COMPARATIVE STUDY OF WEEKLY VERSUS THREE WEEKLY CISPLATIN IN ADVANCED CASES OF CARCINOMA CERVIX ALONG WITH RADIOTHERAPY

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ABSTRACT: OBJECTIVE: To determine the clinical response and compliance of patients with external radiation therapy with concomitant weekly inj. CISPLATIN (30mg/m2) versus external radiation therapy with three weekly inj. CISPLATIN (100mg/m2).

MATERIALS & METHODS: This prospective study was conducted in the Department of Radiation oncology, GOVT. CANCER HOSPITAL, M.G.M. MEDICAL COLLEGE INDORE (M. P). A total of 50 patients were enrolled in study from April 2013 to October 2013 after obtaining written and informed consent. The patients were randomized into two arms. Arm 1 - Concurrent weekly cisplatin with Radiotherapy. Arm 2 - Concurrent 3 Weekly Cisplatin with Radiotherapy. All the patients received external beam radiotherapy (EBRT) along with 2-3 sittings of intracavitary radiotherapy (ICR) with concurrent weekly/3 weekly cisplatin. All the patients were simulated in supine position with proper immobilisation. Pelvic EBRT was given using COBALT 60 THERATRON 780C by two parallel opposed AP-PA portals or by four field techniques. A mid plane dose of 46 Gy 20#.

RESULTS: out of 25 patients, 19 patients from Arm A and 21 from Arm B had a complete response to treatment, whereas partial and progressive diseases responses were not observed in either of the patients of Arm A and Arm B. On the other hand 12 to 8 percent patients had a stable disease. However, from the whole lot, only 2(8%) patients of Arm B had a recurrence of the diseases. Statistically the responses to the different treatment plans on the patients in Arm A and Arm B did not differ significantly from each other.

CONCLUSION: this study showed that tri-weekly cispiatin 100mg/m2 concurrent with radiation is feasible and more effective than the conventional weekly cisplatin 40mg/m2-based regimen in achieving local control of the disease at 1 month follow up, however this difference was not sustained over prolonged follow-up. Longer follow-up is required to assess the delayed toxicity, overall survival and disease free survival.

KEYWORDS: Cervix Cancer, Cisplatin, Radiotherapy.


INTRODUCTION: Cervical cancer is the third most common malignancy in women worldwide. The frequency varies considerably between developed and developing countries, however: Cervical cancer is the second most common cancer in developing countries after carcinoma breast, but only the tenth most common in developed countries. In India, the International Agency for Research on Cancer estimated indirectly that about 63,5000 people died from cancer in 2008, representing about 8% of all estimated global cancer deaths and about 6% of all deaths in India.In our institute from 2002-2004 the total registered patients were 35,438 and out of which the total number of patients with cancer cervix were 3473, comprising 24.31%.

Major risk factors identified in epidemiologic studies are sex at a young age, multiple sexual partner, promiscuous male partners, history of sexually transmitted diseases, poor genital hygiene and smoking. Cervical cancer results from genital infection with HPV (Human Papilloma Virus), which is a known human Carcinogen. A large multinational cervical cancer study found that more than 90% of all cervical cancers worldwide are caused by 8 HPV types: 16, 18, 31, 33, 35, 45, 52, and 58. Three types—16, 18, and 45—cause 94% of cervical adenocarcinomas.1 HIV (Human Immunodeficiency Virus) infection is associated with a 5-fold increase in the risk of cervical cancer, presumably because of an impaired immune response to HPV infection.2 Some HLA (Human Leukocyte Antigen) gene anomalies are associated with an increased risk of HPV infection progressing to cancer.3 while some others have a protective effect.4 Cervical cancers tend to occur most commonly at the squamo-columnar junction, which is an area of active proliferation and metaplasia. Early detection of dysplasia using Papanicolaou (Pap) smear based screening has been an effective tool in reducing morbidity and mortality due to cervical cancer progression from CIN to frank invasive carcinoma takes about 10 to 15 years.
Pap smear based screening techniques have reduced deaths related to cervical cancer by three quarters in the developed world. The prognosis in patients with cervical cancer depends on the disease stage. In general, the 5-year survival rates are stage I - Greater than 90%, stage II - 60-80%, stage III - Approximately 50% and stage IV - Less than 30%.

The management of carcinoma cervix has evolved with time. Earlier in 1960's and 1970's various combinations of external radiotherapy and brachytherapy were used. In late FIGO stage II and stage III lesions whole pelvic irradiation was the main component of the treatment. Intracavitary radium was used after enough regression of parametrial disease. In stage IIIB and IVA external irradiation alone was used.

National Cancer Institute issued an alert in 1999 stating that strong consideration should be given for using cisplatin based chemoradiation instead of radiotherapy alone for invasive cervical cancer based on results of 5 randomized trials.

These 5 trials have shown that the use of concurrent cisplatin based chemoradiotherapy results in 30% to 50% decrease in risk of death compared to radiotherapy alone. Long term follow up of 3 of these trials has confirmed that concurrent cisplatin based chemoradiation improves progression free survival when compared with RT with or without Hydroxyurea.

In 2005, a Cochrane Collaboration review of 24 randomized controlled trials comparing concomitant chemoradiation with radiotherapy was published. This analysis included a total of 4,921 patients and strongly suggested that chemoradiation improves OS (Overall survival) and PFS (Progression Free Survival). More so with Cisplatin-Based Chemoradiotherapy Regimens in Included Clinical Trials. The present study was designed to compare compliance, toxicity, and outcome of weekly and three weekly cisplatin administrations concurrent with radiotherapy in locally advanced cervical cancer.

AIMS & OBJECTIVES: To determine the clinical response and compliance of patients with external radiation therapy with concomitant weekly inj. CISPLATIN (30mg/m2) versus external radiation therapy with three weekly inj. CISPLATIN (100mg/m2). To compare the normal tissue toxicity with weekly & three weekly concomitant cisplatin with external radiotherapy.

METHODS AND MATERIAL: This prospective study was conducted in the Department of Radiation Oncology, GOVT. CANCER HOSPITAL M.G.M. MEDICAL COLLEGE INDORE (M.P.). A total of 50 patients were enrolled in study from April 2013 to October 2013 after obtaining written and informed consent.

Inclusion Criteria: Previously untreated patients, with histologically proven squamous cell carcinoma and adenocarcinoma of uterine cervix. Age range 20-70 years. Eastern cooperative oncology group (ECOG) Performance status less than or equal to 2 & FIGO Stage IIB-IIIIB. Normal hematopoietic parameters with adequate liver function, renal functions and a life expectancy of more than one year and to be able to comply with a follow-up schedule.

Exclusion Criteria: History of past radiotherapy/chemotherapy/surgery.

Other than squamous cell carcinoma and adenocarcinoma, ECOG Performance scale more than 2, history of other malignancy, ongoing pregnancy or lactation, presence of pyometra and frozen pelvis.

History and Clinical Examination: A detailed history was taken, including presenting complaints and duration of symptoms.

General examination was conducted, including supravacular and inguinal lymph nodes. Weight and, height of the patient was recorded as it would be an indirect indicator of the patient’s nutritional status and for cisplatin dose calculations. Systemic examination was conducted, including per abdomen per speculum, per vaginal and per rectal examination. A complete blood count, Blood chemistry profile, Urine routine and microscopic examination, Chest x-ray, Ultrasonography of abdomen and pelvis and CT abdomen and pelvis was done. Histopathological confirmation of diagnosis was done with biopsy from the cervix.

Study Design: The patients were randomised in to 2 arms:

- Arm 1 - Concurrent Weekly Cisplatin with Radiotherapy.
- Arm 2 - Concurrent 3 Weekly Cisplatin with Radiotherapy.

Treatment Plan: All the patients received external beam radiotherapy (EBRT) along with 2-3 sittings of intracavitary radiotherapy (ICR) with concurrent weekly/3 weekly cisplatin.

Radiotherapy: All the patients were simulated in supine position with proper immobilisation. Pelvic EBRT was given using COBALT60 THERATRON 780C by two parallel opposed AP-PA portals or by four field techniques. A mid plane dose of 46 Gy in 20#. After a period of 7-10 days, patients were assessed for Brachytherapy. ICRT was delivered 7.5Gy/# x 2-3# using Selectron high dose radiotherapy (HDR).

Schedule of Cisplatin was as follows: ARM I: Inj. Cisplatin 30mg/m2 (IV infusion with prior hydration) On day 1, 8, 15, 22, 29 and 36 of radiotherapy. ARM II: Inj. Cisplatin 100mg/m2 (1 hour IV infusion with prior hydration) on day 1, 22 and 43. Chemotherapy was delivered only after ensuring adequate blood profile.

Follow up: Patients were followed up in the OPD at monthly interval during first 6 months, every 3 months during the next 1 year then 6 monthly intervals thereafter. At every 6 months Blood chemistry profile, USG abdomen and pelvis, chest x-ray and cytological assessment were done. In case of persistent disease, progression of disease or recurrence suitable symptomatic/palliative treatment was offered.

RESULTS AND ANALYSIS: A total of 50 patients were enrolled for the study from August 2010 to September 2011 and patients were randomised in two arms. Arm A — patients in this Arm received concurrent weekly Cisplatin with radiotherapy. Arm B - patients in this Arm received concurrent 3 weekly Cisplatin with radiotherapy.

It is evident from table 1 that most of the patients in the study were between 30-60 year age group. All of them had biopsy proven cervical carcinoma. The mean age in arm A was 47 years and in arm B was 44 years.
The patients were staged according to the FIGO staging system and according to the study protocol only patients with locally advanced stages of carcinoma cervix were included. In arm A, 3 patients were in stage II B and 22 in stage III B; whereas in arm B, 4 patients were in stage II B and 21 in stage III B. However, majority of the patients in both the arms were stage III.

Majority of the patients in both the arms completed their treatment within a span of 60 days. The maximum number of chemotherapy cycles possible in Arm A was 6 and in Arm B were 3. Out of 25 patients taken in each of the arms, 15 patients in Arm A and 20 patients in Arm B were able to complete all the chemotherapy cycles whereas, 10 patients in Arm A and 5 patients in Arm B were unable to complete all the cycles due to toxicity.

Eua Finding after One Week of Completion of External Radiotherapy: At the completion of external RT, examination of the patient was done under anesthesia after one week, just before ICRT application both per-rectally and per- vaginally. In majority of the cases, in both the groups, the cervix was found to be bulky (19 patients in Arm A and 16 in Arm B) and the parametrium was found to be free (16 patients in Arm A and 14 in Arm B) and there was no statistically significant difference as regards to the findings of P/V and P/R in Arm A and Arm B.

In Arm A most of the patients had normal leucocyte counts, whereas in Arm B most of the patients had Grade 2 leucopenia and the difference was not statistically significant. Majority of the patients had either a grade 2 or grade 3 adverse events in both the Arms, but statistically there was no difference with respect to gastrointestinal events in both the arms. In majority of the patients, there was no genitourinary adverse event in both the Arms. Hence statistically they were at par as regards to genitourinary adverse events in Arm A and Arm B. The observation regarding radiation dermatitis exhibited that most of the patients in both the arms had not experienced any skin reactions.

Follow Up Visits: At every follow up visit, the patients were examined clinically and ultrasonographically and toxicity was assessed by monitoring Gastrointestinal and genitourinary adverse events. Cytological examination was performed at 3 months and 6 months, and Chest X-rays were done at 6 months.

It is evident from Table 11 that majority of patients were found to be normal on USG examination at 1, 3 and 6 months intervals in both Arm A and Arm B. Similarly bulky cervix was also observed in all the patients in descending order of time intervals in both the cases of the patients. As far as residual disease is concerned, at one month follow-up there were 3 patients in Arm A and 1 in Arm B, and this was statistically significant, whereas there was no significant difference at 3 and 6 months follow up visits.

Gastro-Intestinal Toxicity Assessment at Follow Up Visits: Gastro-intestinal toxicity as assessed by colonic obstruction as per CDCAE version 4.0 criteria at follow-up visits. It is evident from Table 12 that the majority of the patients who visited at different time intervals of follow up program were found to be normal (more or less 80 %) whereas rest of the patients either fall in grade 1 or grade 2.

Statistically there was no difference in the impact of gastrointestinal toxicity on the patients, when visited at different time intervals of 1, 3 and 6 month that follow up program. It is clear from the Table 13 that at follow up visits, most of the patient had no genitourinary adverse event both in Arm A and Arm B at different time intervals, whereas 4 to 8 per cent patients had a grade 1 toxicity. None of the patients had a grade 2/3/4 genitourinary toxicity. Statistically the impact of genitourinary toxicity on patients did not differ significantly from each other at different time intervals. At follow up visits, most of the patients had normal cytological examination both in Arm A and Arm B at different time intervals. Statistically the patients in both the arms did not differ significantly with respect to cytological examination at different time intervals.

It is evident from table 15 that the majority of the patients were found to have no evidence of disease on p/v examination after 1, 3 and 6 months intervals in both arm a and arm b. Similarly, growth present was observed in 12 and 8 per cent cases at all the time intervals respectively in both arm a and arm b and there was no statistically significant difference between the two arms. The majority of patient were found to be parametrium free on p/r examination when visited after 1, 3 and 6 months intervals in both arm a and arm b.

Response to Treatment: The data presented in Table 17 and its corresponding fig. IV clearly indicates that out of 25 patients, 19 patients from Arm A and 21 from Arm B had a complete response to treatment whereas partial and progressive diseases responses were not observed in either of the patients of Arm A and Arm B. On the other hand 12 to 8 percent patients had a stable disease. However, from the whole lot, only 2(8%) patients of Arm B had a recurrence of the diseases. Statistically the responses to the different treatment plans on the patients in Arm A and Arm B did not differ significantly from each other.

DISCUSSION: In the present study most of the patients were in the 3-5th decade. All of them had biopsy proven cervical carcinoma. The mean age in arm A was 47 and in arm B was 44, which was consistent with the age related incidences as reported by 1ARC, Globocan 2008. Similar results have also been reported by Parveen et al and Mandal et al. Out of the 178 patients who were diagnosed with the disease in the 3-5th decade, majority of the patients who were diagnosed with the disease were in stage III B. Similar observations have been made by Arulponni et al and Mandal et al. Out of the 1003 patients which were in the 40-60 age groups respectively, 17.18 In developing countries like India, the disease is usually advanced at the time of diagnosis, which is evident from the stage distribution of cases in the present study, as majority of the patients who were diagnosed with the disease were in stage III B. Similar observations have been made by Arulponni et al and Mandal et al. Out of the 1003 patients which were in the 40-60 age groups respectively, 17.18 In developing countries like India, the disease is usually advanced at the time of diagnosis, which is evident from the stage distribution of cases in the present study, as majority of the patients who were diagnosed with the disease were in stage III B. Similar observations have been made by Arulponni et al and Mandal et al. Out of the 1003 patients which were in the 40-60 age groups respectively, 17.18 In the present study majority of patients were in 40-60 age groups whereas in the present study, majority of patients were in 40-60 age groups whereas 12 to 8 percent patients had a stable disease. However, from the whole lot, only 2(8%) patients of Arm B had a recurrence of the diseases. Statistically the responses to the different treatment plans on the patients in Arm A and Arm B did not differ significantly from each other.

Majority of the patients in both the arms were able to complete their treatment within a span of 60 days (17 in weekly arm and 19 in tri-weekly arm) and received all the chemotherapy doses i.e. 6 cycles in weekly arm and 3 cycles in tri-weekly arm (18 patients in weekly arm and 20 patients in tri-weekly arm).

Treatment was delayed for more than 60 days in 8 patients in Arm A and in 6 patients in Arm B. The total elapsed time for completion of external beam to the whole pelvis and intracavitary BT did not exceed eight weeks (56 days)(+20%=67 days is acceptable).
The delays in treatment and inability to complete all the chemotherapy cycles was mostly due to adverse effects such as vomiting, diarrhea, leucopenia or in some cases due to patient compliance related factors. Out of the seven patients who were unable to complete their chemotherapy cycles in weekly arm, two had grade 3 leucopenia, another two had grade 3 vomiting and the rest three had grade 3 diarrhea; whereas out of the 10 patients in tri-weekly arm who were unable to patients in tri-weekly arm who were unable to complete their chemotherapy cycles three had grade 3 leucopenia, four had grade 3 vomiting, one had grade 1 diarrhea and two had grade 3 dermatitis.

The average duration of treatment in weekly arm was 56 days and in triweekly arm was 58 days. Many studies have documented the adverse effect of treatment duration on the outcome of carcinoma cervix patients.\textsuperscript{2,22,23} However since in the present study the difference in treatment durations between the two arms was insignificant, this independent variable did not influence the final outcome and results. The completion rate of chemotherapy was 72% in the weekly arm and 80% in the tri-weekly arm which was statistically not significant.

Ryu et al.\textsuperscript{23} reported that the two cisplatin-based chemoradiation regimens were tolerated very well, with 86.3% and 92.5% completion rate of scheduled chemotherapy cycles for the weekly and triweekly arms, respectively. There was no statistically significant difference of compliance between the two arms (p=0.055).

Chumworathayi Bet al.\textsuperscript{22} while comparing weekly versus three-weekly cisplatin as an adjuvant to radiation therapy in high-risk stage I-IIA cervical cancer after surgery reported a higher rate of incomplete and delayed treatments in the tri-weekly cisplatin group (p=0.001 and p=0.0236 respectively).

As regards to tolerance of the treatment 5 parameters were evaluated according to the Common Terminology Criteria for adverse events version 4.0: Leucopenia was significantly more common and more severe in the tri-weekly arm, whereas there were no statistical differences in the incidence levels of vomiting, diarrhea, dermatitis and hematura between the two arms. Our observations are similar to that of Lee et al and Chumworathayi B et al.\textsuperscript{25,26}

Lee et al who compared weekly with triweekly combination chemotherapy as concurrent adjuvant chemoradiation therapy after radical hysterectomy for cervical cancer and observed that leucopenia, neutropenia, thrombocytopenia, anemia, and hepatopathy were significantly more common in the triweekly combination chemotherapy group.\textsuperscript{27}

Chumworathayi B et al reported that the toxicity-related incompletetreatments rate and G-CSF doses used were significantly higher in tri-weekly arm than in the weekly arm.\textsuperscript{28}Wong et al while evaluating the long-term follow-up of potentiation of radiotherapy by cis-platinum in advanced cervical cancer also reported significantly higher incidence of hematological adverse effects in arm receiving twice weekly cisplatin as compared to the arm receiving weekly or no cisplatin.\textsuperscript{29}

Myelosupression, which is manifested by leucopenia, thrombocytopenia and anemia, is noted in about 25 to 30% of patients receiving cisplatin therapy. Myelosupression is cumulative and tends to be more severe in those patients previously treated with antineoplastic agents, radiotherapy /cisplatin or already immune-compromised.

Leucopenia and thrombocytopenia are dose related and become more pronounced when the dose of cisplatin is greater than 50mg/m\textsuperscript{2} “These findings justify the increased incidence of leucopenia in the tri-weekly arm in which a dose of 100mg/m\textsuperscript{2} was given.

Acute-phase vomiting after cisplatin treatment is thought to be primarily mediated via the serotonin receptors, and is nearly universal. In the present study majority of the patients in both the arms (15 in weekly arm and 17 in tri-weekly arm) had grade 1 or 2 vomiting, while only 2 patients in weekly arm and 4 in the tri-weekly arm had grade 3 vomiting; these changes were not statistically significant.

There were five patients with residual/stable disease, three in weekly arm and 2 in the tri-weekly arm; and two patients with recurrence (Distant) both in the triweekly arm. Out of the three patients with stable disease in the weekly arm two had B/L parametrium involvement (On P/R examination) and one had central nodule, whereas only one patient with stable disease in the tri-weekly arm had unilateral (Right) parametrium involvement at the end of 6 months. This was statistically significant.

The number of chemotherapy cycles administered with radiation appears to significantly impact survival of women with high-risk early stage cervical cancer. The better local control in the tri-weekly arm as evident on USG findings at 1 month and decreased incidence of parametrium involvement of parametrium in case of stable disease at the end of 6 months has many possible explanations.

It may be due to the higher peak concentration of cisplatin achieved in the tri-weekly arm which in turn may be more critical in enhancing the synergy of chemoradiation than the weekly cisplatin exposure; also in the tri-weekly arm the second and third doses of cisplatin are given during or near to the brachytherapy which may further lead to enhancement of the synergy of chemoradiation resulting in a better local control of the disease.

Bonomi P et al while three different cisplatin dose schedules (Cisplatin 50 mg/m\textsuperscript{2} every 21 days, 100 mg/m\textsuperscript{2} every 21 days and cisplatin 20 mg/m\textsuperscript{2} for five consecutive days repeated every 21 days) also observed that the regimen consisting of a 100-mg/m\textsuperscript{2} single dose produced no appreciable differences in complete remission rate, response duration, progression-free interval, or survival\textsuperscript{30} Lee et al evaluated patients with stage IB1 to stage IIB cervical cancer who had undergone radical hysterectomy with pelvic lymph node dissection, followed by concurrent adjuvant chemoradiation therapy with either the tri-weekly combination chemotherapy group or the weekly cisplatin chemotherapy group. They also concluded that the weekly cisplatin chemotherapy group experienced the same therapeutic effect as the tri-weekly combination chemotherapy group but with less toxicity.

When Concurrent radio-chemotherapy is used, chemotherapy is given typically when external beam radiation is administered. The NCCN panel believes that systemic consolidation (Chemotherapy after concurrent chemoradiation) should only be used in clinical trials (RT0G 0724).

Concomitant chemoradiotherapy in general can be used with organ-preserving intent, resulting in improved cosmosis and function compared with surgical resection with or without adjuvant treatment. Second, chemotherapy can act as a radiosensitizer, improving the probability of local control and, in some cases, survival, by aiding the destruction of radio-resistant clones.
Third, chemotherapy given as part of concurrent chemoradiation may act systemically and potentially eradicate distant micro-metastases.

Chemoradiotherapy in cervical carcinoma is thought to exert its major beneficial effects by improving local disease control but it also has a modest systemic effect. The interaction between radiation and chemotherapy is radiation ‘sensitization’, which is either additive or supra-additive: the interaction within the radiation field leads to increased killing of cells (Cytoxic activity) either to the same degree as (additive) or more than (Supra-additive) using both modalities sequentially. Strictly speaking, radio-sensitizers shouldn’t have inherent cytoxic activity. However, the radio-sensitizers most commonly used today (Cisplatin, 5-fluorouracil [5-FU], and taxanes) do have inherent cytoxic activity and can increase damage to normal tissues, with a ‘true’ benefit achieved only if the increase in antitumor effect is larger than the normal tissue damage.

Moreover, ionizing radiation can increase cellular uptake of platinum. Damage to DNA by ionizing radiation that typically would be repairable can become fixed and lethal through cisplatin’s free-electron-scavenging capacity. This inhibition of DNA repair leads to an increased incidence of cell-cycle arrest and apoptotic cell death after radiation.

Cisplatin has long been known to be an active anti-neoplastic agent in the treatment of cervical cancer. A number of randomized phase III trials have failed to demonstrate any additional benefits associated with several modifications of a “standard dose” (Approximately 50 mg/m² every 3-weeks single-agent cisplatin regimen, compared to the use of “standard dose” cisplatin alone.10,31,32 These include the administration of higher dose cisplatin (e.g. 100 mg/m² every 3-weeks), or adding a number of cytotoxic agents (e.g. ifosfamide) to cisplatin.32

In the present study also no statistically significant differences were found between the weekly and tri-weekly arms in terms of response to treatment and overall survival; however the tri-weekly arm can be postulated to provide a better local control as evident on the basis of USG findings at 1 month follow-up visit and a decreased incidence of parametrium involvement in cases of stable disease at 6 months, but this better local control came at the cost of poor tolerance to treatment especially with regards to leukocyte counts. Why the better local control did not transform into a better overall survival and response to treatment is questionable, but it may be due to the limited time period of the follow-up, and the smaller number of patients enrolled in the study.

CONCLUSION: In conclusion, this study showed that tri-weekly cisplatin 100 mg/m² concurrent with radiation is feasible and more effective than the conventional weekly cisplatin 40mg/m²-based regimen in achieving local control of the disease at 1 month follow up, however this difference was not sustained over prolonged follow-up. Although a number of studies provide compelling data to consider chemotherapy in combination with radiotherapy, there is increased toxicity associated with chemoradiation. In the present study also though the triweekly arm seems to provide a better local control at 1 month, it does so at the expense of decreased tolerance with respect to leukocyte counts. In order to overcome this hurdle, future trials should attempt to evaluate new drugs and alternative dosing schedules that may be associated with a more favorable toxicity profile.

A Smaller sample size in each of the arms of 25 patients each, limits the extrapolation of the results to the general population.

Longer follow-up is required to assess the delayed toxicity, overall survival and disease free survival. The number of chemotherapy cycles administered with radiation appears to significantly impact survival of women with high-risk early stage cervical cancer. In the tri-weekly arm 2 doses (the second and third doses) of cisplatin are given during or near to the brachytherapy which may be hypothesized to lead to increased synergy of chemoradiation resulting in a better local control of the disease. With relatively easier dosage schedule, a better compliance can be expected in the tri-weekly arm, although there was no statistically significant difference between the two arms.

There was a concern about the tolerance of concomitant radiotherapy in Indian women with cervical carcinoma, but our study has dispelled such doubts and has shown that concurrent chemoradiotherapy is tolerated well by Indian women and there should no hesitancy in using it on the pretext of unfavorable toxicity profile. Adding chemotherapy to radiotherapy offers a significant, additional benefit on all outcomes and for all stages of disease.

BIBLIOGRAPHY:


![Fig. 1: Showing Age distribution of patients](Image)
**Table 1: USG findings at follow-up visits at 1, 3, and 6 months**

<table>
<thead>
<tr>
<th>USG finding</th>
<th>At 1 month</th>
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<tr>
<td></td>
<td>Arm A</td>
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<tr>
<td>Normal</td>
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<td>Residual disease</td>
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<td>Para-aortic + Pelvic nodes</td>
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Z = 2.2, Significant  
Z = 1.28, Non-Significant  
Z = 1.28, Non-Significant

**Table 2: Assessment of gastrointestinal toxicity at follow up visits**

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<th>Grade of toxicity</th>
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<td>Lost to follow-up/death</td>
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Z = 0.77, non-Significant  
Z = 0.37, non-Significant  
Z = 1.01, non-Significant

**Table 3: Assessment of genitourinary toxicity at follow-up visits**

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<td>Arm B</td>
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<td>Lost to follow-up/death</td>
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Z = 1.04, Non-Significant  
Z = 0.47, Non-Significant  
Z = 0.87, Non-Significant

**Table 4: P/V findings at follow-up visits**

<table>
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<tr>
<th>P/V Findings</th>
<th>At 1 month</th>
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<td>Arm A</td>
<td>Arm B</td>
<td>Arm A</td>
</tr>
<tr>
<td>No evidence of disease</td>
<td>20</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Growth present</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lost to follow-up/death</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Z = 1.22, nonsignificant  
Z = 1.22, nonsignificant  
Z = 1.54, nonsignificant
Fig. 2: Showing response to treatment

<table>
<thead>
<tr>
<th>Response to Treatment</th>
<th>No. of Patients</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>19</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence (Distant)</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Lost to follow-up / death</td>
<td>3</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

$Z = 0.71$, non-significant

Table 5: Response to treatment