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Corresponding Author
Akhilesh Sahu,
Regional Cancer Center, Pt JNM Medical College Raipur CG India M. 9179577544 India

Author Designation
[1,4,8]Assistant Professor
[2,7]Associate Professor
[3,6]Professor
[5]Dean and Director cum HOD

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An Observational Study to Evaluate the Clinical Outcome in Locally Advanced Carcinoma Cervix Using HDR Brachytherapy (4# X7 Gy) in between External Beam Radiotherapy (46Gy/23#)

[1]Umesh Dewangan, [2]Rahul Swaroop Singh, [3]Manjula Beck, [4]Akhilesh Sahu, [5]Vivek Choudhary, [6]Pradeep Kumar Chandrakar, [7]Rajeev Ratan Jain and [8]Divya Fransis
[1-8]Regional cancer center, Pt JNM Medical College Raipur CG India

ABSTRACT
Cervical cancer is a highly curable disease when diagnosed in early stage. In India, due to lack of screening and early detection programmes, 70% to 80% of the women with cervical cancer are diagnosed with locally advanced disease where uncontrolled locoregional pelvic disease is the cause of morbidity. Thus locoregional control is of paramount importance to improve survival. to evaluate the efficacy and feasibility of using high dose rate Brachytherapy (4#x7Gy) in between external beam radiotherapy (46Gy/23#) and to shorten the overall treatment time for better patient compliance and also to observe the loco-regional control of disease. The study was performed in the Department of Radiotherapy, Regional Cancer Institute, DR. B.R.A.M. Hospital, Raipur(C.G.) Total 50 patients of cervical cancer up to IIIB who were diagnosed as cervical cancer are taken in the study. Most of the patients (>50%) belonged to menstruating age group. Maximum patients (68%) had 3-5 pregnancies. Histopathologically most of the patients (96%) had squamous cell carcinoma. Majority of the patients (48%) reported with stage IIIB. Majority of the patients (66%) were classified under moderately differentiated carcinoma. 37(74%) patients completed their treatment before 56 days and remaining 13(26%) patients completed their treatment after 56 days due to mechanical errors. Patients in case study received Cisplatin 40mg/m^2 weekly on day 1, 8, 15, 22 and 29 at least 4-6 hours before EBRT concurrently with HDR Brachytherapy in between External Beam Radiotherapy. Response after 1 month of completion of treatment: 1(2%) patient showed partial response and 49(98%) patients showed complete response. Response after 3 months of completion of treatment: 34(68%) patients showed complete response, 1(2%) patient showed progressive disease (para aortic node and multiple lung metastasis) and 15(30%) patients lost to follow up due to illiteracy, lack of awareness and poverty. Response after 6 months of completion of treatment: 34(68%) patients showed complete response, 1(2%) patient died due to distant para aortic and lung metastasis and 15(30%) patients lost to follow up due to illiteracy, lack of awareness and poverty.

INTRODUCTION

Worldwide, Cervical carcinoma is the fourth most common cancer in women and seventh most common overall[1] (GLOBOCAN 2018). Carcinoma cervix accounts for about 569,847 patients around the world out of which 311,365 accounts for death worldwide. Total 14,389 patients were registered in Dr. BRAM Hospital (2012-2015). Out of these 2738 patients registered were of carcinoma cervix. Carcinoma cervix consists of 18% of total cancer registered. International incidence of cervical cancer reflects differences in cultural attitudes towards sexual promiscuity and penetration of mass screening programmes. In developing countries, cervical cancer is the leading cause of cancer related death[2]. Cervical cancer is more common in areas where women have less assess to screening. Uterine cervix is the commonest site to be involved by malignant growth transformation[3]. More than 90% of cervical cancers are of squamous variety 5% are adeno carcinoma, 1-2% is clear cell variety. There is strong relationship between Human papilloma virus type (16, 18, 31 and 33), cervical intraepithelial neoplasia and squamous cell carcinoma[4,5]. The components of inhaled cigarette smoking are secreted in the cervical mucus, raising the possibility of oncogenesis[17]. Similarly women with immune compromised status due to HIV infection or immunotherapy are the greater risk[6]. The present study is undertaken to evaluate the efficacy and feasibility of using high dose rate Brachytherapy (4#x7Gy) in between external beam radiotherapy (46Gy/23#) and to shorten the overall treatment time for better patient compliance and also to observe the loco-regional control of disease.

MATERIALS AND METHODS

The study was performed in the Department of Radiotherapy, Regional Cancer Institute, DR. B.R.A.M. Hospital, Raipur (C.G.) Total 50 patients of cervical cancer up to IIIB who were diagnosed as cervical cancer are taken in the study. Detailed history of patients, including age, age at marriage, socioeconomic status, menstrual status, pregnancy and previous treatment history was obtained. Complete physical examination was carried out including general physical examination as well as per-speculum, per-vaginal, per-rectal and bimanual examination. For tissue diagnosis punch biopsy was taken from cervical growth and sent to pathology lab. For further clinical staging, X-ray chest and pelvis, ultrasonography, CT scan abdomen and pelvis, haemogram, renal function test, VDRL test, HIV test, Hepatitis-B and C test were obtained. Patients were simulated on CT SIMULATOR then contouring for CTV, PTV and OAR was done after the planning with 3D CRT with weekly Cisplatin 40mg/m^2 along with HDR Brachytherapy. Then the analysis of treatment planning was done by guide and co guide. Informed written consent was taken from every patient. Patients were included with Hb >10 gm % after correction of anemia. After initiation of treatment, patient was assessed for disease response after 10 fractions of EBRT along with weekly Cisplatin for negotiability of external os. Then we started HDR Brachytherapy (7Gy*4 #) weekly once on staurdays only. And when the treatment was complete patients were called for fore mentioned follow up weekly for 6 weeks along with weekly routine blood investigations (CBC,RFT,LFT). And on each follow up there was assesment of tumor response and toxicity.

Inclusion Criteria:

- Age less than 75 years
- All patients of cervical cancer upto stage IIIB
- All non operated cases
- Histopathology proven carcinoma cervix
- ECOG PERFORMANCE Status 1
- Haemogram: Haemoglobin > or =10gm/dl
- WBC count: 4000-11000 per cubic mm
- Platelet count: 1.5-4.5 lakh per cubic mm
- Normal renal function test: Creatinine - <1.5 mg/dl
- No renal abnormalities (e.g.pelvic kidney, horse shoe kidney or renal transplantation) that would require modification of radiotherapy fields. No ureteral obstruction allowed unless
- Normal liver function test: Bilirubin-not more than 1mg/dl

Exclusion Criteria:

- Patient who lost to follow up
- Patient with co-morbidity (like CKD, DM, Heart disease,HTN)
- Patient with stage more than IIIB.
- Patient with altered RFT

Radiotherapy: Every patient was treated with HDR intracavitary Brachytherapy of 700cGy/4# weekly on Saturday in between external beam radiotherapy to whole pelvis region in 23 fractions for a total of 4600cGy for 5 days a week from Monday to Friday along with Cisplatin. Timing of HDR Intracavitary Brachytherapy-After 10-15# of EBRT when os is negotiable. Total duration of treatment is within 56 days. TDF given by EBRT: 23 fractions: 200 cGy per fraction 5 fraction per week = 76 Gy BED (biologically effective dose) = nd (1+d/alpha/beta) EQD_2 = BED/(1+2/alpha/beta) Where, n is total number of fraction d is dose per fraction alpha/beta is ratio of 10 used for early responding tissue and tumors EQD_2 is equivalent dosein 2 Gy fractions Therefore, BED of

EBRT = 55.2 Gy_{10} EQD_2 = 46 Gy and BED of HDR Brachytherapy = 47.6 Gy_{10} D2 = 39.7 Gy Hence, Total BED = BED of EBRT + BED of HDR Brachytherapy = 55.2 + 47.6 Gy = 102.8 Gy And, Total EQD_2 = 46 + 39.7 Gy = 85.7 Gy Pelvic radiotherapy was delivered by using linear accelerator machine of energy 6 MV and 15 MV. The usual field border for anterior and posterior field were superior at the L4-L5 interspace, inferiorly at the bottom of obturator foramen or 2-3 cm below the lower extent of the disease and 1.5-2 cm lateral to lateral margin of true pelvis[7,8].

Chemotherapy: Cisplatin[9] of 40 mg/m^2 dose was administered in 60 minutes before 4-6 hours of radiotherapy weekly on day [1,8,15,22,29]. Thus a total of 4-5 doses of Cisplatin were administered during full course of treatment. Haemogram and toxicities were assessed on weekly basis during treatment on monthly basis after treatment along with chest X-ray, USG/ CT scan abdomen and pelvis. Responses were evaluated on weekly basis, after 1 month of completion of treatment, after 3 months of completion of treatment and after 6 months follow up.

RESULTS AND DISCUSSIONS

The present study was carried on 50 patients of cervical cancer at the Department of Radiotherapy, Pt. J.N.M., Medical College and Dr. B.R.A.M. Hospital, Raipur, C.G. from March 2018-September 2019. All the patients completed the full course of treatment as planned. Patients evaluated belonged to age group between 30-70 years. The median age of the patients is 48 years. 3(6%) patients were between 31-40 years, 24(48%) between 41-50 years, 17(34%) between 51-60 years and 6(12%) between 61-70 years. It is an important aspect to evaluate the causative factors of cervical cancer. In this study it revealed that age at marriage of the patients is mostly early age i.e., as lower as 12 years. Median age at marriage is 18 years. 19(38%) patients got married before 18 years and 31(62%) patients got married at 18 years of age or after 18 years.

Table 1: figo staging of case study

FIGO Staging	No. of cases	Percentage (%)
IIA	6	12
IIB	17	34
IIIA	3	6
IIIB	24	48
Total	50	100

Table 2: response after 10# of ebrt along with cisplatin 40mg/m2 weekly

Response	No. of patients	Percentage (%)
N.R.*	32	64
P.R. (<50%)*	7	14
P.R. (50%)*	11	22
C.R.*	0	0
Total	50	100

N.R.* - No response, stable disease

Table 3: response after 15# of ebrt and 1# of hdr brachytherapy along with cisplatin

Response	No. of patients	Percentage (%)
N.R.	0	0
P.R. (<50%)	10	20
P.R. (50%)	18	36
P.R. (>50%)*	22	44
C.R.	0	0
Total	50	100

Table 4: response after 20# of ebrt and 2# of hdr brachytherapy along with cisplatin:

Response	No. of patients	Percentage (%)
N.R.	0	0
P.R. (>50%)	28	56
P.R. (75%)*	15	30
P.R. (>75%)*	7	14
C.R.	0	0
Total	50	100

Table 5: response after 23# of ebrt and 3# of hdr brachytherapy along with cisplatin:

Response	No. of patients	Percentage (%)
N.R.	0	0
P.R. (>50%)	8	16
P.R. (75%)	15	30
P.R. (>75%)	19	38
C.R.	8	16
Total	50	100

Table 6: response after 4# of hdr brachytherapy:

Response	No. of patients	Percentage (%)
N.R.	0	0
P.R. (75%)	1	2
P.R. (>75%)	21	42
C.R.	28	56
Total	50	100

Table 7: response after 3 months of completion of treatment

Response	No. of patients	Percentage (%)
P.R.	0	0
C.R.	34	68
P.D.	1	2
Lost to follow up	15	30
Total	50	100

Table 8: response after 6 months of completion of treatment

Response	No. of patients	Percentage (%)
P.R.	0	0
C.R.	34	68
P.D.	0	0
Death	1	2
Lost to follow up	15	30
Total	50	100

Table 9: duration of treatment of case study

Duration of treatment	No. of cases	Percentage (%)
29-35	2	4
36-42	8	16
43-49	15	30
50-56	12	24
57-63	7	14
64-70	5	10
71-77	0	0
78-84	1	2
Total	50	100

Early age of marriage leads to early first intercourse and history of multiple sexual During history taking, patients were asked about their socioeconomic status. Majority of the patients belonged to lower group i.e., (50%), lower middle group i.e., (42%) and only 4(8%) from upper middle group. There were no patients from higher socioeconomic group. As per menstrual history of the patients, 28(56%) were menstruating and

22(44%) belonged to post menopausal category. In obstetric history, number of pregnancies of each patient was noted. Women having more than two children are called multipara. Majority of the patients have borne 3-5 pregnancies, 6-8 pregnancies group was second largest, 2 Patients have more than 8 pregnancies and no one was nulliparous. In this study, locally advanced cervical cancers i.e., stage IIA to IIIB of FIGO staging were considered. 6(12%) patients presented with stage IIA, 17(34%) patients had presented with stage IIB, 3(6%) patients had presented with stage IIIA and 24(48%) patients had presented with stage IIIB.

Histopathological Grade of Differentiation: On histopathological examination of biopsy obtained from cervical growth, 48(96%) were diagnosed as squamous cell carcinoma, 1(2%) was adenocarcinoma 1(2%) was clear cell carcinoma. Out of 50, 12(24%) had well differentiated tumor cells, 33(66%) had moderately differentiated tumor cells and 4(8%) had poorly differentiated tumor cells. In this study, 37(74%) patients completed their treatment before 56 days and remaining 13(26%) patients completed their treatment after 56 days due to mechanical errors.

Clinical Response: Response to chemotherapy and radiotherapy were evaluated clinically, by comparing reports of abdominal and pelvic U.S.G./C.T.-Scan and cytologically at the time of presentation with that after completion of treatment and subsequent follow ups. The response evaluation was done at the following points:

- After receiving 10# of External Beam Radiotherapy along with Cisplatin 40mg/m^2 weekly
- After receiving 15# of External Beam Radiotherapy and 1# of HDR Brachytherapy along with Cisplatin
- After receiving 20# of External Beam Radiotherapy and 2# of HDR Brachytherapy along with Cisplatin
- After completion of External Beam Radiotherapy i.e., 23# and 3# of HDR Brachytherapy along with cisplatin
- After completion of both External Beam Radiotherapy and 4# of HDR Brachytherapy along with Cisplatin
- After 1 month of completion of treatment
- After 3 months of completion of treatment
- After 6 months of completion of treatment

P.R. (<50%)*-Partial response, < ½ reduction of tumor size on clinical examination P.R. (50%)*-Partial response, ½ reduction of tumor size on clinical examination C.R.*-Complete response, complete regression of disease This is the first point of response evaluation of the study. This evaluation is done to look for negotiability of cervical os for HDR Brachytherapy. 32(64%) patients showed no response and 18(36%) patients showed partial response. P.R. (>50%)*-Partial response, > ½ reduction of tumor size on clinical examination. There seems regression of tumor size after introduction of HDR Brachytherapy. All the 50(100%) patients showed partial response. P.R. (75%)*-Partial response,3/4 reduction of tumor size on clinical examination. P.R. (>75%)*-Partial response, >3/4 reduction of tumor size on clinical examination. There seems further regression of tumor size after 2# of HDR Brachytherapy. All the 50(100%) patients showed partial response.

Tumor size regression occurred as the treatment advanced. 42(84%) patients showed partial response and 8(16%) patients showed complete response. It showed maximum regression of tumor size. 22(44%) patients showed partial response and 28(56%) patients showed complete response. When response to concurrent Chemoradiation was observed after 1 month of completion of treatment only 1 (2%) patient had persisting residual disease whereas rest of the 49(98%) patients were disease free. All the patients were kept on close monthly follow up. Out of 50 patients, 15(30%) patients were not regular on follow up till 3rd month follow up. Response evaluation revealed 34 (68%) patients presented complete response and 1 (2%) patient was detected with progressive disease. All the patients were kept on close monthly follow up. Many of the patients 15(30%)did not remain abide for the fore mentioned follow up. Only 34 (68%) patients regularly came for monthly follow ups till 6th month but 1(2%) patient died due to lung and paraaortic metastasis. When response was evaluated, it was found that all the 44 patients had loco-regional control with no distant metastasis.

Patients corresponding to Stage IIA Grade I showed 100% response, Stage IIA Grade II showed 66.7% response , Stage IIB Grade I patients showed 25% response, Stage IIB Grade II patients showed 91% response, Stage IIB Grade III patients showed 0% response, Stage IIIA Grade I patients showed 100% response, Stage IIIA Grade II patients showed 50% response, Stage IIIB Grade I patients showed 75% response, Stage IIIB Grade II patients showed 53.3% response and Stage IIIB Grade III patients showed 66.7%. It has been observed that earlier the stage of the disease better is the response. Same is evident in this study too. All the stages other than stage IIB shows better response. Here complete response has been considered in all the stages.

Significance: Perez *et al.,* prolongation of overall treatment time beyond 56 days resulted in an increased failure rate of 0.59% per day in stage IB and

IIA and 0.86% per day in stage IIB17 Although chemoradiation therapy as a sole treatment could provide a good result for carcinoma of cervix and also provide longer survival rates. In carcinoma of cervix as stage of the disease increases, tumor bulk and probability of lymph node metastasis increases. Various chemotherapeutic agents for the treatment of cervical cancer as induction chemotherapy or as a radiosensitizer have been studied. Improvements in overall survival and disease free survival were found in patients treated with chemoradiotherapy than with radiation therapy alone. All the patients completed full course of treatment as planned. Patients received Cisplatin at a dose of 40 mg/m^2 of body weight as 60 minutes intravenous infusion at least 4-6 hours before external beam radiotherapy on days 1, 8, 15, 22 and 29. Thus a total of 4-5 dose of Cisplatin were administered during full course of treatment. Every patient was treated with HDR intracavitary Brachytherapy of 700cGy/4# weekly on Saturday in between external beam radiotherapy to whole pelvis region in 23 fractions for a total of 4600cGy for 5 days a week from Monday to Friday along with Cisplatin.

Timing of HDR Intracavitary Brachytherapy: After 10-15# of EBRT when os is negotiable. Patients enrolled belonged to the age ranging from 30-70 years, with median age of 48 years. 3(6%) patients were between 31-40 years, 24(48%) between 41-50 years, 17(34%) between 51-60 years, 6(12%) between 61-70 years . Delaloye JF, Pampallona S, Coucke PA, *et al*.-Younger women with carcinoma of cervix are at increased risk of death. Risk increases when the disease is diagnosed at an advanced stage which implies that disease is more aggressive in younger women[10]. Age at marriage plays an important role in assessing the causative factor of cervical cancers. In adolescent girls maximum squamous metaplasia is seen and coitus during this time increases the risk of atypical transformation leading to cervical intraepithelial neoplasia CIN which in due course of time gets converted into carcinoma of cervix. This study reveals age at marriage of patients is mostly early. Median age at marriage is 18 years. Nahmias AJ, Naib ZM, Josey WE *et al*-Early age intercourse, STDs such as gonorrhea, Chlamydia, multiple sexual partners are risk factors for carcinoma of cervix[11]. Epidemiology of carcinoma of cervix reveals that it is commonest among the women of low socioeconomic status. (50%) patients belonged to lower group, lower middle group contained 21 (42%) patients and only 4 (8%) patients from upper middle group. Shankaranarayana R *et al*-In developing countries, lack of awareness, low socioeconomic status, illiteracy, poverty and lack of healthcare facilities maximum number of females remain devoid of screening programmes[12]. Peak incidence of carcinoma cervix is around 45-50 years of age. This fact is being supported in this study i.e., 22(44%) were in post menopausal age group while 28(56%) were in menstruating group. Chirstopher M. Tarney and Jasmine Han *et al*.-Post coital bleeding, inter menstrual bleeding (metrorrhagia), heavy menstrual flow (menorrhagia) are risk factors for carcinoma of cervix[13]. Among the etiological factors of carcinoma of cervix parity is also one of the most important determinants, as it is infrequent among nuns and spinsters and common in multiparous women. Most of the patients in this study 6(12%) patients had 1-2 pregnancies, 34(68%) patients had 3-5 pregnancies, 8(16%) patients had 6-8 pregnancies and 2(4%) patients had more than 8 pregnancies. Christopherson WM, Parker JE *et al*-multiple numbers of pregnancies, early marriage at child bearing age is risk factor for carcinoma of cervix[14].

Carcinoma of cervix usually spreads by direct extension and through draining lymphatics. Symptomatology of the disease is not different from common pathological condition of cervix. Affected population mostly belongs to low socioeconomic status and not aware of the potential risks hence they come in advanced stage. In this study, 6(12%) patients presented with stage IIA, 17(34%) patients had presented with stage IIB, 3(7%) patients had presented with stage IIIA and 24(48%) patients had presented with stage IIIB. Benedetti-Panici P, Maneschi F, Scambia G, *et al.*[15]- Pelvic lymph nodes were dissected in 225 patients with cervical carcinoma treated with radical hysterectomy; positive pelvic nodes were identified in 13 of 91 women (14.2%) with stage IB and IIA, 16 of 81 (19.8%) with stage IIB 11 of 40 (28%) with stage IIIB diseases.The most commonly involved groups were the parametrial, obturator, external iliac common iliac nodes. PALNs were involved in 3 of 91 patients (3.3%) with stage IB or IIA tumors 4 cm or less and in 5 of 38 patients (13.1%) with stage IIB or III disease. More than 90%of invasive cervical cancers are squamous cell carcinoma. In this study, 48 (96%) were diagnosed as squamous cell carcinoma, 1 (2%) was adenocarcinoma 1 (2%) was clear cell carcinoma but the grade of differentiation was 12 (24%) had well differentiated tumor cells, 33(66%) had moderately differentiated tumor cells and 4 (8%) had poorly differentiated tumor cells. Drescher CW, Hopkins MP, Roberts JA *et al*[16]-squamous cell carcinoma responds very well to chemoradiation when compared to adenocarcinoma and clear cell carcinoma. Duration of treatment is a major factor for patient compliance. In this study, 37 (74%) patients completed their treatment before 56 days and remaining 13 (26%) patients completed their treatment after 56 days due

to mechanical errors. In this study, patient compliance improved due to short duration of overall treatment.

CONCLUSION

Response after 1 month of completion of treatment: 1(2%) patient showed partial response and 49 (98%) patients showed complete response. Response after 3 months of completion of treatment: 34 (68%) patients showed complete response, 1 (2%) patient showed progressive disease (para aortic node and multiple lung metastasis) and 15 (30%) patients lost to follow up due to illiteracy, lack of awareness and poverty. Response after 6 months of completion of treatment: 34 (68%) patients showed complete response, 1 (2%) patient died due to distant para aortic and lung metastasis and 15 (30%) patients lost to follow up due to illiteracy, lack of awareness and poverty.

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