 months (95% CI, 11.958 to 18.042 months). The median survival time was 19 months (95% CI, 14.312 to 23.688 months). The estimated 12 months, 18 months and 24 months survival was 79%, 52%, and 18% respectively. It was noticed that the Para aortic lymph nodes was the main site of relapse (9.3%), followed by liver (6.9%), then the lung (4.6%), and bone (4.6%) (Figures 6 and 7).

Discussion

We evaluated the use of paclitaxel and carboplatin as a NACT regimen for 6 weeks followed by the CRT in locally advanced cervical cancer patients. We found this regimen to be feasible with high response rate and acceptable toxicity.

It was investigated in many trials using different schedules and was correlated with survival improvement by adding synergistic interactions through different mechanisms of actions [5].

Duenas-Gonzales et al. [6] achieved 95% response rate and 37% pathological response rate with FIGO IB2-IIIB disease using paclitaxel &carboplatin every 3 weeks for 3 cycles prior to surgery followed by adjuvant CRT.

Table 2. Toxicity to CRT.

Toxicity	G1		G2		G3	
	N	%	N	%	N	%
Anemia	-	0	1	2.3	1	2.3
Vomiting	-	0	2	4.6	-	0
Diarrhea	-	0	2	4.6	2	4.6
Cystitis	-	0	3	6.9	3	6.9
Fatigue	-	0	2	4.6	-	0
Skin desquamation	-	0	1	2.3	-	0

*No patients developed grade 4 toxicity

Table 3. Response rate to CRT (Radiological).

Variables	Number (43)	Percentage
CR	29	67.4
PR	2	4.7
SD	8	18.6
PD	4	9.3

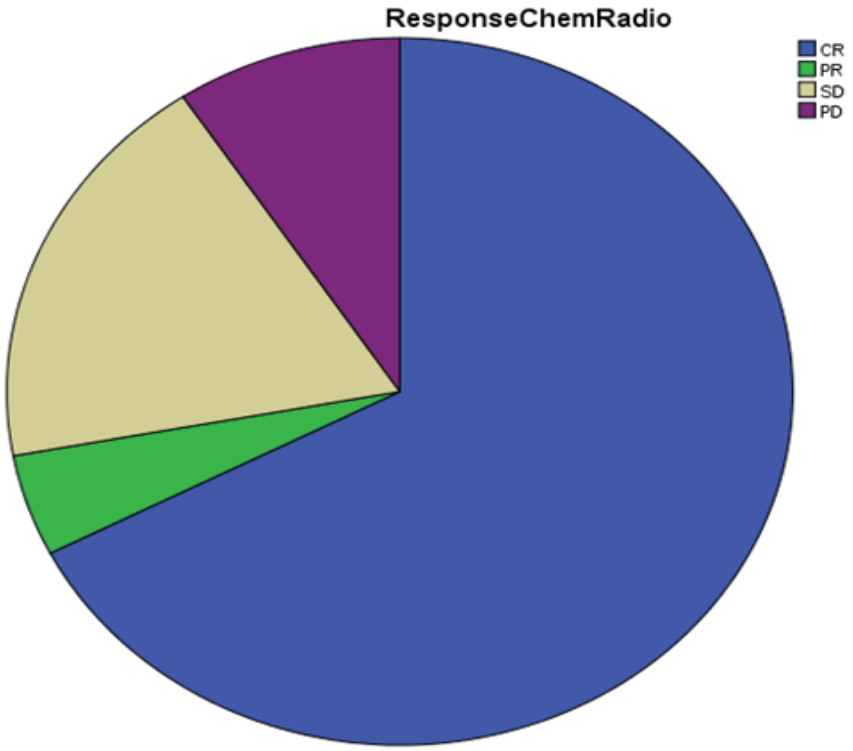

Figure 3. Response rate.

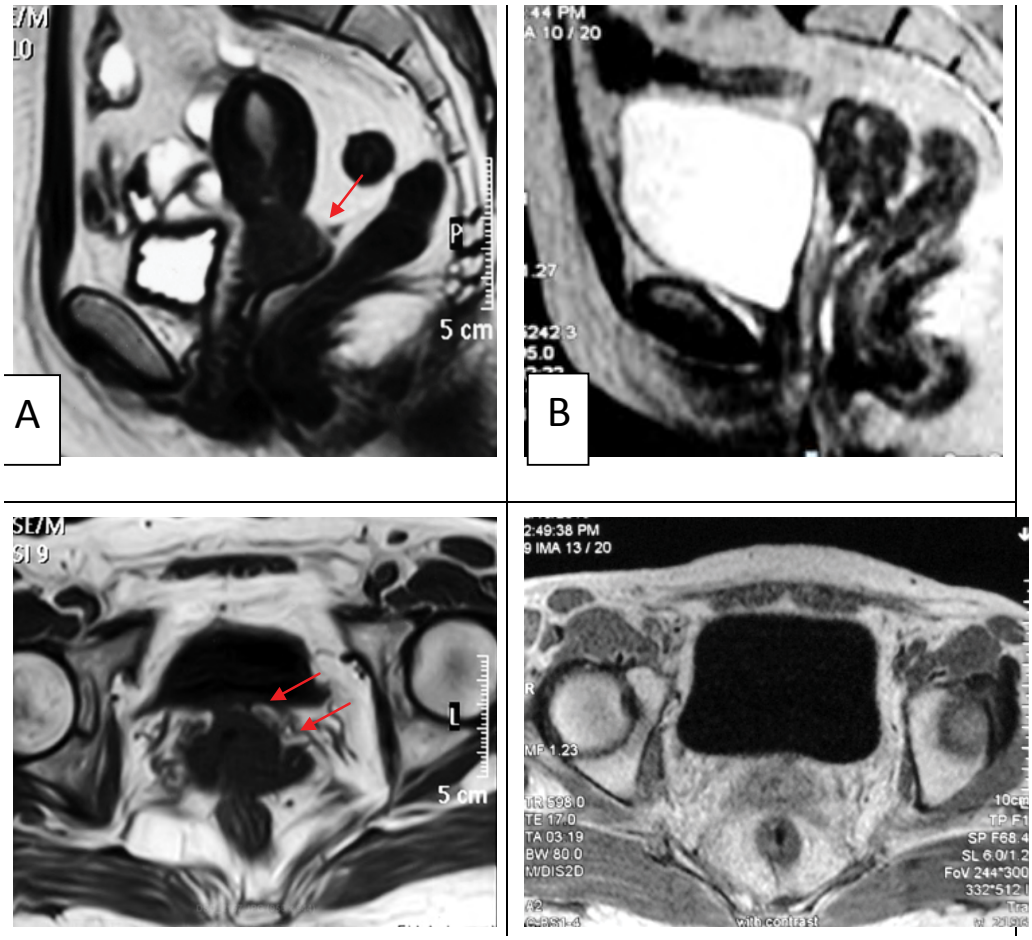

Figure 4. (A) Pre NACT, (B) Post NACT complete response for stage IIB cervical cancer.

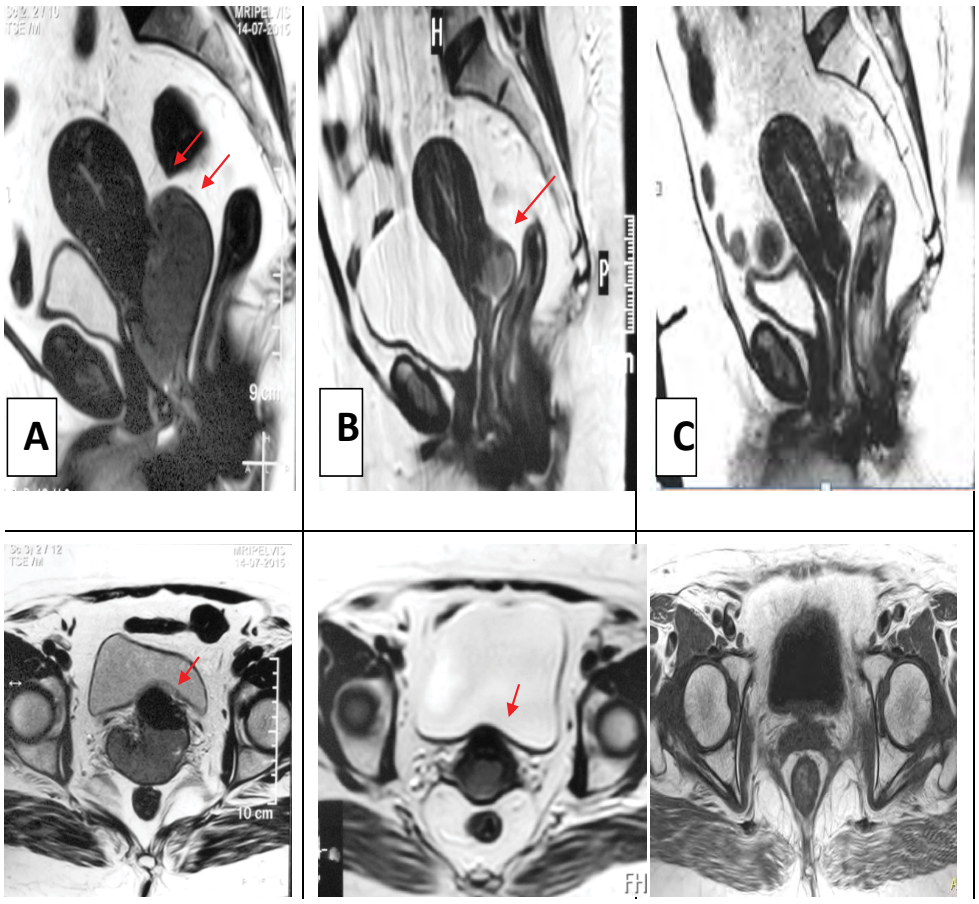

Figure 5. (A) Pre NACT, (B) Post NACT partial response, (C) Post CRT complete response for stage IIIB cervical cancer.

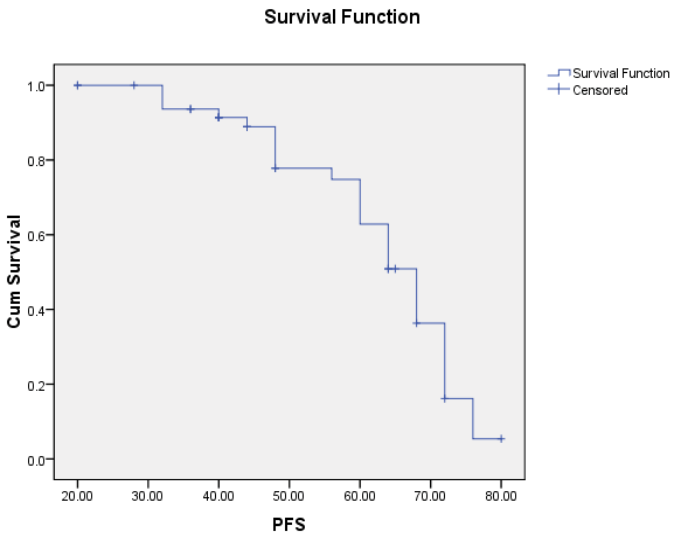

Figure 6. Progression free survival curve in weeks.

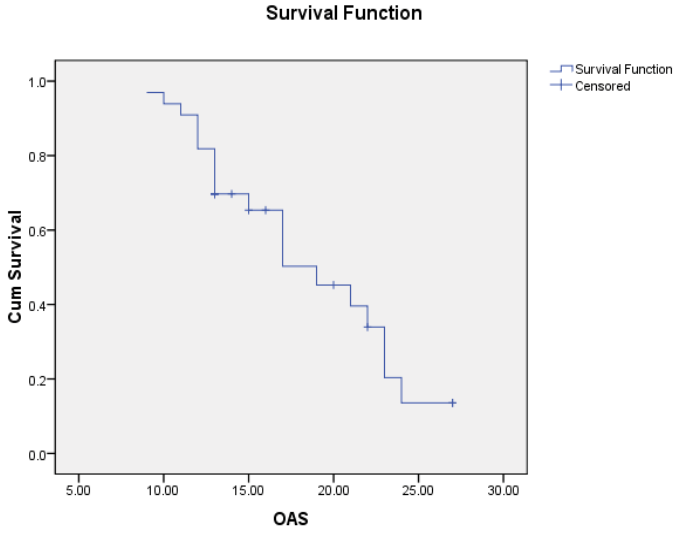

Figure 7. Overall survival curve in months.

Angioli et al. [7] reported 78.3% response rate of in 23 patients with stage IB2-IIB cervical cancer with only 8.7% grade 3 and 4 hematological toxicity and 17.4% sensory neuropathy. These promising results improved the safety of paclitaxel and carboplatin in the neoadjuvant setting. McCormack et al. [8] (The CxII trial) included 46 patients with stage IB2-IVA and demonstrated an acceptable toxicity (grade 3\4 toxicities were 20% following NACT & 52% following CRT) with high compliance to radiotherapy (98%). Complete or partial response rate was 70% following NACT and 85% following CRT, OAS and PFS at 3 years were 67% and 68% respectively.

Singh et al. [5] included 24 patients with FIGO stage IIB-IVA and showed comparable results. Following chemotherapy, 67.8% responded with 28.5% grade 3\4 toxicities. 95% complete response following CRT with 29%grade 3\4 toxicities.

Weekly schedule used in our study allowed us to continue therapy in 93.3% of patients. 88.3% of 43 patients responded to NACT with 14.8% grade 3 toxicity and 0% grade 4 toxicity. This was better than the study done by McCormack et al. [8] who found 70% response rate to NACT and 20% grade 3 &4 toxicities in nearly the same number of patients included, the same stage of disease and the same paclitaxel (80 mg/m^2). Our results were better than Singh et al. [5] achieving a higher response rate and lesser grade 3\4 toxicities following NACT although we used in our study larger paclitaxel (80 mg/m^2) dose than Singh et al who used paclitaxel (60 mg/m^2)and include higher number of patients (43 vs. 28).

In comparison with the previous studies using 3 cycles of 3 weekly neoadjuvant paclitaxel and carboplatin, Our response rate (88.3%) is less than what achieved by Duenas et al. [6] (95%), (may be due to less advanced stages) and better than what showed by Angioli et al. [7] (78.3%) although they included a less number of patients (23) and less advanced stages (IB2-IIB).

Our patients had a high compliance to RT (91%); this may be less than RT compliance achieved by McCormack et al. [8]. It may be because we had four (8.5%) patients who did not complete CRT due to disease progression, social troubles or shortage of radioactive material. All patients who completed CRT were able to receive all the scheduled concomitant cisplatin. Two of our patients had hydronephrosis and underwent percutaneous nephrostomy before starting NACT. Considering all the previous facts, we can suggest that this regimen is feasible and can be administered safely on outpatient basis. Following CRT, our study showed 72.1% response rate with 13.8% grade 3 toxicity and 0% grade 4 toxicity that was less than McCormack et al. [8] and Singh et al. [5] results. This may be due to the higher radiation dose used by them (50.4 Gy instead of 45 Gy in our study).

We believed that the ongoing multicenter phase III trial (INTERLACE) which is comparing the induction weekly chemotherapy (paclitaxel/carboplatin) for 6 weeks before CRT with the standard CRT alone (ClinicalTrials.gov NCT01566240) will give more information about the efficacy and safety profile of this protocol.

Conclusion

In conclusion, this study has investigated NACT followed by CRT in patients with locally advanced cervical cancer. Its results demonstrate a good response rate to dose dense paclitaxel/carboplatin as a neoadjuvant protocol with acceptable toxicity and high compliance to radiotherapy. Further studies are needed to decide which patient is suitable for this protocol without affection of quality of life and also to compare between this management and the standard CRT.

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