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Original Research

Neoadjuvant chemotherapy with paclitaxel and carboplatin followed by definitive chemoradiation in locally advanced cervical carcinoma. Experience of a cancer hospital in Pakistan

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Objective: To report the efficacy and toxicity of neoadjuvant chemotherapy (NACT) before standard concurrent chemo radiation (CCRT) in locally advanced carcinoma of cervix. *Methods*: Between January 2007 and December 2016, 75 patients with locally advanced cervical cancer treated with neoadjuvant chemotherapy comprising carboplatin area under curve (AUC) 5 and Paclitaxel 175 mg/m^2 followed by chemo radiotherapy 45–59 Gy in 25–28 fractions with concurrent cisplatin and high dose rate (HDR) brachytherapy at our institution were analyzed. Clinical response rate, disease free survival, overall survival and toxicity was evaluated and documented using European organization for research and treatment of cancer (EORTC) criteria. *Results*: Baseline characteristics were median age at diagnosis 48 years; 86% squamous, and 14% adenocarcinoma histology; The international Federation of Gynecology and Obstetrics (FIGO) stage IB2–IIB (47%), III–IVA (53%). 64% had nodes involved and 84% had primary more than 4 cm in diameter. Complete or partial response rate was (95%) post-NACT and 92% (95% CI: 71–94) post-CRT. The median follow-up was 39.1 months. Overall and progression-free survivals at 4 years were 77% and 80% respectively. Grade ¾ hematological toxicities were 7% during NACT (11% hematological, 9% non-hematological) and 8% during CRT. The most common non hematological toxicity was diarrhea in 10%. The delayed toxicities at 24 months or later after CRT completion were rectal (11%), bladder (3%), and vaginal (28%). *Conclusion*: Neoadjuvant chemotherapy in locally advanced cervical cancer offers a favorable paradigm as reflected by acceptable toxicity and is associated with a high response rate in locally advanced cervical cancer. However, further randomized clinical trials are needed to support this evidence.

Keywords

Neoadjuvant chemotherapy (NACT); Locally advanced cervical cancer; Radiotherapy

1. Introduction

Globally cervical cancer is the fourth most common cancer in the women, with almost 85% of cases occurring in developing countries [1]. A large majority of patients in low-income countries present with locally advanced disease due to paucity of effective screening program and human papilloma virus (HPV) vaccine.

Since 1999, concurrent chemo radiation (CCRT) has been established as the standard modality in treating locally advanced cervical cancer (LACC) [2–6]. The survival rates achieved with CCRT range between 58–66%, reflecting the need for additional interventions to further improve survival [7]. The addition of chemotherapy to radiotherapy offers distinct advantage regardless of histology, grade and age, but this benefit is lower in patients with advanced Disease. Moreover, irrespective of treatment, tumors dimension of greater than 4 cm in any direction is associated with worse prognosis. In comparison to smaller tumors [8–10].

The addition of neoadjuvant chemotherapy (NACT) has been addressed in different trials [11–13]. It increases the efficacy of radiotherapy by decreasing the hypoxic cell fraction and treats micro metastatic disease to prevent the relapses [14]. NACT in the treatment of carcinoma cervix has been attempted before definitive surgical management. Many studies were conducted, and results were ambiguous. Compiling all these data, a large meta-analysis concluded that although there was a trend of improved overall survival with the use of NACT, it was still not clear enough to make any definite recommendation. They also concluded that NACT followed by definitive surgical intervention might be a reasonable alternative [15].

Unfortunately, trials attempting NACT before definitive chemo-radiation therapy are less in number, accruing far lesser number of patients and come with more conflicting results. Recently, newer chemotherapeutic agents, e.g., paclitaxel in combination with cisplatin showed remarkable activity against cervical cancer. Also, trials using PVB (Cisplatin, Vincristine, and Bleomycin) came out with encouraging results. In one such trials, Tattersall *et al.* [16], found that use of neo adjuvant chemotherapy was not only associated with better tumor response but also a smaller number of systemic relapses.

Due to prolonged radiotherapy long waiting times, starting induction chemotherapy is the only available option. Radiotherapy alone offers a 5-year survival rate of about 60% in stage IIB, 30–35% in Stage IIIB, and less than 15% in stage

IVA disease. Almost 40–60% of these patients will develop local recurrence while distant failure in about 20–25% patients [17].

Hence, we seek to evaluate the toxicity and efficacy of neoadjuvant chemotherapy followed by radical concurrent chemo radiation in patients with locally advanced cervical cancer.

2. Materials and methods

After obtaining an exemption from institutional review board, medical records of women diagnosed with cancers of cervix uteri and treated with neo adjuvant chemotherapy, from January 2007 to December 2016, were retrospectively reviewed.

All patients had full clinical history and examination including examination under anesthesia (EUA), tissue biopsy, magnetic resonance imaging (MRI) pelvis, and staging computed tomography (CT) chest and abdomen to determine the stage of disease. Lymph nodes with diameter greater than 1 cm in short axis were considered as involved. International Federation of Gynecology and Obstetrics (FIGO) staging for cervical cancers 2009 was used to document the stage. All patients had multidisciplinary team meeting discussion before starting treatment.

Patients with FIGO stage IB–IVA, eastern cooperative oncology group (ECOG) performance status 0–2, adequate renal, liver and bone marrow function treated with neoadjuvant chemotherapy were included. Patients with poor performance status, distant metastatic disease, or clear cell histology was excluded from the study.

NACT comprised of two cycles of paclitaxel (175 mg/m^2) and carboplatin (area under curve [AUC] 5) given every 21 days. Patients were clinically evaluated for any chemotherapy induced toxicity before each cycle using common terminology criteria for adverse events version 4 (CTCAE v4.0, National Cancer Institute 9609 Medical Center Drive Rockville, MD 20850). After completion of recommended courses of chemotherapy, a comprehensive gynecological examination was done to assess the response to chemotherapy, and they were booked for concurrent chemoradiotherapy.

The planning scan was acquired with full bladder and empty rectum as per departmental protocol at slice thickness of 3 mm. Intravenous Iodinated contrast was used to delineate the vessels and aid in contouring The primary tumor present at the time of radiotherapy was countered as GTV (Gross tumor volume) on all CT slices. Any pelvic or paraaortic nodes measuring more than 1cm in short axis were contoured at GTV-N. Clinical target volume (CTV-P) included GTV primary along with entire uterus, cervix, parametria, and upper half of the vagina. Entire length of Vagina was included in CTV case of vaginal involvement. GTV nodal was given an isotropic margin of 0.5 mm all around and then extended to include lower common iliac starting from L4/L5 or at least two cm above the gross nodes, external iliac. internal iliac and Presacral lymph nodes anterior to first and second vertebrae. For patients with paraaortic lymph node involvement, entire paraaortic chain was included in CTV-N. Both CTV-N and CTV-P were combined to make a Final CTV and then 0.8 mm margin was given all around for PTV (Planning target volume).

The prescribed dose was 45.0–50.4 Gy in 25–28 fractions to the PTV followed by 9–16 Gy boost to the involved nodes and parametrium. These plans were generated using VMAT (Volumetric Modulated Arc Therapy) with 2 Full arcs on Aria 15.6 with 6 MV (Mega Voltage) Photons. Online KV CT (Kilo voltage CT) was used to verify position on first three days and subsequently once every week to ensure reproducibility.

These patients were prescribed concurrent chemotherapy with cisplatin 40 mg/m^2 for maximum of 6 cycles. During the last week of external beam radiotherapy, all patients received High dose rate intracavitary brachytherapy 24 Gy/4 fractions Gynecological GEC-ESTRO working group recommendations were used to contour high risk and intermediate risk CTVs, and organs at risk (rectum, sigmoid colon and urinary bladder). Every effort was made to complete the entire radiation treatment within 56 days.

During radiation therapy, *p* was examined weekly for acute toxicity and after treatment, they were evaluated initially after 6 weeks and then at 3 months with MRI. Further follow up visits were scheduled every 3–4 months for first 2 years and then every 6 months thereafter. Patients had first MRI at 12 weeks and then 6 monthly for two years and then annually. Acute and chronic toxicity including genitourinary and gastrointestinal were recorded at each visit using CTCAE v4.0.

Overall survival (OS) and Disease free survival (DFS) were calculated using Kaplan Maier survival curve. Patient characteristics, treatment details and toxicities were presented in tables. IBM SPSS Statistics version 20 (Chicago, USA) was used for recording and data analysis.

3. Results

Between January 2014 to December 2017, a total of 75 patients diagnosed with stage IB2 to IVA cervical cancer at Shaukat Khanum Memorial cancer hospital and research center treated with NACT followed by radical chemoradiotherapy were included. The median follow-up period was 40 months Mean age at presentation was 48 years. About 47% of the patients had stage II disease and 62% of the patients had a tumor size more than 4 cm. About 86% of the patients had evidence of pelvic lymph nodes enlargement on baseline MRI scan. The patient and tumor characteristics, including histological type, stage and grade, are summarized in Table 1.

3.1 Treatment compliance

Of the 75 patients, 50 (66.7%) patients completed planned 2 cycles of NACT while 24 patients received 3 cycles due to delay in radiotherapy appointments while 6 patients were switched to CRT after first cycle. In 5 (6.7%) patients,

Table 1. Patient and treatment characteristics.

Characteristic	Value
Mean age years (range)	48 (29–72)
ECOG PS	
0–1	85
≥2	15
Histology	
Squamous	64 (85.2)
Adeno carcinoma	10 (13.4)
Others (adenosquamous)	1 (1.34)
FIGO stage	
IB–IIB	36
III–IVA	39
Lymph nodes	
Positive	65
Negative	10
Tumor diameter	
Median in cm	5 (1–9)
≥4 cm	85%
Neoadjuvant chemotherapy cycles	
1	6 (8)
≥2	69 (92)
Concurrent chemotherapy	
Yes	73 (97.3)
No	2 (2.70)
Concurrent chemotherapy cycles	
≤3	2
≥4	71

chemotherapy dose was reduced to 25%. Total 73 patients completed 6 weeks of concurrent chemoradiotherapy while two patients received radiotherapy alone. The median time to complete the NACT was 7.5 weeks. All 75 patients underwent intercavitary HDR brachytherapy after completion of EBRT. Median time to start CCRT was 31 days (range 25–45). Majority of the patients (n = 71; 97.2%) more than 4 cycles of concomitant chemotherapy with radiation whereas only 2 (2.8%) patients received 3 due to poor tolerance. Details of treatment characteristics are shown in Table 1.

3.2 Toxicity

During NACT 7% of the patients developed ≥grade III hematological toxicity (thrombocytopenia in 3 patients, and neutropenia in 2 patients). 3 (4%) patients developed febrile neutropenia and received oral antibiotics and granulocyte colony-stimulating factor. 10% of the patients had ≥grade II diarrhea which was managed with loperamide and antibiotics (Table 2). During CCRT, 6 (7%) patients developed ≥grade III hematological toxicity during CRT and two had febrile neutropenia There was no treatment-related deaths. There was no grade III skin, lower genitourinary, or gastrointestinal toxicity during CRT (Table 3).

Table 2. Severity and frequency of induction chemotherapy induced acute toxicity (n = 75).

Toxicity	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n
Hematological				
Anemia	5	3	0	0
Thrombocytopenia	0	1	3	0
Neutropenia	1	3	1	1
Non-hematological				
Diarrhea	8	7	1	0
Vomiting	16	1	0	0
Neuropathy	12	4	0	0

Table 3. Severity and frequency of concurrent chemo radiation induced acute toxicity (n = 73).

Toxicity	Grade 1, n	Grade 2, n	Grade 3, n	Grade 4, n
Hematological				
Anemia	4	3	1	0
Thrombocytopenia	8	4	1	0
Neutropenia	10	7	4	0
Non-hematological				
Proctitis	12	3	0	0
Cystitis	9	2	0	0
Dermatitis	4	0	0	0

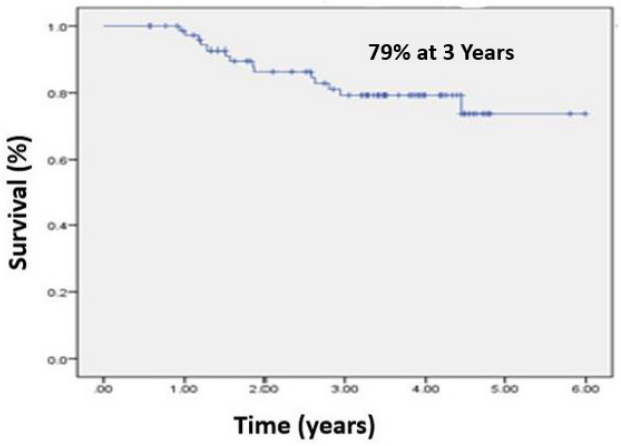

Fig. 1. Kaplan-Meier plots for overall survival (75 pts).

3.3 Response and failure

71 (95%) patients had a good clinical partial or complete response after NACT. One patient had no response, and three (4%) patients had progressive disease. At 12 weeks after CRT, 54 (72%) patients had a complete response to therapy, 15 (20%) patients had partial response, and 4 (5%) patients had progressive disease (Table 4). Currently 44 patients continued to be in CR at a median follow-up of 32 months (range, 12 to 69 months). Of the 19 patients, who developed progressive disease while on follow-up, 3 patients had a local recurrence and 16 had distant metastasis. The median overall survival was not reached and 3-year overall survival was 79% (95% CI: 70–88), The median progression-free survival was not

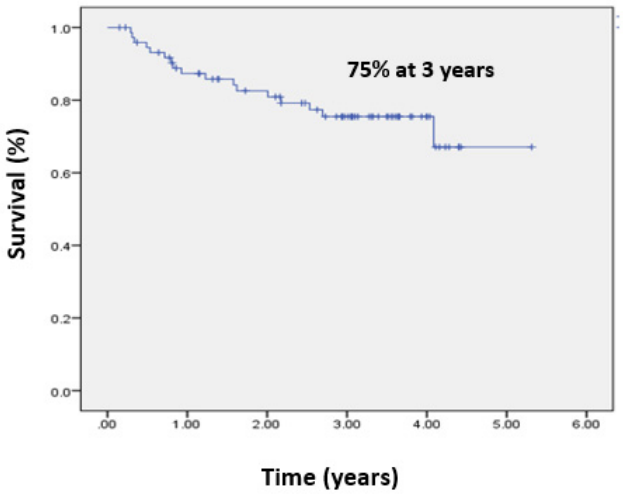

Fig. 2. Kaplan-Meier plots for disease free survival (75 pts).

Table 4. Response to neoadjuvant and CCRT.

Response	n (%)
Neoadjuvant chemotherapy	
Complete response	19 (25%)
Partial response	52 (69%)
Stable disease	1 (1%)
Progression	3 (4%)
Concurrent chemoradiotherapy	
Complete response	54 (72%)
Partial response	15 (20%)
Stable disease	2 (3%)
Progression	4 (5%)

CCRT, Concurrent chemoradiotherapy.

reached and 3-year progression-free survival was 75% (95% CI: 68–80) (Figs. 1,2). The 3 years overall survival for stage I–II and III–IV is 85% and 75% respectively while DFS for early stage (I and II) and advanced stage (3 and 4) is 82% and 78% respectively. 26% (20 patients) developed relapse and 13 patients had disease associated death. The median time to relapse was 11 months (2–44 months). 3 patients progressed locally, 6 in regional and paraaortic nodes and 11 patients had distant disease. In patients with local relapse two patients were treated with salvage surgery while others were treated with palliative chemotherapy and radiotherapy depending upon site of relapse, their performance status and symptoms.

4. Discussion

Our data shows that addition of neoadjuvant chemotherapy with carboplatin and paclitaxel followed by standard concurrent Chemoradiotherapy, and brachytherapy achieves a high response rate with local control of the disease comparable to other studies. This also facilitates the radiotherapy plane in locally advanced cases with no inferiority of the PFS and OS compared to the standard.

The best possible treatment for locally advanced cervical cancer remains debated and different modalities have been used in an attempt to improve outcomes and quality of life. A retrospective review concludes that NACT in locally advanced cancer improved DFS in high risk population. Recently, a randomized study comparing surgery vs. brachytherapy after chemoradiotherapy in locally advanced cervical cancer patients showed no significant survival advantage while in another retrospective review addition of surgery to chemoradiotherapy showed no survival advantage [18–20].

Rising incidence of locally advanced cervical cancer in imposes a serious oncological dilemma in developing countries. NACT offers a theoretical advantage of tumor downstaging and eradicating micrometasis which could lead to improved progression free and overall survival but till date efficacy and safety of NACT remains debatable and there is lack of agreement worldwide on this approach. Although a metanalysis showed that neoadjuvant chemotherapy plays a role in downstaging the primary tumor and reduce the chance of lymph node and distant metastasis in patients with stage IB1 to IIA cervical cancer [21]. On the contrary no significant benefit of NACT was observed in other studies [22, 23]. Hence more studies are needed to investigate the benefit of NACT on patients with locally advanced cervical cancer and the role remains undefined.

NACT for cervical cancer include various chemotherapeutic doublet agents like cisplatin with 5-FU o vincristine, paclitaxel and paclitaxel with carboplatin The GOG-204 trial showed a trend in Response rates, and progression free survival with paclitaxel and cisplatin in patients with advanced cervical cancer [24]. Another GOG trial also showed that adding paclitaxel to cisplatin increased the response rates from 19% (6% complete plus 13% partial) to almost 36% [25].

As per our institutional experience NACT with carboplatin/paclitaxel is a feasible approach in locally advanced bulky cervical cancers with no increased toxicity and a it did not compromise the chemoradiotherapy as well with 97% of the patients completed their planned radical chemoradiotherapy and 71% received at least 4 cycles of concomitant cisplatin.

In general, NACT in our experience was well tolerated with only 7% of patients developed any grade 3/4 toxicity and with deaths attributed to chemotherapy. The G3/4 neutropenia rate of 7% in our experience is much lower than the 15% reported by Dueñas-Gonzãlez *et al.* [26].

The response rate of 95% with neoadjuvant chemotherapy in our study is quite comparable with that reported in other studies of neoadjuvant chemotherapy. A study by Park *et al.* [27] noted a response rate of 91% (assessed clinically and radiologically 10 days post treatment) in women with FIGO Ib2-IIb treated with neoadjuvant chemotherapy. Similarly, a study by Dueñas-González *et al.* (2003) [28] in which 43 patients of FIGO IB2–IIIB treated with three cycles of carboplatin and paclitaxel prior to hysterectomy and CRT reported response rates of 95.

The rate of adverse events found in our study is significantly different from the incidence reported in other trials. Grade 3–4 hematologic and non-hematologic toxicity was reported in 28.5% and 7% of patients respectively by Singh *et al.* [29]. Angioli *et al.* [30] reported grade 3–4 hematologic toxicity in 8%. Post neo adjuvant chemotherapy, grade 3–4 toxicity was 20% in a study conducted in UK, where as we have reported it to be 7% only [27], further favoring NACT as a very tolerable and feasible treatment option for locally advanced cervical tumors.

Patients who received CCRT, grade 1–2 hematological toxicity were reported to be 48% while 3–4 were 8% only, with neutropenia being the most observed. R.B. Singh *et al.* [29] described 29% hematological toxicity whereas McCormack *et al.* [31] described toxicity in 52% of patients.

The overall clinical/radiological response rate to neoadjuvant chemotherapy in current study (complete and partial response) is 92% at 12 weeks post-CRT, and the 3-year PFS and OS rates were 79 and 75% respectively. In a recent study where Radical surgery was performed after standard CRT in locally advanced cervical cancer the overall disease free survival and overall survival was 73% and 80% respectively which is comparable to our study [32]. As per an Audit report of Royal College of Radiologists' a 5-year overall survival of these historical controls was 56% [33]. INTERLACE (Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer, NCT01566240) is an ongoing multicentric trial comparing the induction chemotherapy with weekly carboplatin/paclitaxel for 6 weeks followed by standard concurrent chemoradiotherapy CCRT and standard concurrent chemoradiotherapy with cisplatin 40 mg/m^2 weekly followed by Brachytherapy. In our study relapse rates were 26% which compares favorably to other studies where relapse is reported to be in the range of 20–28% [34, 35]. One of the main limitations of our study is the retrospective study design and single institutional study.

In summary, our data has demonstrated an excellent response rate to neoadjuvant chemotherapy with no additional toxicity.

5. Conclusions

In conclusion, countries like Pakistan bear a disproportionate high burden of cervical cancer due to insufficient infrastructure, lack of preventive HPV vaccines program, national screening drives, and access to radiotherapy facility. Adaptive and tailored approach with neoadjuvant chemotherapy followed by chemoradiation in all locally advanced cases of cancer cervix is an attractive strategy for locally advanced cervical cancer without compromising their outcome with no additional toxicity and potential benefit of eradicating micrometasis. However prospective and randomized phase III trials with longer follow up are required to further clarify the role of this approach.

Author contributions

TS—designed the study, manuscript writing; AR—data collection, analysis; SJ—analysis, writing manuscript; SN: data collection, analysis; AS: data collection, analysis; MAM—data collection, anwalyse the data; RM—data collection and planning. All authors contributed in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol was approved and granted exemption by Institutional Review Board Shaukat Khanum Memorial cancer hospital and research center, Lahore (Exemption number: EX-06-07-20-01).

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Conflict of interest

The authors declare no conflict of interest.

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