*Original Article*

# Comparative Study of External Beam Radiotherapy with Cisplatin Verses Paclitaxel In Locally Advanced Cervical Carcinoma

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## ABSTRACT

**Objective:** The purpose of the study was to identify the value and response of four field radiotherapy, combined with concurrent chemotherapy (cisplatin vs. paclitaxel) as radio a sensitizer.

**Method:** Fifty patients with diagnosis of Carcinoma of Cervix were consecutively enrolled in this study 25 assigned in each group. Gr 1 was assigned for Cisplatin as sensitizer and Gr 2 received Paclitaxel. Radiation fields were similar. The response and adverse effects were evaluated in fixed interval or at the time when it occurred.

**Result:** Fifty patients were enrolled. FIGO stage of disease were stage IIB (n=33) and stage IIIB (n=14). The most commonly used field size for anterior / posterior field 15 x 15 cm and 15 x 18 cm. The lateral field size from right and left are 15 x 7 cm and 15 x 6 cm. Cisplatin 30 mg /m2 or Paclitaxel 230mg/m2 were used as assigned in each group of 25. During weekly assessment of chemo-irradiation, the reaction was seen from second week to fifth week of the treatment which were mild to moderate in severity. Vesico-Vaginal Fistula were seen in 8.0% of patient. Eighteen patients came for one follow up, 15 patients attended two follow up, and 17 patients attended all three scheduled follow up. Complete response was evaluated in 25 patients (p=0.002), partial response in 14 patients (p=0.03) and poor response in 11 patients (P=0.50).

**Conclusion:** There are no significant differences in cisplatin or paclitaxel as a sensitizer in concurrent radiotherapy in response for cancer of uterine cervix. Rate of side effects were also similar. Further large scale studies may evaluate the difference in response of concurrent chemo-radiotherapy of these two drugs to confirm the optimal duration and schedule of concurrent chemotherapy.

***Keywords***: External beam radiotherapy, Concurrent chemotherapy, locally advanced cervical cancer, Radio-sensitizer.

## Introduction

Carcinoma of the uterine cervix is one of the most common malignant neoplasms among women in Asia. Globally, it is second commonest neoplasia in women.[3] It is the commonest neoplasia in women of the developing countries including Nepal. Carcinoma Cervix ranks fifth most common cancer in women of developed countries. In Nepal, according to the data of National Cancer Registry Program-2012, Kathmandu, Kaski, Morang, Chitwan, Sunsari, Jhapa, Nawalparasi, Rupandehi, Saptari and Dhanusha were found the top ten districts where the cancer cases were reported and the distribution is almost the same among the Hindus and the Muslims. Among them carcinoma of cervix (25%) was the number one cancer site followed by breast (15%)and lung (10%). Locally advanced cervical Cancer (LACC) are very common.

The standard treatment modalities, advised in different stages of carcinoma of the cervix are surgery, radiotherapy and chemotherapy. Pelvic irradiation plays a major role in the standard, definitive therapy for these LACC, with overall 5 years survival rate between 25% and 55% depending on the extent of the disease.[20]

The conventional two main modalities of irradiation to cervix are external photon beam with or without weekly concomitant chemotherapy and brachytherapy. Not all the radiotherapy centers in other part of the nation have this facilities, so the patients are given radiotherapy alone

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or radiotherapy plus concurrent chemotherapy with out brachytherapy. Technique wise, four field box technique and two anterior-posterior fields were applied. The first technique is considered superior in terms of radiation related morbidity.[3] The ability of Radiotherapy to treat LACC is very much limited by the size of the tumors, because the doses required to treat large tumors exceed the limit of toxicity in normal tissue.[12] Concurrent chemotherapy inhibits the repair of sub lethal damage from radiation, synchronizes cells to a particularly radiosensitive phase of the cell cycle. This method aims at enhancement of tumor cell kill and possible improvement in the sensitivity of the cancer cells to radiation.[3] The Cisplatin and Paclitaxel are the widely used molecules as a radio-sensitizing agents. Cisplatin is found to be the most active agent in this tumor and act as a good radio-sensitizer and hypoxic cell sensitizer resulting in higher progression-free survival. When cisplatin and irradiation are used concomitantly, substantial enhancement of cell killing is observed. Paclitaxel has demonstrated a radio-sensitizing effect because of its ability to block cells in the G2M phase of the cell cycle with a novel mechanism of action that involves stabilization of the mitotic spindles in micro-tubular polymer complex and cell replication.[21]

## Materials and Method

This is a prospective study undertaken in the Department of Radiotherapy of Bir Hospital Kathmandu. **This** Cohort recruited subjects of age > 25 years in open label randomized fashion in which radio-sensitizing dose of active drugs were used. The study parameters included Pathological/Radiological / Biological / Histopathological/Cytological-parameters.

## Study Population and Sampling Techniques

This study included all sexually active, non-pregnant women presenting to the OPD with diagnosis of cancer of Cervix. Patient Written consents were taken, confidentiality will be maintained. Long term and short term effect of treatments were explained.

**Inclusion Criteria were:**

1. Patient with confirmed histopathological report
2. Patient with karnofsky performance status >70%
3. Leukocyte Count >4000/cu.mm
4. Hemoglobin>10g/dl
5. Platelets count >150000/ml
6. S. Urea <45 mg/dl
7. S. creatinine <1.4mg/dl
8. Patient with USG abdomen and pelvis or CT scan abdomen report (if affordable patients only).
9. Patient willing to sign informed consent letter and come for follow up regularly.

Exclusion Criteria included:

1. Patient with non-evaluable disease.
2. Patient with symptomatic Ischemic Heart Disease or Congestive Heart Failure
3. Patient with pre-existing neuropathy
4. Patient is pregnant or breast feeding
5. Patient is with any other anticancer therapy / experimental drugs/participation into another clinical trial.
6. Patient with serious concurrent medical illness.

## Methodology

Total of **50** patients were selected according to inclusion criteria. Patients were subjected to clinical examination including per speculum examination. Internal pelvic examination was done for proper staging according to the FIGO Classification (Table.1).

The patients were divided into two groups, using box technique, 25 patients in each group. First group, treated with Radiotherapy plus cisplatin 30 mg/m$^2$.Second group treated with Radiotherapy plus paclitaxel 30mg.

Radiotherapy- External beam radiation treatment (EBRT) was delivered using a telecobalt machine(Theratronics, Canada).

A four-field box technique was used to treat all these 50 patients in Anterior/posterior portals and two lateral portals as shown in Figure 1 and Figure 2. The field size used is given in Table 4. The total dose of 6000 cGy was given in 30 fractions over 6 weeks, daily delivering 200 cGy per fraction per day for five days a week for six weeks.

The planning and surface marking were done manually according to the anatomical landmark and by the help of the Aluminums wire are placed on the surface mark, and a check x-ray films were taken to see the actual field size matching.

The upper border of the Anterior-posterior field passes through the upper border of the sacro-iliac joint (extended from the middle of L5-S1 or L4- L5), laterally covers the pelvic brim with a margin of 1.5 cm and inferiorly to cover the obturator foramen and the lower

border to cover superior 2/3rd of the vagina. If there is vaginal spread downwards the lower border covers it with a margin of 2cm from caudal as shown above in figure 1. In the lateral field, the upper border and the lower border are same as in Anterior-posterior field, the anterior border taken from mid-symphysis and the posterior border taken from mid rectum as shown in figure 2.

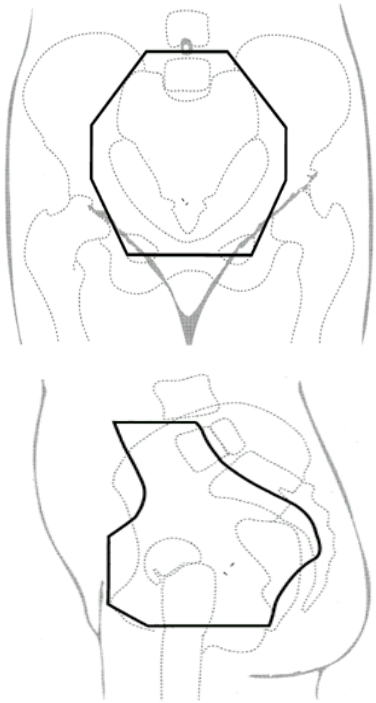

Figure.1 **Field - Anterior- Posterior portals** Figure.2. **Field – Lateral port** (Diagrammatic) (Diagrammatic)

**Chemotherapy:** The concurrent chemotherapy was given intravenous before EBRT. In group-1, injection cisplatin 30 mg/m$^2$, mixed in injection normal saline 250ml and infused over 30 minute, once a week for total 6 weeks. In group-2, injection paclitaxel 30mg was mixed in injection normal saline 250ml and infused over 30 minute, once a week for total 6 weeks.

The patients were evaluated for complications using the Common Toxicity Criteria (CTC) of the National Cancer Institute (CTC.NCI, 1999) and RTOG/EORTC acute radiation scoring criteria – Skin (1995).

**Statistical methods:** Data were expressed as mean, SEM and median. Chi-square tests were performed to compare two categorical variables. p value of <0.05 was considered statistically significant.

**Evaluation:** Response to chemo irradiation were evaluated at the end of the treatment. Complete response was registered when no clinical or cytological evidence of disease existed at the end of treatment. Partial response was registered when there was an equal or more than 50% reduction of the disease. Poor response was registered when they're clinically or cytological evidence of disease exist, less than 25% of the disease or more than 25% increase of the disease or the appearance of new lesion.

## Results

This study was conducted in the outpatient unit of Department of Radiotherapy. All patients were previously untreated and histology proved. All patients were stage IIB to IIIB according to the FIGO classification of cancer of uterine cervix.

The details of 50 patients enrolled which were divided into 2 groups is elaborated in table 1.

**Table.1 FIGO stage Characteristics of the patients (n=50)**

| Stage | Cisplatin (n =25) | Paclitaxel (n=25) | p value |
|---|---|---|---|
| | No. (%) | No. (%) | |
| IIB | 16 (64.0%) | 17 (68.0%) | 0.83 |
| IIIA | 2 (8.0% ) | 1 (4.0 %) | |
| IIIB | 7 (28.0%) | 7 (28.0%) | |

The entire 50 patient were diagnosis and had histopathlogical reports and was stage according to the FIGO stage and in this study as shown in Table 1 mostly was diagnosis stage IIB (n=33) and stage IIIB (n=14) p=0.83 >0.05. Only 22 patients had proper grading in histology report which is shown in Table.3. In cisplatin group (n=10) from which Grade II has n=8(80%) and Grade III has (n=2)20% and in paclitaxel group (n=12) having Grade I (n=3) 25%, Grade II (n=2) 16.7% and Grade III (n=7) 58.3%.

**Table.2 Histological Grade of uterine of cervix cancer**

| Grade's | Type | Cisplatin (n=10) | Paclitaxel (n=12) | p value |
|---|---|---|---|---|
| | | No. (%) | No. (%) | |
| I | Well Differentiated | 0 (0.0%) | 3 (25.0%) | 0.01 |
| II | Moderate Differentiated | 8 (80.0%) | 2 (16.7%) | |
| III | Poorly Differentiated | 2 (20.0%) | 7 (58.3%) | |

**Table 3 External Radiotherapy Portal and Field Size (n=50)**

| Anterior/Posterior Portal | | | | Lateral Portal | | | |
|---|---|---|---|---|---|---|---|
| Field Size | Cisplatin (n =25) | Paclitaxel (n = 25) | p-value | Field Size | Cisplatin (n =25) | Paclitaxel (n = 25) | p-value |
| | No. (%) | No. (%) | | | No. (%) | No. (%) | |
| 15 x 15 | 19 (76.0%) | 20 (80.0%) | 0.54 | 15 x 6 | 8 (32.0%) | 3 (12.0%) | 0.17 |
| 15 x 16 | 0 | 2 (8.0%) | | 15 x 7 | 15 (60.0%) | 19 (76.0%) | |
| 15 x 18 | 3 (12.0%) | 1 (4.0%) | | 15 x 8 | 0 | 2 (8.0%) | |
| 16 x 16 | 1 (4.0%) | 1 (4.0%) | | 16 x 6 | 1 (4.0%) | 0 | |
| 17 x 15 | 0 | 1 (4.0%) | | 16 x 7 | 0 | 1 (4.0%) | |
| 18 x 15 | 1 (4.0%) | 0 | | 18 x 7 | 1 (4.0%) | 0 | |

In both the groups radiotherapy was planned in four field box technique and the total dose of 6000 cGy in 30 fractions over 6 weeks, daily delivering 200 cGy per fraction per day for five days a week for six weeks. In Table 3 shows the most commonly used field size for anterior / posterior field 15 x 15cm in cisplatin group (n=19) 76.0% and in paclitaxel group (n=20) 80.0% and 15 x 18 cm in cisplatin group (n=3) 12.0% and in paclitaxel group (n=1) 4.0% followed by 16 x 16 cm and 18 x 15 cm {(n=1) 4.0%} and for right and left lateral field most commonly used are 15 x 7 cm in cisplatin group (n=15) 60.0% and in paclitaxel group (n=19) 76.0% and 15 x 6 cm in cisplatin group (n=8) 32.0% and in paclitaxel group (n=3) 12.0% followed by 16 x 6 cm and 18 x 7 cm{(n=1) 4.0%}. But this field size did not show any statistical significance.

**Table 4 Assessment of Chemoirradiation reaction (n=50)**

| weeks | Reaction site | Cisplatin ( n=25) | | | Paclitaxel ( n=25) | | |
|---|---|---|---|---|---|---|---|
| | | No (%) | | | No (%) | | |
| | | mild | moderate | severe | mild | moderate | severe |
| second | skin | 5 (55.6%) | 2 (22.2%) | | 1 (16.7%) | 3 (50.0%) | |
| | OC,pharynx | 1 (11.1%) | | | 3 (50.0%) | | |
| | GI | 2 (22.2%) | 2 (22.2%) | | 2(33.3%) | 2 (33.3%) | |
| | GU/rectal | 2 (22.2%) | | | 1 (16.7%) | | |
| third | skin | 8 (57.1%) | 0 (0.0%) | 1 (7.1%) | 5 (38.5%) | 3 (23.1%) | 1 (7.7%) |
| | OC,pharynx | 6 (42.9% ) | 0 (0.0%) | | 5 (38.5 %) | 1 (7.7%) | |
| | GI | 4 (28.6%) | 1 (7.1%) | 0 (0.0%) | 3 (23.1%) | 2 (15.4%) | 1 (7.7%) |
| | GU/rectal | 6 (42.9%) | | | 2 (15.4%) | | |
| fourth | skin | 0 (0.0%) | 0 (0.0%) | | 2 (28.6%) | 1 (14.3%) | |
| | OC,pharynx | 2 (50.0%) | 0 (0.0%) | | 2 (28.6%) | 1 (14.3%) | |
| | GI | 1 (25.0%) | 0 (0.0%) | 0 (0.0%) | 1 (14.3%) | 1 (14.3%) | 1 (14.3%) |
| | GU/rectal | 2 (50.0%) | | | 4 (57.1%) | | |
| fifth | skin | 2(33.3%) | 1 (16.7%) | | 3 (75.0%) | 0 (0.0%) | |
| | OC,pharynx | 1 (16.7%) | 1 (16.7%) | | 0 (0.0%) | 0 (0.0%) | |
| | GI | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) | 0 (0.0%) | 1 (25.0%) | 0 (0.0%) |
| | GU/rectal | 1 (16.7%) | | | 2 (50.0%) | | |
| sixth | skin | 1 (33.3%) | 0 (0.0%) | | 1 (33.3%) | 1 (33.3%) | |
| | OC,pharynx | 1 (33.3%) | 0 (0.0%) | | 0 (0.0%) | 1 (33.3%) | |
| | GI | 0 (0.0%) | | | 1 (33.3%) | | |
| | GU/rectal | 1 (33.3%) | | | 1 (33.3%) | | |

As shown in Table 4 during weekly assessment of reaction, it was mainly seen in the second week to fifth week of the treatment which were mild to moderate. On the second week of the treatment skin reactions were mild to moderate in cisplatin group 55.6% (n=5) to 22.2% (n=2) and in the paclitaxel group 16.7% (n=1) to 50.0% (n=3) and GI,GU/Rectal reaction were mild to moderate in cisplatin group 22.2% (n=2) and in paclitaxel group 33.3% (n=2) during GI reaction. Where as in the third week of the treatment in the cisplatin group reaction were mild - Skin 57.1% (n=8), OC, pharynx 42.9% (n=6), GI 28.6% (n=4), GU/rectal 42.9% (n=6) and in paclitaxel group were mild to moderate, skin 38.5% to 23.1% (n=5 and n=3), OC, pharynx 38.5% (n=3), GI 23.1% to 15.4% (n=3 and n=2), GU/rectal 15.4% (n=2). On the fourth week of treatment there was no skin reaction in the cisplatin group but mild skin reaction in the paclitaxel group 28.6% (n=2) and other site also shows mild reaction during treatment in cisplatin group - OC, pharynx and GU/rectal 50.0% (n=2) and in paclitaxel group - OC, pharynx 28.6% (n=2). And finally on the fifth week of the treatment only mild skin reaction was observed in cisplatin group 33.3% (n=2) and in paclitaxel group 75.0% (n=3).

**Table 5 Post treatment follow up (n=50)**

| Sign and Symptom | Cisplatin ( n=25) | Paclitaxel ( n=25) | p value |
|---|---|---|---|
| | No (%) | No (%) | |
| VVF | 2 (8.0%) | 0 | 0.49 |
| Vaginal Discharge | 9 (36.0%) | 6 (24.0%) | 0.36 |
| P/R Bleeding (mild) | 1 (4.0%) | 2 (8.0%) | 1.0 |

During post treatment follow up, 8% of patients (2) in Cisplatin group developed VVF, 36.0% (n=9) appeared with vaginal discharge and 4.0% (n=1) with mild P/R bleeding. In paclitaxel group 24.0% (n=6) appeared with vaginal discharge and 8.0% (n=2) with mild P/R bleeding.

**Table 6 Follow up of chemo irradiation patients (n=50)**

| Follow up | Cisplatin (n=25) | Paclitaxel (n=25) | p value |
|---|---|---|---|
| | No (%) | No (%) | |
| I | 7 (28.0%) | 8 (32.0%) | 0.76 |
| II | 5 (20.0%) | 13 (52.0%) | 0.02 |
| III | 13 (52.0%) | 4 (16.0%) | 0.02 |
| Irregular | 8 (32.0%) | 17 (68.0%) | 0.01 |

Out of 50 patients, 15 patients came for one follow up, 18 patients attended only two follow up, and 17 patients attended all the three follow up. 25 patients follow up was irregular who gave follow up only between one or two month after treatment and did not come for follow up or appeared only when severe complications were developed.

**Table 7 Evaluation of patients (n=50)**

| Response | Cisplatin ( n=25) | Paclitaxel ( n=25) | p value |
|---|---|---|---|
| | No (%) | No (%) | |
| Complete | 18 (72.0%) | 7 (28.0%) | 0.002 |
| Partial | 3 (12.0%) | 11 (44.0%) | 0.03 |
| Poor | 4 (16.0%) | 7 (28.0%) | 0.50 |

Complete response was seen in 25 patients (p=0.002), partial response was assessed in 14 patients (p=0.03) and poor response were assessed in 11 patients (P=0.50) (Table 7).

## Discussion

Cervical cancer continues to be a major public health problem in developing countries. A substantial number of women are still dying of cervical cancer because majority of the affected patients present at late stage. Carcinoma of the cervix is one of the most common malignant neoplasms among women in Asia.[3]

In this study, four field box techniques with concurrent chemotherapy weekly with cisplatin was preferred to avoid maximum rectal and bladder complication. In this four field box technique study, the most common effective field size was 15 x 15 cm and 15 x 18 cm in anterior / posterior portal and 15 x 7 and 15 x 6 in the lateral portal. In a study done by B.E.Greer et al.[20] reported, that the median length and width of the anterior / posterior fields were 20cm and 17.5cm respectively. Lateral fields had a median width of the 16.5cm and the posterior border encompassed the entire sacral silhouette and G. A. Perez et al.[1] has also written in a book Principles and Practice of Radiation Oncology that for patients with stage IIA, IIB, III and IVA carcinoma, somewhat larger portals (18 x 15 cm at the surface) are required to cover all of the common iliac nodes in addition to the cephalad half of the vagina. So comparing with this study the field size did not show any statistically significant.

In this study, Cisplatin and Paclitaxel are used as concurrent chemotherapy weekly along radiotherapy as a radiosensitizer. The response rate of cisplatin was very

significant in Stage II B and paclitaxel in in stage III. The relation ship of histological grade to response was evaluable in 22 patients, in which Grade II (n=8) showed maximum response with cisplatin and in Grade III (n=7) with paclitaxel. Comparing squamous cell variant and others, cisplatin has 100% response compared to 90.0% with paclitaxel. The reaction during chemo-irradiation was seen from second week to fifth week of of the treatment. The common reaction observed in the cisplatin as well as in paclitaxel group was skin, OC, pharynx, GI and GU/rectal reaction. Two patients (8.0%) in Cisplatin group developed VVF in the post treatment follow up.

Total cumulated, response rate was seen in complete response in 25 patients, partial response was assessed in 14 patients, and poor response were assessed in 11 patients (p=0.50).

A study done by De Palo, et al, [20] reported paclitaxel was administrated as 40mg/m$^2$ on the first day of each week of radiotherapy. Response was seen in four of seven patients, complete response in three of seven. All complete responders were still in remission after a median follow-up of 14 months. In and another study done by Abbie L Field et al., [17] irradiation with cisplatin achieved 87.3% (complete response), 9.0 %( partial response) and 3.6% (poor response). Peter G. Rose et al.[12] also noted a statistically significant improvement in patients using chemo radiation with cisplatin as compared to controls (55.0% Vs 20.0%) p<0.025. Compared with the above study groups of chemo irradiation, this study shows that cisplatin has better response than paclitaxel in stage IIB, moderately differentiated than poorly differentiated, squamous cell carcinoma but paclitaxel gave some good response 58.3% in stage IIB and IIIB, poorly differentiated, squamous cell carcinoma Whereas poor response has grade III type with stage IIIB with poor prognostic factor to chemo irradiation and has recurrent growth with adjacent organ involvement.

## Conclusion:

To conclude, its still recommended to use cisplatin as the standard drug for concurrent chemo-radiotherapy. Further studies are required to evaluate the response of concurrent chemo-radiotherapy of these two drugs to confirm the optimal duration and schedule of concurrent chemotherapy and target dose of radiotherapy.

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