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**RESEARCH ARTICLE**

# Concurrent External Beam Radiotherapy with High Dose Rate Brachytherapy in Carcinoma Cervix.

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## *Abstract*

A quasi-experimental study, to evaluate the outcome of external beam radiotherapy with concurrent weekly high dose rate brachytherapy in management of carcinoma cervix.

All the 60 patients completed the planned treatment and were available for the data analysis.

The radiation dose of 5000 cGy to whole pelvis with midline shielding at 2000 cGy with 5 fractions of concurrent High dose rate brachytherapy, 7 Gy per fraction at weekends was found to be effective and safe schedule in the treatment of stage II carcinoma cervix. In view of the therapeutic ratio cumulative biological effective dose of 83.5 $Gy_{10}$ point A is appropriate for stage II patients. Whereas for stage III it was observed that the radiation dose of 5000 cGy to whole pelvis with midline shielding at 4000 cGy with concurrent 3 fractions of high dose rate brachytherapy, 7 Gy per fraction at weekends is suboptimal as, only 78% of disease free survival could be achieved with 22% survival with disease at 6 months of follow up.

The cumulative biological effective dose 83.7 $Gy_{10}$ need to be increased by parametrial boosting to improve the therapeutic ratio. The cumulative biological effective dose at rectal point showed the rectal dose need to be kept below 110 $Gy_3$ - 140 $Gy_3$ to avoid late toxicities. Late toxicities for stage III is significantly higher than stage II at 0.05 level of probability. Median treatment duration was 44 days. The results might be improved by increasing the point "A"dose by boosting or by chemosensitization.



## Introduction:-

Cervical cancer is highly prevalent in developing nations; it is estimated that close to 500,000 women worldwide develop this tumor and 233,000 die of the disease.[1] Uterine cervix is the commonest cancer in female in India, followed by carcinoma breast except in Mumbai where carcinoma breast predominates. Presently, the age adjusted incidence rate for carcinoma cervix ranges from 19-44 per 100,000 women in various cancer registries in India. The highest incidence is seen in registries of Madras and Bangalore, lowest incidence is seen in Bombay.[2] According to Population Based Cancer Registry, Manipur state, 2009-10, the incidence of carcinoma cervix was 161 out of the total 1478 cases in female. The mean age of carcinoma cervix in the United States is 47 years and the distribution of cases is bimodal with peaks at 35 to 39 years and 60 to 64 years.[3] Carcinoma cervix with stage IIB and IIIB are treated with RT alone, reported no significant correlation of 5-year disease free survival (DFS) with size of the cervical tumor.[4] Squamous cell carcinoma constitute 75-90% and the incidence of adenocarcinoma has been observed to rise from 5% in the past to 10-15% in recent years affecting younger age group which may be due to the actual increase in incidence or due to changing pathological diagnostic criteria.[5] As most of the cases present at advanced stages such as stage III and IV, in which surgery is not possible, radiotherapy plays an important role in the management of these patients. Radiation has been used successfully to treat cervical cancer for nearly a century. The combination of external beam radiotherapy (EBRT) and high dose rate brachytherapy (HDR) has been shown to be effective for carcinoma cervix patients. The external beam irradiation is usually intended to shrink the primary

tumor to a size that can adequately be encompassed with a boost volume of intracavitary irradiation. American Brachytherapy Association (ABS) recommends keeping the total duration of treatment with EBRT brachytherapy in carcinoma cervix to less than 8 weeks, because prolongation of treatment duration can adversely affect local control and survival. The overall treatment duration will be unduly prolonged if the HDR is started after completion of EBRT, because multiple insertions are required for HDR. If the geometry is optimal, they recommend HDR once a week, with the EBRT being given on the other 4 days of the week. In large volume tumors it is necessary to delay the start of HDR brachytherapy, and to perform two implant per week after the EBRT has been completed, to keep the total treatment duration in less than 8 weeks.[6] The purpose of the present work was to assess the local tumor control, bladder and rectum complications, overall survival, disease free survival, and survival with disease, of fractionated HDR when given concurrently with EBRT in carcinoma cervix stage IIA, IIB, IIIA and IIIB.

## Materials and Methods:-

1. **Study design**: Quasi - experimental study.
2. **Setting**: Hospital setting - the study was conducted in the Department of Radiotherapy, Regional Institute of Medical Sciences, Imphal, Manipur, North East India
3. **Duration**: The study was carried out in a period of 24 months, starting from August 2009.
4. **Study population**: Sixty women with histopathologically confirmed squamous cell carcinoma of cervix attending radiotherapy OPD were included in the study. It is expected that there would be around 120 cases in a year, out of which around 80 - 100 patients are expected to be new cases in different stages.

**a. Inclusion Criteria:**

- Stage IIA, IIB, IIIA and IIIB (according to FIGO staging),
- Karnofsky Performance status ≥ 70 %,
- Adequate cardiac and pulmonary function,
- Normal hematological parameters,
- Normal renal and liver function test and
- Normal blood sugar.

**b. Exclusion Criteria:**

- Patients operated for carcinoma cervix,
- Fibrosed uterine canal,
- Having severe degree of uterine prolapse,
- Cystocele and rectocele,
- Malnutrition,
- Medical or psychological conditions precluding treatment,
- Concomitant diseases which may adversely affect the outcome,
- Having a second neoplasm,
- Recurrent disease and having distant metastasis and
- Patients who were not willing to participate.

**c. Sample size:** 60 patients

**d. Sampling:** Patients were enrolled sequentially.

**Study tools**:

After enrolment, particulars of the patients and complete history was recorded and clinical tests as mentioned in the proforma was undertaken. All the patients were treated by external beam radiation by $^{60}$Cobalt teletherapy machine (Theratron780-C) to the whole pelvic area by 4-field box technique, upto a dose of 5000 cGy over 25 fractions over 5 weeks. Midline shielding was done in the anterior and posterior fields after completion of 2000 cGy of EBRT and lateral fields was removed thereafter for stage IIA and stage IIB. Fractionated High dose rate (HDR) intracavitary brachytherapy, was given by HDR microselectron using $^{192}$Ir and Nucletron plato brachytherapy treatment planning system. For stage IIA and stage IIB, HDR 7Gy/# every weekend (on Saturdays) with a total dose of 35Gy (i.e. 5 fractions), was given, starting from 2$^{nd}$/3$^{rd}$ week of EBRT depending upon the resolution of tumor bulk. However, for patients with stage IIIA and IIIB, HDR was started at the end of 3$^{rd}$/4$^{th}$ weeks of EBRT depending on the resolution of tumor bulk, by giving 7Gy/# weekly for 3 fractions. Midline shielding was done in anterior and

posterior fields after 40 Gy of EBRT and lateral fields were removed thereafter. No EBRT was given on the day of HDR for both. During the treatment, complete hemogram and kidney function test (KFT) were performed weekly in all the patients. Patients were evaluated at the end of 4th week during treatment to note the early treatment response of the primary disease by clinical examinations(PV, PR and USG) and for early complications like vaginitis, GIT problems, nausea, vomiting, enteritis and cystitis by using RTOG criteria, weekly during treatment from week one. After completion of treatment, patients were followed monthly for the 1st year. To detect late treatment response (by clinical examinations) and late complications to urinary bladder and rectum, vaginal synechia and dryness (RTOG criteria) patients were assessed after six months of completion of treatment, on three monthly basis for a minimum of six months or till the study period was completed.

Study variables were tumor size, rectal and urinary bladder complications. Tumor status/size were assessed by inspection, per vaginal, per rectal and USG examinations. For disease with poor response and recurrence PAP smear examination was carried out.

Descriptive statistics and Chi square test for comparing between stages was employed. Institutional ethical clearance was sought. Written informed consent were taken from all the patients. Confidentiality is maintained by removing all the identifiers.

## Results and Observation:-

In the present study the early CR and PR rates in stage II were 32(76%) and 10(24%) and that of stage III were 12(67%) and 6 (33%) respectively. The overall early CR rate was 44(73%) and PR rate was 16(27%). The early treatment response was assessed at one month after completion of treatment. There were no cases of no response( NR) and progression of disease POD. The complete response rate for stage II and stage III are significantly different at 0.001 level of probability. The partial response rate for stage II and stage III are also significantly different at 0.001 level of probability. The late tumor response as observed at the end of 6 months of completion of treatment for stage II were, DFS of 38(90%) and SWD of 4(10%). The same for stage III were 14(78%) and 4(22%) respectively. The overall late DFS and SWD were 52(87%) and 8(13%), there were no cases with POD at 6 months. The OS was 100% at the end of 6 months. The median duration of follow up was 18 months. The median DFS for stage II was 32(76.2%) with SWD of 4(10%). For stage III the median DFS was 12(67%) with SWD of 4(22%). The DFS rate at 6 month for stage II and stage III are significantly different at 0.001 level of probability. The SWD rate at 6 month for stage II and stage III are also significantly different at 0.001 level of probability.

The cumulative BED to point A for stage II was 83.5 $Gy_{10}$ with the LDR equivalent dose of 69.58 Gy. The dose to point B was 58 Gy. For stage III the cumulative BED and LDR equivalent dose were 83.7 $Gy_{10}$ and 69.75 Gy respectively; and the dose to point B was 52.7 Gy. The median treatment duration was 44 days; which was well within the recommendations of the American Brachytherapy Society.

Favorable outcome was presented also in the present study with DFS 95% and SWD 5% in those tumor whose diameter was less than 4 cm; and that of tumor > 4 cm were 70% and 30% respectively at 6 months follow up. The corresponding BED was 83.5 $Gy_{10}$ and 83.7 $Gy_{10}$ and the dose response relationship was observed. The calculated point B dose was 52.7 Gy and so the further dose escalation would be necessary to control the advanced disease, may be in the form of parametrial boost in the side with gross disease. In the present study for tumor < 4 cm**,** CR was seen in 80%, PR — 20%, and for tumor ≥4cm CR was 60% and PR – 40% as assessed after one month of completion of treatment. And the tumor control in relation to tumor size at six months of follow up was - for tumor < 4 cm DFS was 95% and SWD was 5% and OS was 100%. For tumor ≥ 4 cm DFS was 70% and SWD was 30% and OS 100%.

In the present study the total BED ranged from 83.5 $Gy_{10}$ - 83.7 $Gy_{10}$**.**

**Early treatment toxicity:-**

In the present study the, maximum acute toxicities were seen to be having at the end of 4-5 weeks. Vaginitis was the commonest acute toxicity 34/60 (56.6%) followed by GIT toxicity 20/60(33.3%) and dysuria were seen in 8/60 cases. Grade I vaginitis was observed in 20/60(33.3%), grade II vaginitis in 14/60(23.3%), and grade III in 1/60(3.3%). For GIT toxicity grade 1 toxicity was seen in 6/60(10%), grade II in 14/60(23.3%). Grade I dysuria was observed in 2/60(3.3%) and grade II dysuria in 6/60(10%).The toxicity criteria grade I for stage II and stage III are

not significantly different at 0.05 level of probability. The grade II toxicities for stage II and stage III are also not significantly different at 0.05 level of probability

The patients were treated conservatively and there were no treatment interruptions. Genitourinary toxicities were mild grade I and did not disrupt treatment.

**Late complications:-**

The actuarial 6 month late complication rates observed in the present study is almost similar to the findings of other authors. For stage II, at 6 month follow up there was 2(3.3%) case of cystitis grade 1, not correlating with BED; at 9 month there were 4 (6.6%) patient having proctitis two with grade II correlating with $BED_3$ - 110.6$Gy_3$ and another two with grade III correlating with $BED_3$ -140 $Gy_3$. The corresponding LDR equivalent doses for those suffering from proctitis were 72.8 Gy and 90 Gy respectively. There was also two cases of vaginal synechia of grade II. The Median BED to the rectum for stage II is 65.3 $Gy_3$ with a range from 40.71 -140 $Gy_3$. The median bladder BED for stage II is 68 $Gy_3$. For stage III at 6 month follow up there was two(3.3%) patient having grade I cystitis and grade I proctitis correlating with BED 114 $Gy_3$ and 118 $Gy_3$. Grade II vaginal synechia and vaginal dryness was seen in two patient. The median rectal BED for stage III is 70.17 $Gy_3$. The median bladder BED for stageIII is 75.03 $Gy_3$.

The grade I urinary bladder toxicity was seen in 2 patients, grade II proctitis was seen in 2/60 (3.3%) grade III proctitis was observed in 2 patient (3.3%). There were 2/60(3.3%) patients having multiple grade II toxicity, vaginal synechia and vaginal dryness. The grade III proctitis may be explained by the inadequate vaginal packing, increased BED to the rectum may be due to the increase input of radiation dose as the AP/PA and the lateral separation in this particular case was large even though the four field technique was practiced. Late toxicities for stage III is significantly higher than stage II at 0.05 level of probability. The reason could be, in stage II the mid line shielding was done at 20 Gy of EBRT, where as in stage III the midline shielding was done at 40 Gy of EBRT.

## Discussion:-

Most cervical carcinomas arises at the junction between the primarily columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. The incidence is 33.3% for proliferative/exophytic, 26.7% for ulceroproliferative and 16.7% for infiltrative lesion in this study. The incidence of cancer cervix stage IIB and IIIB (FIGO) are the commonest stages at which the patient present to the clinician. In this study the incidence of Stage IIB and IIIB are 63.3% and 30 % respectively. The findings thus agrees with the available incidence pattern of clinical stage at the time of presentation as observed in the literature of Singh TT et al[6] where they got 23, 2,and 15 in stage IIB, IIIA and IIIB in their study group. Also in a study done by Pooja KN et al[7] they also observed the number of cases be more in stage IIIB when compared with stage IIB(24 vs 6).

The incidence of pelvic and para-aortic node involvement is correlated with tumor stage and with other tumor characteristics such as size, histologic type, depth of invasion, presence of lymphovascular invasion.[8] The incidence of pelvic node involvement as per the literature shows the lymphnode involvement in the pelvis in FIGO stage I disease is 15 - 20%, in stage II 25 – 40%, and in stage III approximately 50% or more. The para – aortic node involvement by clinical stage: stage IB is 6%, Stage IIA is 12%, stage IIB 19% and stage IIIB is 29%.[9] The higher the stage there is a higher incidence of pelvic and para aortic adenopathy. Thus the radiation beam must be able to cover the potential areas in the high dose zone of the beam.

External beam irradiation is used to deliver a homogenous dose to the primary cervical tumor and to potential sites of regional spread. An initial course of external irradiation may also improve the efficacy of subsequent brachytherapy/intracavitary treatment by shrinking bulky tumor and bringing it within the range of the high dose portion of the brachytherapy dose distribution. For this reason patient with locally advanced disease usually begins with a course of external beam treatment. Subsequent brachytherapy exploits the inverse square law to deliver high dose to the cervix and paracervical tissues, while minimizing dose to the adjacent normal tissues.

Some practitioners prefer to maximize the brachytherapy component of treatment and begin as soon as the tumor has responded enough to permit a good placement of the brachytherapy applicators. Traditionally, cervical brachytherapy has been performed with sources that yield a dose rate at point A of approximately 40-50 cGy/hr. These low dose rate permit repair of sublethel cellular injury, preferentially spare normal tissues and optimize therapeutic ratio. It is found that HDR brachytherapy is attractive because it does not require patients to be hospitalized and may be more convenient for patient and physician. However, unless it is heavily fractionated, HDR brachytherapy may lose the radiobiologic advantage of LDR treatment, potentially narrowing the therapeutic window for complication - free cure.[8]

The fraction size is the dominant factor in determining late effects and overall treatment time has little influence. The fraction size and overall treatment time both determine the response of acutely responding tissues. Treatment should be completed as soon after it has begun as is practicable. If the treatment time is too long the effectiveness of dose per fraction is compromised because the surviving clonogens in the tumor have been triggered into rapid population.[10] The strategy of giving external beam radiotherapy concurrent with high dose rate brachytherapy in patients of squamous cell carcinoma cervix stage II and stage III was with the objective of increasing tumor control keeping the duration of treatment within 6 - 7 weeks, while keeping toxicity at the acceptable level**.**

American Brachytherapy Society (ABS) recommends keeping the total duration of treatment with EBRT with brachytherapy in carcinoma cervix to less than 8 weeks, because prolongation of treatment duration can adversely affect local control and survival. The overall treatment duration will be unduly prolonged if the HDR is started after completion of EBRT, because multiple insertions are required for HDR. If the geometry is optimal, they recommend HDR once a week, with the EBRT being given on the other 4 days of the week. In large volume tumors it is necessary to delay the start of HDR brachytherapy, and to perform two implants per week after the EBRT has been completed, to keep the total treatment duration less than 8 weeks.[11]
Radiobiologically, compared to LDR brachytherapy, HDR treatments has worse therapeutic ratios. An approach to mitigating this effect is to fractionate the treatment of HDR. Although LDR therapy is on single session, or possibly two, most curative HDR regimens use around five fractions. The absolute dose used may depend on the stage of the disease, the number of fractions used, and other concomitant therapy including external beam therapy and chemotherapy.[12]

The present study was performed to assess the response rate and toxicity of external beam radiotherapy when given concurrently with fractionated high dose rate brachytherapy of 7 Gy/fraction weekly. In the present study, patient categorization scheme defined by American brachytherapy society – early disease as nonbulky stage I/II, less than 4 cm diameter, and advance disease is defined as greater than4 cm diameter or stage IIIB was followed.[13] This is determined by combination of FIGO stage and tumor size. Whereas an assessment method of tumor size was not defined, in this study Ultrasonography abdomen –pelvis was used for this purpose. A wide variation of treatment schedules, both for EBRT and ICBT also makes it difficult to analyze dose response in uterine cancer. The linear quadratic model has been considered to be one of the most reliable methods for converting each dose into a comparable value.[14, 15] In these studies BED was calculated in addition to cumulative total dose.

Petereit DG and Pearcey R[16] suggested that dose schedules with a total point A BED of 50 -80 Gy are adequate to achieve local control for patients with tumor less than 4cm diameter without massive parametrial disease. Favorable outcome was presented also in the present study with DFS 95% and SWD 5% in those tumor whose diameter was less than 4 cm; and that of tumor > 4 cm were 70% and 30% respectively at 6 months follow up. The corresponding BED was 83.5 $Gy_{10}$ and 83.7 $Gy_{10}$ and the dose response relationship was observed. The calculated point B dose was 52.7 Gy and so the further dose escalation would be necessary to control the advanced disease, may be in the form of parametrial boost in the side with gross disease. In the present study for tumor < 4 cm**,** CR was seen in 80%, PR — 20%, and for tumor ≥4cm CR was 60% and PR – 40% as assessed after one month of completion of treatment. And the tumor control in relation to tumor size at six months of follow up was - for tumor < 4 cm DFS was 95% and SWD was 5% and OS was 100%. For tumor ≥ 4 cm DFS was 70% and SWD was 30% and OS 100%.

Patel FD et al[17] studied on HDR brachytherapy in uterine cervical carcinoma; they used 9 Gy/ fraction in 2 - 5 fractions. The 5 yr actuarial local control and DFS were 74.5% and 62.0% respectively. 5 year actuarial DFS rate was 76.52% for stage II, and 50.4% for stage III patients which is comparable to the present study, but better for stage III in the present study. Local failure rate occurred in 2(11.1%) in stage 1B - IIB and 20 (21.0%) in stage IIB - IIIB patients. In the present study HDR dose per fraction was 7 Gy, for 5 fractions in stage II and 3 fractions in stage III. DFS in both the stages are more in our case. The increase in DFS in the present study may be due to the reduced time gap in between the treatment as we gave ICRT during the week ends starting from 2nd week for stage II and 4th week for stage III, thereby reducing or inhibiting sublethal damage repair and tumor repopulation. This may be due to the short overall duration of treatment in our case with the median duration of treatment of 44 days. Whereas in their study the treatment duration ranges from < 6 weeks to > 8 weeks. In our study the CR rate at the end of treatment for tumor < 4 cm was 80%, which is comparable and that of tumor ≥4 was70% which is better than their result**.**

Takafumi T et al[18]studied on combination external beam radiotherapy and high dose rate intracavitary brachytherapy for uterine cervical cáncer: analysing the dose fractionation schedule. The actuarial 3 year pelvic control rate, DFS rate, and overall survival rate were 82%, 73%, and 77%, respectively. In stage II, 3 year actuarial DFS and pelvic control rate was 100% but in stage III the rates were 79% and 85% respectively. According to tumor size less than 4 cm DFS rate was 84% and pelvic control rate was 88%. For tumor more than and equal to 4 cm size the DFS rate and pelvic control rates were 67 % and 78% respectively. American Brachytherapy Society early stage and advanced stage (early –nonbulky stage I/II, <4 cm, advanced -≥4 cm or stage III B) the DFS were 91% and 66%, and pelvic control rates were 96% and 76% respectively.

In a study by Robson F et al[19] the HDR dose of 6 Gy/ fraction was given for 4 fractions. The total BED ranged from 82.2 $Gy_{10-}$ 96.4 $Gy_{10.}$ The overall treatment time was 60 days. The median follow up time was 38 months. They achieved an OS of 53.7%, DFS of 52.7% and local control of 62% at 5 years. In the present study the total BED ranged from 83.5 $Gy_{10}$ - 83.7 $Gy_{10}$**.** The median time of follow up was 9 months. The median DFS for stage II was 16(76.2%) and SWD was 2(10%). For stage III the median DFS was 6(67%) and SWD was 2(22%). The difference with the better result in the present study may be due to the short duration of treatment that is 44 days compared to 60 days in their study. They found that the overall treatment time was the only statistically significant variable that influences the local control and survival. They suggested that the fractionation schedule of 6 Gy per fraction used in their series was effective if performed in an overall treatment duration ≤ 50 days.

When EBRT and HDR brachytherapy are combined, the goals are to treat point A to an LDR equivalent of 80 - 85 Gy for early-stage disease and 85 - 90 Gy for advanced stage. The pelvic side wall dose recommendations are 50 - 55 Gy for smaller lesions and 55 - 60 Gy for larger lesion. Concurrent chemoradiotherapy in the treatment of cervical cancer offers definite improvement in pelvic control and overall survival and this is the acceptable treatment modality for advanced cases. The Cochrane Collaborative meta-analysis included data from 19 trials, 12 of which used platinum-based chemotherapy. The second, a Canadian study, based on 8 randomized trials, exclusively examined platinum-based chemo radiation. An absolute improvement in survival was estimated as 12% by the Cochrane group and 11% in the Canadian study. Controversy persists about the most appropriate drug for chemotherapy, and its dose and schedule with optimally delivered radiotherapy, to get similar or better results for tumor control and minimum toxicity. Use of concurrent chemo radiation, with weekly cisplatin, for advanced cancer cervix case is ideal for developing countries. CT - and MRI - based 3 - DCRT and IMRT has shown improved results in locally advanced cervical cancer. Use of interstitial brachytherapy to achieve better dose distribution in cases with a narrow vagina, inability to enter the cervical os, extension to the parametrium and lower vagina and bulky lesions (where ICRT is not possible or possible only with suboptimal dose distributions) have been described.[8]

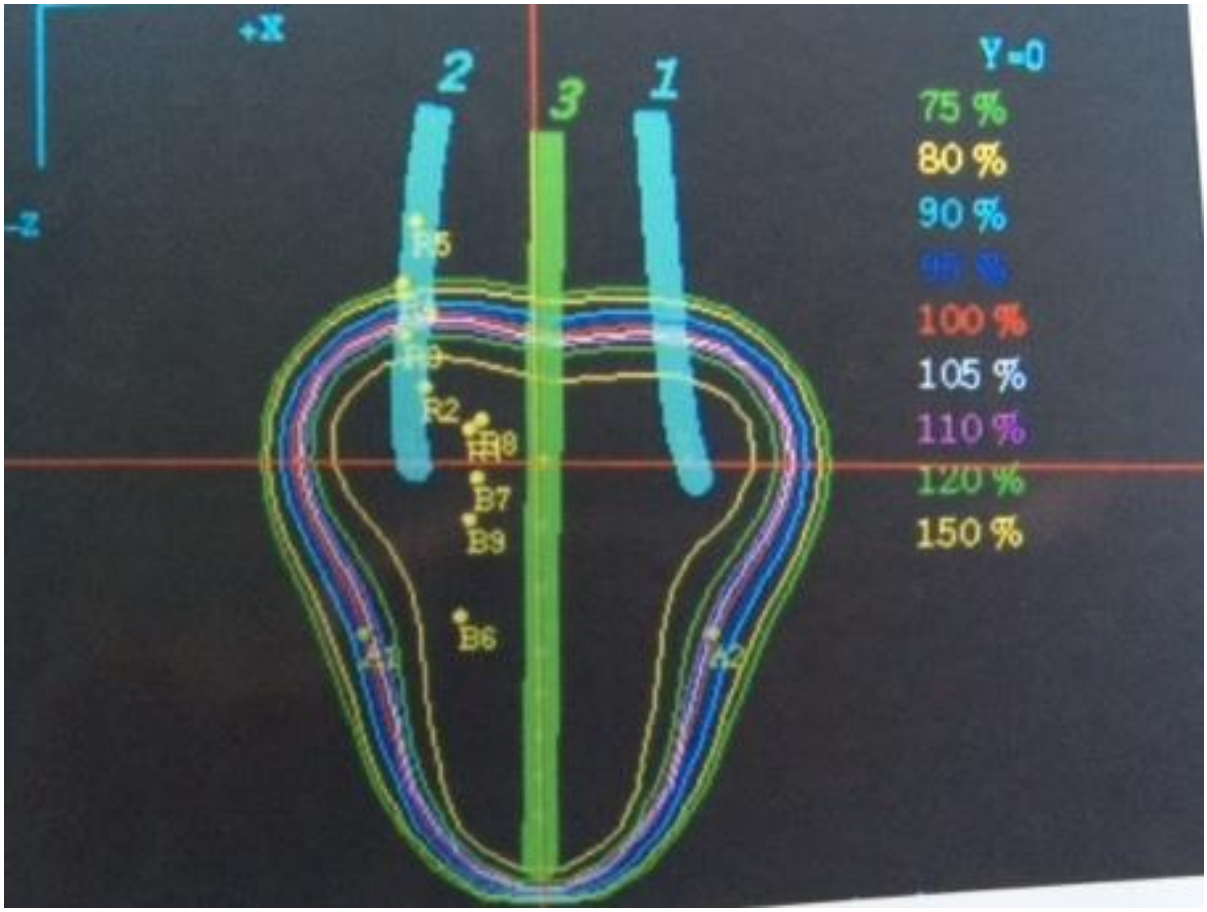
The early grade II toxicities for stage II and stage III are also not significantly different at 0.05 level of probability. Ntekim A et al[20] in their prospective study of high dose rate brachytherapy in the treatment of cervical cancer: preliminary experience with cobalt 60 radionuclide source, two patients had grade III gastrointestinal toxicity while others had ≤ grade II toxicity. The median dose to ICRU bladder point $Gy_3$ was 5.6 Gy and the median dose to ICRU rectal point Gy3 was 5.4 Gy. Percentage of proctitis grade 0 was 43%, grade I was 50%, grade II was 7% and there were no grade III and IV proctitis. Diarrhoea – grade 0 was observed in 38%, grade I was observed in 46%, grade II in 13%, grade III in 3%, but no grade IV toxicity.

The percentage of grade I toxicity was more in the study of Ntekim et al[20], which may be due to the addition of cisplatin and 5 FU in the treatment regime. The high percentage grade II toxicity compared to that of Ntekim et alin the present study may be due to the increase input of the radiation dose per week, poor general conditions of our patients, or superadded infections and poor nutrition. But no grade III toxicity was observed in our study. The patients were treated conservatively and there were no treatment interruptions. Genitourinary toxicities were mild grade I and did not disrupt treatment. According to Chung et al[21]grade III and IV gastrointestinal (GI) and genitourinary (GU) acute toxicity was 2% and 0% respectively. According to Kim et al[26] grade III GI acute toxicity was 8% and GU acute toxicity was 3%.
There is not enough literature commenting on acute toxicities. Maximum of the studies available were done on late toxicities

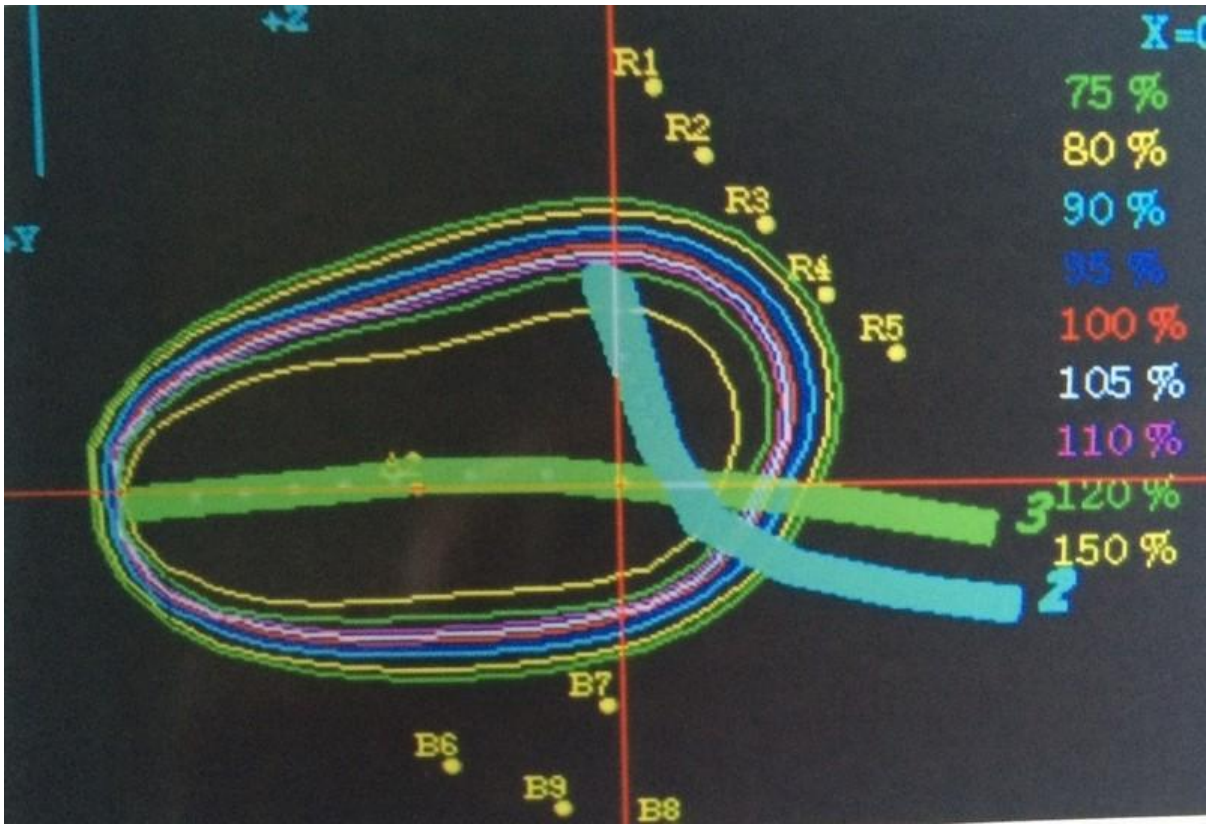
Patel FD et al[17] 11/113 patients experienced grade - 1 late rectal toxicity. Grade II toxicity was observed in only 1 patient, none of the patients developed grade III rectal toxicity. The mean time of onset was 12.08 months (range 8-22 months). 5 and 2 patients experience grade I and II bladder toxicity, respectively. Grade III bladder toxicity was

observed in 2 patients. Both the patients with grade III toxicity received weekly sessions of 9 Gy HDR brachytherapy to a total of 5 sessions. The intracavitary treatment was interdigited with EBRT and the patients did not receive EBRT on the day of intracavitary treatment. The mean time to the onset of toxicity was 24.4 months (range, 18-38 months).

The late grade I urinary bladder toxicity was seen in two patients, grade II proctitis was seen in 2/60 (3.3%) grade III proctitis was observed in two patient (3.3%). There were 2/60(3.3%) patients having multiple grade II toxicity, vaginal synechia and vaginal dryness. The grade III proctitis may be explained by the inadequate vaginal packing, increased BED to the rectum may be due to the increase input of radiation dose as the AP/PA and the lateral separation in this particular case was large even though the four field technique was practiced. Late toxicities for stage III is significantly higher than stage II at 0.05 level of probability. The reason could be, in stage II the mid line shielding was done at 20 Gy of EBRT, where as in stage III the midline shielding was done at 40 Gy of EBRT




Isodose curves in the frontal plane as shown in the screen of the Nucletron plato Treatment Planning System



Isodose curves in the lateral plane as shown in the screen of the Nucletron Treatment Planning System

**Stages of cervical cancer**

| FIGO Stage | Number of cases | % |
|---|---|---|
| II A | 4 | 6.7 |
| II B | 38 | 63.3 |
| III A | 0 | 0 |
| III B | 18 | 60 |

**Tumor size grouping with stage**

| Tumor size | Stage IIA | Stage IIB | Stage IIIA | Stage IIIB | Total |
|---|---|---|---|---|---|
| <4 | 4 | 36 | - | - | 40 |
| ≥4 | - | 2 | - | 18 | 20 |

**Dose distribution**:

| FIGO Stage | EBRT /whole pelvis | To the parametrium following mid line shielding | HDR | Cumulative BED to point A (BED of WPRT+BED HDR ICRT) | LDR equivalent (WPRT dose+ LDR equivalent of HDR ICRT) | Dose to point B (90% WPRT dose +LDR equivalent of 26 % HDR dose) |
|---|---|---|---|---|---|---|
| Stage II | 20 Gy | 30 Gy | 7 Gy x 5=35 Gy | 83.5 $Gy_{10}$ | 69.58 Gy | 45+13 Gy=58 Gy |
| Stage III | 40 Gy | 10 Gy | 7 Gy x 3= 21 Gy | 83.7 $Gy_{10}$ | 69.75 Gy | 45+7.7=52.7 Gy |

**Grade of acute toxicity**

| Toxicity | Stage II | | | | Stage III | | | |
|---|---|---|---|---|---|---|---|---|
| | Gr-I | Gr-II | Gr-III | Gr-IV | Gr-I | Gr-II | Gr-III | Gr-IV |
| Vaginitis | 16 | 10 | - | - | 4 | 4 | - | - |
| GIT | 2 | 12 | - | - | 4 | 2 | - | - |
| Dysuria | 2 | 4 | - | - | - | 2 | - | - |

Gr - Grade

**Early tumor response**

| Month | Stage II | | | | Stage III | | | |
|---|---|---|---|---|---|---|---|---|
| | C/R | P/R | N/R | PD | C/R | P/R | N/R | PD |
| 1st month | 32(76%) | 10(24%) | - | - | 12(67%) | 6(33%) | - | - |
| Overall | C/R -- 44(73%), P/R-- 16(27%) | | | | | | | |

**C/R - complete response, P/R - partial response, N/R - no response, PD - progression of disease**

**Late tumor response**

| Post treatment months | Stage II | | | Stage III | | |
|---|---|---|---|---|---|---|
| | DFS | SWD | OS | DFS | SWD | OS |
| 6 | 38(90%) | 4(10%) | 100% | 14(78%) | 4(22%) | 100% |
| 9 | 40 | 2 | | 14 | 4 | |
| 12 | 40 | 2 | | 14 | 4 | |
| Overall response at 6 months | **DFS** (Disease free survival)—52/60(87%), **SWD** (Survival with Disease)—8/60(13%), **OS**(overall survival)—60/60(100%) | | | | | |

**Late tumor control (12 months follow up)**

| Size of the Tumor | Stage II | | | Stage III | | |
|---|---|---|---|---|---|---|
| | DFS | SWD | OS | DFS | SWD | OS |
| <4 cm | 38 | 2 | 40(100%) | - | - | |
| ≥ 4 cm | | 2 | 2(100%) | 14 | 4 | 18(100%) |

**Late complication grade wise**

| Complica-tions | Stage II | | | | Stage III | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade -I | Grade-II | Grade-III | Grade - IV | Grade -I | Grade-II | Grade-III | Grade-IV |
| Urinary bladder | 2(3.3%) | - | - | - | 2(3.3%) | - | - | - |
| Rectum | - | 2(3.3)% | 2(3.3%) | - | 2(3.3%) | - | - | - |
| Vaginal synechia | - | 2(3.3%) | - | - | - | 2(3.3%) | - | - |
| Vaginal dryness | - | - | - | - | - | 2(3.3%) | - | - |

## Conclusion:-

A total of 60 patients were registered out of which there was no incomplete treatment or loss to follow up. All the patients completed the planned treatment and were available for the data analysis. The early and late treatment responses were analyzed as per Miller's WHO criteria for objective response. The early and late treatment toxicities were analyzed as per RTOG toxicity criteria. The study suggest that the radiation dose of 5000 cGy to whole pelvis with midline shielding at 2000 cGy with 5 fractions of concurrent HDR brachytherapy, 7 Gy per fraction at weekends is an effective and safe fractionation schedule in the treatment of stage II carcinoma cervix. In view of the therapeutic ratio cumulative BED of 83.5 $Gy_{10}$ point A is appropriate for stage II uterine cervical cancer patients treated. Whereas for stage III it was observed that the radiation dose of 5000 cGy to whole pelvis with midline shielding at 4000 cGy with concurrent 3 fractions of HDR brachytherapy, 7 Gy per fraction at weekends is suboptimal as in this study only 78% of DFS could be achieved with 22% SWD at 6 months of follow up. The cumulative BED 83.7 $Gy_{10}$need to be increased by boosting to the parametrium to improve the therapeutic ratio. Overall response according to size - for tumor < 4 cm DFS was 95% and SWD was 5%. For tumor ≥ 4 cm DFS was 70% and SWD was 30%. The median time of follow up was 18 months. The median DFS for stage II was 32(76.2%) with SWD of 2(10%). For stage III the median DFS was 12(67%) with SWD of 4(22%). The median treatment duration was 44 days. The cumulative BED at rectal point showed that it needs to be kept below 110 $Gy_3$ -

140 $Gy_3$ to avoid late toxicities. HDR is high tech and able to conform the dose to the tumor and possibly minimize the dose to the surrounding normal tissues with 3 dimensional imaging may permit biologically higher doses with a greater degree of accuracy, thus translating into high cure rates. However for stage III disease, results might be improved by increasing the overall dose to point "A" by boosting or by tumor sensitization with chemotherapy. Tumor localization through image based planning and by using perineal templates in cases with extensive involvement of the parametrium may be able to improve the cure rate in selected cases of carcinoma cervix. For long term survival and late complications/toxicities the study need to be followed up.

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