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# Efficacy And Tolerance Of Double-Agent Neo-Adjuvant Chemotherapy Followed By Concurrent Chemoradiation For Locally Advanced Cervical Cancer

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**Abstract**

**Background:** This study aims to investigate the feasibility, safety and efficacy of neoadjuvant chemotherapy (NACT) with carboplatin and paclitaxel followed by CCRT.

**Methods**

Patients were randomised to two arms: In the conventional arm (Arm 1, n=20 ), patients were managed by the standard protocol of weekly Inj Cisplatin 40mg/m$^2$ concurrently with pelvic EBRT followed by ICRT. Patients in interventional arm (Arm 2, n=20) were managed by six cycles of weekly neo-adjuvant chemotherapy using Inj. Paclitaxel (80 mg/m$^2$) and Inj. Carboplatin (AUC 2.0) followed by CCRT and ICRT.

**Results**: At 6 months of follow up, 13 patients in Arm-1 and 14 patients in Arm-2 were in complete response. In Arm-1, at 03 months, anaemia (20% Grade 2 and 3) and neutropenia (50% Grade 2 and 3) were the commonest acute toxicities while at 6 months, anaemia (20% Grade 2 and 3) and vaginal stricture (35% Grade 2 and 3) were the commonest delayed toxicities. In Arm-2, at 03 months, anaemia (45% Grade 2 and 3), neutropenia (55% Grade 2 and 3) and neuropathy (35% Grade 2 and 3) were the commonest acute toxicities while at 6 months, anaemia (55% Grade 2 and 3) and neuropathy (50% Grade 2 and 3) were the commonest delayed toxicities.

**Conclusion:** There is no statistically significant difference between the two arms regarding the tumor response and disease outcome although there was a marginal benefit seen in complete response rate in arm 2. However, arm 2 has more incidences of anemia and neuropathy with statistically significant p-value.

**Keywords**: Ca Cervix, chemoradiation, locally advanced, neoadjuvant chemotherapy, toxicities, survival

## Introduction

Globally, an estimated 662,044 cases and 348,709 deaths from cervical cancer occurred in 2022, corresponding to the fourth cause of cancer morbidity and mortality in women worldwide. India, in particular, carries a substantial burden, accounting for roughly one-fifth of new cases and nearly one-fourth of deaths globally. In India, it is the second most common cancer, contributing to approximately 122,844 new cases and 67,477 deaths annually. It is a major health concern for Indian women, with a cumulative lifetime risk of 2.5 % and a cumulative death risk of 1.4 %. The peak age for developing cervix cancer is typically between 45 and 54 years. In developing countries, the disease is usually advanced by the time of diagnosis, the prevalence is much higher, and cervical cancer is the principal cause of

death due to cancer in women.[1-4] Since 1999, the National Cancer Institute Alert has strongly supported the use of concurrent radiochemotherapy (CCRT) as standard treatment of locally advanced cervical cancer (LACC). In 5 phase III clinical trials reported in 1999, CCRT was shown to reduce the incidence of LACC recurrence by 50% compared to radiotherapy alone. [5] A meta-analysis covering 13 clinical trials revealed that CCRT in patients with LACC could improve 5-year overall survival (OS) and progression-free survival (PFS) by 10% and 13%, respectively.[6.7]

Despite CCRT, the overall survival (OS) for stage IIB and III-IV cervical cancer is approximately 60–65% and 25%-50%, respectively, which are frustratingly low.[8] About 30-40% of patients with locally advanced cervical cancer fail to achieve complete response to CCRT; alternative approaches are needed to improve the outcome for such patients.[9] Neoadjuvant chemotherapy (NACT) prior to surgery or radiotherapy has been investigated as a new therapeutic strategy for a voluminous or locally advanced disease. The reasons for using neoadjuvant chemotherapy (NACT) are several. Reducing the size of the tumor can later facilitate local therapy, either radiotherapy or surgery. This reduction can convert inoperable tumors to resectable ones. It has also been suggested that NACT increases the radiosensitivity and decreases the fraction of hypoxic cells. Moreover, NACT treats the micrometastatic disease, preventing a significant proportion of relapses. Finally, the NACT response was identified as an important prognostic factor in several studies.[10-12] On the other hand, some concerns have been associated with the use of NACT. In patients who do not respond to chemotherapy, the administration of curative treatment will have been delayed unnecessarily. Moreover, some chemotherapy agents could have cross-resistance with radiotherapy, inducing the development of radioresistant cellular clones.[13]

In the last two decades, there has been a renewed interest to explore alternative approaches to improve the outcome for patients with LACC. Weekly paclitaxel and carboplatin for 4-6 weeks as dose-dense chemotherapy prior to CCRT could be one such potential approach.[14] Traditional triweekly (once every 3 weeks) regimens of NACT followed by CCRT may not be superior to CCRT alone for the treatment of LACC and there is a need to explore the feasibility of improved survival with weekly NACT regimens.[15]

There is paucity of published Indian studies as well as any prospective randomized data in world literature to study the outcome and toxicity profile of 6 cycles of Inj Paclitaxel and Inj Carboplatin before standard concurrent chemoradiation (Pelvic EBRT concurrently with weekly Inj Cisplatin). The present study is being designed with this purpose. The aim of this study was to compare the efficacy and tolerance of double-agent neo-adjuvant chemotherapy followed by concurrent chemoradiation with the standard protocol of concurrent chemo-radiation alone for locally advanced cervical cancer.

**Methodology**

It was an experimental prospective randomized comparative interventional study that was carried out at the Oncology Centre at a tertiary care super speciality hospital with academic and research interests in government setup in India. A total of 40 patients were randomised to two arms: In the conventional arm (Arm 1, n=20 ), patients were managed by the standard protocol of weekly Inj Cisplatin 40mg/m$^2$ concurrently with pelvic EBRT followed by ICRT. Patients in interventional arm (Arm 2, n=20) were managed by six cycles of weekly neo-adjuvant chemotherapy using Inj. Paclitaxel (80 mg/m$^2$) and Inj. Carboplatin (AUC 2.0) followed by CCRT and ICRT. The inclusion criteria were patients with histologically confirmed Squamous Cell Carcinoma/ Adenocarcinoma cervix, patients with cervical cancer stage IIB to IVB (limited to para aortic lymph node involvement or spread of growth to adjacent organs without any distant metastasis) as per FIGO 2009 staging, no previous malignancy/radiation to pelvis/chemotherapy, age group < 70 yrs., non pregnant/ non-nursing females, and normal biochemical parameters.

The descriptive statistics was measured by mean SD for quantitative variables and median with range for qualitative variables. Varieties of charts and diagrams are used to represent data graphically for comparison. The statistical comparison between two groups for quantitative variables are assessed by student t test. The Pearson chi square test is also used to assess the association between categorical variables.The data was entered in MS EXCEL VERSION 2007. All statistical analysis was performed by using SPSS software version 16.0.



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In our study we have treated our patients with external beam radiotherapy by 2D planning to pelvis on a linear accelerator with 15 MV photons by two/four field technique (depending upon patient separation ratio, >21 to use four field) to a dose of 5040 cGy @ 180cGy/fraction, 5 days a week over a period of 5-6 weeks along with concurrent chemotherapy in both the arms and if indicated para-aortic field will be treated to a total dose of 4500 cGy @ 180 cGy/fraction. In both the arms, Brachytherapy was done on an HDR (High dose rate) machine remote after loading machine with Iridium-192 radioactive source at a dose of 7Gy/# for 03 fractions at 5-7 days inter-fraction interval.

The toxicities were assessed in patient and highest grade was recorded as per the prevalent version of RTOG/EORTC & CTCAE 4.03 grading system in the two groups.[16,17] After completion of ICRT , the patient were followed up meticulously at 03 months and then at 06 months and subsequently every 12 weeks up to the end of this study period, for response assessment incorporating RECIST (Response assessment criteria in solid tumors) & PERCIST criteria (PET response criteria in solid tumors).[1]

**Observation And Results**

The mean age of the patients in the conventional arm (Arm 1, n=20) was 56.5 years (range 39-69 years) and for the interventional arm (Arm 2, n=20) was 52.8 years (range 33-69 years) All patients were homemakers and were non smokers too. 5/20 patients in Arm 1 and 7/20 in Arm 2 had comorbidities like Hypertension, Diabetes Mellitus and Hypothyroidism and COPD (chronic obstructive pulmonary disease). The average pretreatment hemoglobin in Arm 1 was 11.10 gm/dl and in Arm 2 was 11.01 gm/dl. The relevant clinical characterisitcs of the study population are given in Table-1.

Histopathologically, in both Arms, 19 patients (19/20, 95%) had Squamous cell carcinoma (SCC) & 1 patient (1/20, 5%) had Adenocarcinoma (ADC) in each of the arms**.** **T**he commonest pool in which maximum number of patients were enrolled in this study as per FIGO staging was stage IIB followed by stage IIIB. All the patients in Arm 2 were offered neo-adjuvant chemotherapy in the form six cycles of weekly Inj. Paclitaxel and Inj. Carboplatin. All 20 patients, could endure and complete the planned 6 cycles of neo-adjuvant chemotherapy protocol on day 1, day 8, day 15, day 22, day 29 and day 36.

Majority of patients in both the treatment arms received ≥5 cycles of weekly concurrent Inj. Cisplatin along with radiation. One patients in arm 1 and two patient in arm 2 could receive only 3 cycles of chemotherapy in view of acute toxicities (grade 3 Acute). Apart from these four patients in arm 1 and five patients in arm 2 could receive only 4 cycles of chemotherapy. Taken together 28 out of 40 patients (70%) including both the arms could tolerate the desired 5 or more cycles of weekly concurrent Inj. Cisplatin (15/20 in arm 1, 13/20 in arm 2.) The mean treatment time of completing definitive CCRT followed by ICRT in Arm 1 was around 63.25 days (range 54-72 days) and in Arm 2 was 64.20 days (range 57-71 days).

Acute significant toxicities (Table-2) were observed in a small subset of patients of both the study arms upto first 3 months of follow up. In both the study arms, majority of the patients tolerated respective protocol treatments without significant toxicities warranting any interruption/delay of treatment. In Arm 1, 9/20 (45%) of the patients had anemia of which 55% had Grade 1, 22% Grade 2 and 22% had Grade 3**.** In Arm 2, 11/20 (55%) of the patients had anemia, with 18% having Grade 1, 36% having Grade 2 and 45% having Grade 3. It was noted that Grade 3 neutropenia occured in 4/20 (20%) patients of Arm 1 and 7/20 (35%) of Arm 2, thus grade 3 neutropenia is one of the major acute toxicity present post therapy in patient population of interventional arm. In Arm 1, not even a single patient exhibited features of neuropathy whereas in Arm 2, 7/20 (35%) of the patients had neuropathy, with 71% having grade 2 and 29% having grade 3. In Arm 1, the incide nce of alopecia as an acute toxicity was nil whereas in Arm 2, 2/20 (10%) of the patients had alopecia and all were grade1. Various other adverse events like AKI (acute kidney injury), cystitis, enteritis, proctitis, skin reactions and vaginal stricture were also noticed in patients of both the arms within 3 months of their follow up and were comparable in both the arms.

Late toxicities after 3 months of completion of treatment protocol till last follow up of the patient are as shown in Table no. 3. In Arm 1, 9/20 (45%) patients had anemia, of which 55% had grade 1, 22% had grade 2 and 22% had grade 3**.** In Arm 2 (interventional arm,



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n=20), 11/20 (55%) of the patients had anemia, with 0% having grade 1, 64% having grade 2 and 36% having grade 3. In Arm 1, not even a single patient exhibited features of neuropathy whereas in Arm 2, 10/20 (50%) of the patients had neuropathy, with 0% (0/20) having grade 1, 45% (9/20) having grade 2 and. 5% (1/20) having grade 3 effects. Thus considerably more number of patients in arm 2 developed neuropathy as compared to patients in arm 1 (50% Versus nil respectively; p-value 0.001). In Arm 1, the incidence of alopecia as a late toxicity was nil whereas in Arm 2, 4/20 (20%) of the patients had alopecia and they were grade 1 (3/4, 75%) or grade 2 (1/4, 25%). In Arm 1, 8/20 (40%) patients had vaginal stricture of which 12.5% had Grade 1, 50% had Grade 2 and 37.5% had Grade 3**.** In Arm 2 (interventional arm, n=20), 4/20 (20%) of the patients had vaginal stricture, with 0% having Grade 1, 75% having Grade 2 and 25% having Grade 3. Apart from above mentioned toxicities, various other adverse events like cystitis, enteritis and proctitis were also noticed in patients of both the arms from 3 months till 6 months of their follow up. All of them were almost equally observed in both the arms without any statistically significant correlation. No patient from any of the two arms developed neutropenia as a late toxicity.

Clinico-radiological response assessment was done at 12 weeks and 24 weeks of completion of planned treatment in both the arms. At 3 months (Table-4), in Arm 1, three (3/20, 15%) patients had local residual disease detected clinically and proven by biopsy and were offered surgery or palliative chemotherapy. Another three (3/20, 15%) patients who had well controlled primary on clinical examination showed progressive disease on CECT scan; out of whom 2 had only para-aortic nodal chain involvement and were offered Radiotherapy (RT) to para-aortic region; while the remaining 1 had distant metastasis and was switched to palliative chemotherapy. Remaining 14/20 (70%) patients attained CR (complete response) as per RECIST 1.1 criteria. 2 out of these 14 patients who were in CR based on CECT findings still had a FDG avid residual disease on PET scan and were placed in PMR (partial metabolic response) group as per PERCIST criteria. These 2 patients who attained PMR at 3 months of evaluation were later found to be in CMR (complete metabolic response) on repeat PET-CT at 6 months of follow up.

In Arm-2 (Table-4), three (3/20, 15%) patients had residual disease (PR/PMR as per RECIST/PERCIST criteria respectively) on clinicoradiological examination. Two of these three patients were found to have local residual disease on the basis of clinical examination. Out of these two patients, one had partial response and another had progressive disease on CECT as per RECIST criteria, whereas they had stable metabolic disease and progressive metabolic disease on PET CT examination as per PERCIST criteria respectively. One patient, who was clinically NAD, was found to have progressive disease and progressive metabolic disease on CECT and PET CT examination respectively. **Two** of them were proven on biopsy, of whom one underwent exenteration surgery and one received palliative chemotherapy. One patient could not be proved to be harbouring residual disease despite multiple biopsies and ultimately became widely metastatic and was put on palliative chemotherapy at 6 months follow up. Rest all (17/20, 85%) were in CR/CMR as per RECIST/PERCIST criteria .

At 6 months, in Arm-1, out of 14/20 patients who were labelled clinicoradiologically as in CR/CMR at 3 months, one out of them was found harbouring a local recurrence on clinical and radiological assessment which was confirmed on biopsy. This patient was started on palliative chemotherapy as she was not willing for any surgery. Two patients who have undergone surgery were still having residual disease. Out of two patients, who were offered palliative chemotherapy after three months, one did not respond to chemotherapy either and her disease had further progressed. Another patient who was offered palliative chemotherapy on evaluation at later stage revealed further progression of the disease. Two patients who were offered radiotherapy to para-aortic lymph nodes, were found to have progressive disease and progressive metabolic disease on CECT and PET CT scan as per RECIST/PERCIST criteria respectively. Thus at 6 months of follow up of this study, 13 patients (13/20, 65%) were deemed disease free (in CR/CMR) in arm 1.

In Arm-2 at 6 months of follow up, after excluding the **three** (3/20) patients who have either had a local or distant metastatic disease and were already been subjected to additional treatment at 3 months of follow up, 3 out of remaining 17 patients who were in CR/CMR at three months, now detected with either local recurrence or metastasis to distant sites. 1 out of



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these 3 patients had only central recurrence and underwent exenteration surgery after histopathological confirmation of recurrence and rest 2 were offered palliative chemotherapy. Thus at 6 months of follow up, 14 patients (14/20, 70%) were deemed disease free (in CR/CMR) in arm 2. Accordingly, it can be said that out of 20 patients in interventional arm, three had undergone surgery for local residual disease/local recurrence and three were receiving palliative chemotherapy after 06 months of follow up.

To summarize, at 6 months of follow up, in arm 1,out of 20 accrued patients, 13 patients were confirmed to be in CR, 2 patients who underwent exenteration for central local recurrence were in poor general condition because of disease process and toxicity of various treatment modalities, and remaining 5 patients who had either unresectable local disease, were unwilling for surgery or had distant metastasis were undergoing palliative chemo/supportive care at medical oncology department at the time of last follow up. In arm 2, 14 patients out of 20 were in CR at 6 months of follow up, 2 underwent exenteration surgery and remaining 4 patients were started on palliative chemo/supportive care when reported for last review.

**Discussion**

Since 1999, the standard treatment of locally advanced cervical cancer (LACC) has been pelvic radiation with concurrent cisplatin, with an absolute improvement of 12% in overall survival compared with radiotherapy alone.[19] It is important to investigate better treatment strategies considering that approximately 40% of patients experience recurrence within 5 years. The use of NACT before radiotherapy could potentially eradicate subclinical distant metastasis, reduce the tumor size and correct pelvic anatomy distortion, and ultimately allow better delivery of radiation.[15]

In our study, post completion of planned therapy, 13 patients out of 20 in arm 1 and 14 patients out of 20 in arm 2 (who received NACT with Inj Paclitaxel and Inj Carboplatin) were in CR at 6 months of follow up. Li J and coworkers investigated the feasibility, safety and efficacy of NACT with weekly cisplatin and paclitaxel (TP) followed by CCRT in locally advanced ca cervix (LACC). Among 50 patients enrolled in the NACT + CCRT arm, the complete and partial response rates were 10.4% and 68.8%, post-NACT. Twelve weeks after treatment completion, the complete response rate was 72.0%, whereas the total response rate (complete and partial response) was 90.0%. After a median follow-up of 28 months, the 3-year OS rate was 83.9%, and the 3-year PFS rate was 73.6%. NACT response was related to superior PFS and OS compared with NACT nonresponse ($P < 0.01$). Late adverse effects (AEs) were exiguous, while early AEs mainly included myelosuppression and gastrointestinal AEs. This study showed a good response rate achieved by dose-dense weekly cisplatin and paclitaxel followed by standard CCRT.[15,20]

In our study, anaemia, neutropenia and neuropathy were the commonest acute complications while anaemia and neuropathy were the commonest remote complications in the interventional arm. In another Indian study, Singh RB and colleagues evaluated the role of dose dense NACT prior to standard CCRT in locally advanced cervical cancer. 28 patients with locally advanced cervical cancer received NACT using paclitaxel (60 mg/m(2)) and carboplatin (AUC-2) weekly for 6 doses. After a mean interval of 15 days (range 7-23 days), the patients then received definitive radiation and concomitant weekly infusion of cisplatin (40 mg/m(2) for 6 doses). Following NACT, 67.8% of patients responded; complete (CR) - 2(7.1%), Partial (PR) - 17 (60.7%), stable 7 (25.0%) and 2 patients (7.1%) progressed. 24 of 28 patients received CCRT; 23/24 achieved CR. 22 of 23 complete responders continue to be in CR at a median follow-up of 12 months (range, 7 to 24 months). Grade III/IV neutropenia was the main hematological toxicity seen in 28.5% and 29% of patients, respectively during NACT and CCRT. The authors concluded that neoadjuvant chemotherapy with dose dense weekly paclitaxel and carboplatin followed by standard CCRT is a feasible approach and is associated with a high response rate in locally advanced cervical cancer. [21]

We have used weekly NACT regimen of Paclitaxel and Carboplatin in our study. Studies have shown traditional thrice-weekly platinum-based NACT followed by CCRT has been applied to LACC patients. Narayan et al. [20] retrospectively compared the effect of 2 cycles of thrice-weekly TPF (cisplatin + paclitaxel + 5-flurical) or TF (cisplatin + 5-flurical) followed by CCRT vs. CCRT alone in 723 stage IIB–IIIB cervical cancer patients. They found that NACT followed by CCRT could improve 5-year progression-free survival (58.3% vs. 41.8%) but had no impact on the overall survival. Marita et al.[12] retrospectively



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analyzed the survival of 207 stage IIB–IIIB cervical cancer patients who received 2–4 cycles of three-weekly platinum-based NACT prior to CCRT. The results revealed that the 5-year survival rates for stage IIB–IIIA and IIIB were 84% and 61%, respectively, which are superior to the survival rates of traditional CCRT reported in the literature. Another randomized open-label phase II trial enrolled 107 patients, 55 randomly assigned to the NACT arm with three cycles of cisplatin and gemcitabine followed by standard CRT with weekly cisplatin plus pelvic radiotherapy; and 52 to the CCRT-alone arm. NACT was associated with an inferior 3-year PFS (40.9% vs. 60.4%), a lower 3-year OS rate (60.7% vs. 86.8%), and a lower complete response rate (56.3% vs. 80.3%).[22] A recent landmark development was the INTERLACE trial which was a multicentre, randomised phase 3 trial done to determine whether induction chemotherapy (once-a-week intravenous carboplatin area under the receiver operator curve 2 and paclitaxel 80 mg/m$^2$ for 6 weeks) followed by standard cisplatin-based chemoradiotherapy improves both progression-free survival and overall survival in locally advanced cervical cancer. Between Nov 8, 2012, and Nov 17, 2022, 500 eligible patients were enrolled and randomly assigned to the chemoradiotherapy alone group (n=250) or the induction chemotherapy with chemoradiotherapy group. After a median follow-up of 67 months, 5-year progression-free survival rates were 72% in the induction chemotherapy with chemoradiotherapy group and 64% in the chemoradiotherapy alone group with a hazard ratio (HR) of 0·65 (95% CI 0·46-0·91, p=0·013). 5-year overall survival rates were 80% in the induction chemotherapy with chemoradiotherapy group and 72% in the chemoradiotherapy alone group, with an HR of 0·60 (95% CI 0·40-0·91, p=0·015). Grade 3 or greater adverse events were reported in 147 (59%) of 250 individuals in the induction chemotherapy with chemoradiotherapy group versus 120 (48%) of 250 individuals in the chemoradiotherapy alone group. This trial shows that short-course induction chemotherapy followed by chemoradiotherapy significantly improves survival of patients with locally advanced cervical cancer.[23] In our study, the mean treatment time of completing definitive CCRT followed by ICRT in Arm 1 was around 63.25 days (range 54-72 days) and in Arm 2 was 64.20 days (range 57-71 days). Shih-Min Lin et al[24] evaluated the correlation between overall treatment duration and clinical outcome in cervical cancer patients treated primarily with curative CCRT. In this population-based cohort study, 2,594 patients diagnosed with FIGO stage I-IVA uterine cervical cancer were studied. The median irradiation duration was 59 days. Significant prognostic factors related to poor cancer-specific survival (CSS) and overall survival (OS) included old age, non-squamous cell cancer type, high-grade histology, increased tumor size, advanced FIGO stage, and prolonged OTT. After multivariate analysis, prolonged treatment time remained as a significant factor for poor CSS (hazard ratio, HR = 1.33; $p < 0.001$) and OS (HR = 1.15; $p = 0.05$). Further subgroup analysis showed that the 5-year OS rates after a treatment time of ≤ 56 days compared with > 56 days in patients with FIGO stages I-IIB and III-IVA were 70% and 65% ($p = 0.002$) compared with 43% and 42% ($p = 0.67$), respectively. In conclusion, completion of CCRT within 8 weeks is recommended, particularly for patients with FIGO stage I-IIB disease.

## Conclusion

Taxane and platinum based neo-adjuvant chemotherapy before definitive concurrent chemoradiotherapy is an effective and well tolerated treatment for locally advanced cervical cancer, without any major functional limiting or disabling impairment/toxicity. Moreover, the simple and convenient administration schedule is likely to be acceptable to patients because treatment can be administered on an outpatient basis. All the patients could tolerate the neo-adjuvant chemotherapy followed by definitive treatment and are still coming for follow up at the time of concluding this study. Hence it is a feasible option provided the patients can be meticulously supervised and offered timely supportive care.

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**Table 1: Population Clinical Characteristics**

| Parameter | | Arm 1 | Arm 2 |
|---|---|---|---|
| **Age** | Mean (Years) | 56.5 | 52.8 |
| | Range (Years) | 39-69 | 33-69 |
| **Comrbidities** | Hypertension | 2 | 3 |
| | DM-II | 2 | 2 |
| | COPD | 1 | 1 |
| | Hypothyroidism | 0 | 1 |
| **KPS*** | 90% | 19 | 19 |
| | 80% | 1 | 1 |
| **Mean Hb (gm/dl)** | (Pre-treatment value) | 11.10 | 11.01 |



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| | | | |
|---|---|---|---|
| **Histology** | SCC | 19 | 19 |
| | ADC | 1 | 1 |
| **Grade of Tumour** | Well differentiated | 7 | 7 |
| | Moderately differentiated | 9 | 10 |
| | Poorly Differentiated | 4 | 3 |
| **FIGO staging##** | II B | 7 | 6 |
| | III A | 3 | 2 |
| | III B | 4 | 6 |
| | IV A | 4 | 4 |
| | IV B | 2 | 2 |
| **LN involvement positive** | Pelvic | 16 | 16 |
| | Inguinal | 0 | 1 |
| | Paraaortic | 2 | 2 |
| **No of cycles of concurrent chemo** | 3 | 1 | 2 |
| | 4 | 4 | 5 |
| | 5 | 3 | 8 |
| | 6 | 12 | 5 |
| **Mean treatment time** | (Definitive CCRT followed by ICRT) | 63.25 | 64.20 |

* Karnofsky Performance Scale

# SCC- Squamous Cell Carcinoma, ADC- Adenocarcinoma

## The International Federation of Gynecology and Obstetrics (FIGO) staging 2009

@ Lymph node involvement on clinical examination/CECT/PET-CT

**Table 2: Data Showing Site Specific Acute Toxicities In Both Arms.**

| **Acute toxicities (within 3 months)** | **Group** | | | | | | | | **Pearson Chi-Square** | **p-value** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Conventional** | | | | Interventional | | | | | |
| | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | | |
| **Nausea** | 13 | 1 | 6 | 0 | 15 | 1 | 4 | 0 | 0.543 | 0.762 |
| **Vomiting** | 13 | 1 | 6 | 0 | 15 | 1 | 4 | 0 | 0.543 | 0.762 |
| **AKI** | 17 | 3 | 0 | 0 | 19 | 1 | 0 | 0 | 2.361 | 0.307 |
| **Anaemia** | 11 | 5 | 2 | 2 | 9 | 2 | 4 | 5 | 2.867 | 0.413 |



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| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Neutropenia** | 9 | 1 | 6 | 4 | 12 | 1 | 4 | 7 | 1.129 | 0.048 |
| **Skin** | 17 | 2 | 1 | 0 | 15 | 0 | 5 | 0 | 4.792 | 0.091 |
| **Neuropathy** | 20 | 0 | 0 | 0 | 13 | 0 | 5 | 2 | 8.485 | **0.014** |
| **Cystitis** | 16 | 0 | 3 | 1 | 16 | 0 | 4 | 0 | 1.143 | 0.565 |
| **Proctitis** | 18 | 1 | 1 | 0 | 15 | 5 | 0 | 0 | 3.939 | 0.139 |
| **Enteritis** | 18 | 0 | 2 | 0 | 17 | 0 | 3 | 0 | 0.229 | 0.633 |
| **Vaginal stricture** | 18 | 2 | 0 | 0 | 17 | 1 | 2 | 0 | 2.362 | 0.307 |
| **Alopecia** | 20 | 0 | 0 | 0 | 18 | 2 | 0 | 0 | 4.444 | **0.035** |

**Table 3: Data Showing Site Specific Late Toxicities In Both Arms.**

| **Late toxicities (after 3 months)** | **Group** | | | | | | | | **Pearson Chi-Square** | **p-value** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Conventional** | | | | **Interventional** | | | | | |
| | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 | | |
| **Anaemia** | 11 | 5 | 2 | 2 | 9 | 0 | 7 | 4 | 2.867 | 0.413 |
| **Neutropenia** | 20 | 0 | 0 | 0 | 20 | 0 | 0 | 0 | 1.129 | 0.048 |
| **Neuropathy** | 20 | 0 | 0 | 0 | 10 | 0 | 9 | 1 | 8.485 | **0.014** |
| **Cystitis** | 18 | 0 | 2 | 0 | 18 | 0 | 2 | 0 | 1.143 | 0.565 |
| **Proctitis** | 17 | 0 | 2 | 1 | 15 | 0 | 5 | 0 | 3.939 | 0.139 |
| **Vaginal stricture** | 12 | 1 | 4 | 3 | 16 | 0 | 3 | 1 | 2.362 | 0.307 |
| **Alopecia** | 20 | 0 | 0 | 0 | 16 | 3 | 1 | 0 | 4.444 | **0.035** |

**Table 4: Response Assessment (RA) At 3 Months: Clinically, On CECT And On PET-CT**

| | | **Group** | | **Total** | **Pearson Chi-Square** | **p-value** |
|---|---|---|---|---|---|---|
| | | **ARM 1 (n=20)** | **ARM 2 (n=20)** | | | |
| **Clinical RA at 3 months** | NAD | 17 | 18 | 35 | 0.274 | 0.601 |
| | Local Residual Disease | 3 | 2 | 5 | | |
| **CECT scan for RA* (3months)** | CR | 14 | 17 | 31 | 4.561 | 0.102 |
| | PR | 1 | 1 | 2 | | |
| | PD | 5 | 2 | 7 | | |
| | CMR | 12 | 17 | 29 | 5.381 | 0.146 |



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| | | | | | | |
|---|---|---|---|---|---|---|
| **PET-CT RA at 3 months** | PMR | 2 | 0 | 2 | | |
| | SMD | 1 | 1 | 2 | | |
| | PMD | 5 | 2 | 7 | | |

**Table 5: Response Assessment At 6 Months: Clinically, On CECT And On PET-CT**

| | | **Group** | | | | |
|---|---|---|---|---|---|---|
| | | **ARM 1 (n=20)** | **ARM 2 (n=20)** | **Total** | **Pearson Chi-Square** | **p-value** |
| **Clinical RA at 6 months** | NAD | 16 | 17 | 33 | 3.339 | 0.503 |
| | Local Residual Disease | 1 | 1 | 2 | | |
| | Local Recurrence | 1 | 1 | 2 | | |
| | Not Done* | 2 | 1 | 3 | | |
| | Local Recurrence/ Metastasis | 0 | 0 | 0 | | |
| **CECT scan for RA* (6 months)** | CR | 13 | 14 | 27 | 6.678 | 0.154 |
| | PR | 0 | 0 | 0 | | |
| | PD | 2 | 4 | 6 | | |
| | Not Done** | 4 | 1 | 5 | | |
| | Local Recurrence | 1 | 1 | 2 | | |
| **PET-CT RA at 6 months** | CMR | 13 | 14 | 27 | 6.345 | 0.096 |
| | PMD | 2 | 4 | 6 | | |
| | Not Done** | 4 | 1 | 5 | | |
| | Local Recurrence | 1 | 1 | 2 | | |

* Response assessment not done as patient was on pall chemo /underwent surgery

** Response assessment not done as patient underwent surgery



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