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Corresponding Author
Akhilesh Sahu,
Regional Cancer Center, Pt JNM Medical College Raipur CG India
akhilesh.sahu1007@gmail.com

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

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Early and late Toxicity in Locally Advanced Carcinoma of Cervix (Stage-IIB to IIIB) During Using High Dose Rate (HDR) Brachytherapy (4#x7Gy) in Between External Beam Radiotherapy (46Gy/23#)

[1]Umesh Dewangan, [2]Manjula Beck, [3]Rahul Swaroop Singh, [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
To observe the early and late toxicity in locally advanced carcinoma of cervix (STAGE-IIB' to IIIB) during using high dose rate (HDR) Brachytherapy in between External Beam Radiotherapy. 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. Acute toxicities were noted, 0.28% patient developed grade I skin toxicities , 10.85% patients developed grade I and II gastrointestinal toxicities (nausea ,vomiting , abdominal pain, diarrhoea), 9.43% patients developed grade I and II haematological toxicities(anemia , neutropenia) and 32% patients developed grade I and II genitourinary toxicities(burning micturition, increased frequency of urination) according to R.T.O.G. toxicity criteria. Late toxicities were noted, 11% patients developed grade I and IIhaematological toxicities (anemia and neutropenia), 11% patients developed grade I and II gastrointestinal toxicities (abdominal pain, anorhexia, nausea, vomiting, diarrhoea, pain during defecation and rectal bleeding) and 9% patients developed grade I and II genitourinary toxicities (dysuria and haematuria) according to R.T.O.G. toxicity criteria. In this study, early toxicities such as skin toxicities, diarrhoea, vomiting, burning micturition, pain during defecation, anaemia, neutropenia occurred which were well manageable.

INTRODUCTION

The predisposing factors for cervical carcinoma have been well defined. The incidence of cervical carcinoma is frequent in women who have intercourse at an early age i.e. early marriage, a history sexual promiscuity, a large number of pregnancies, multiple male sex partner and infestation with HPV virus[1-3]. In the adolescent girls maximum squamous metaplasia is seen and coitus during this period increase the risk of atypical transformation leading to cervical intra epithelial neoplasm (CIN)[4]. The husband who has more number of sexual partners provides an increased risk to his wife[5,6]. Other factor in male partner includes "venereal" pathogens like HPV, penile, condyloma, trichomonas Neisseria gonorrhoeae and Cytomegalo virus (CMV)[7].There is strong relationship between Human papilloma virus type (16, 18, 31 and 33), cervical intra epithelial neoplasia and squamous cell carcinoma[8,9]. The components of inhaled cigarette smoking are secreted in the cervical mucus, raising the possibility of oncogenesis[10]. Similarly women with immune compromised status due to HIV infection or immunotherapy are the greater risk[11]. There is an association between cervical cancer and poor genital hygiene. An increased risk is observed in women belonging to the low socioeconomic status. Carcinoma of cervix is less commonly seen in sexually inactive or nulliparous women like nuns, spinsters[12]. The uterine cervix is easily accessible for mass screening, as more and more patients are being detected in pre invasive or dysplastic states in properly assessed population. Cervical malignancy has declined in incidence since the introduction of PAP smear. Despite this dramatic reduction of current death rate is far higher than it should be and reflects that even today PAP smear are not done on approximately one third of eligible women especially in under developed and developing countries. Thus evaluation of cancer cervix patient for early detection, diagnosis, clinical staging by the help of general and pelvic examination, application of cytological and tissue sampling and radiological examination with haemogram, Renal function test, Liver function test and other relevant laboratory test especially in eligible patients will help in further management. Among the major factors that influence prognosis are stage, volume and grading of tumors, histology-types, lymphatic spread and vascular invasion. High chances of cure are seen with radical radiotherapy and concomitant chemotherapy to improve the loco regional control of the disease and improve the disease free survival. The present study is undertaken to observe the early and late toxicity in locally advanced carcinoma of cervix (STAGE-'IIB' to IIIB).

Cisplatin: It is used as a radio sensitizer in the present study. Synonym-CDDP (cis-diamminedichloroplatinum). Mechanism of action It is a pseudoalkylating agent. It covalently binds to DNA and disrupts DNA function, after cisplatin enter into the cell the chloride ligand are replaced by water molecules. This reaction results in the formation of positively charged platinum complex that react with the nucleophilic sites on the DNA. This platinum complex covalently binds to DNA base using intra strand and inter strand cross link creating cisplatin DNA adducts thus preventing DNA RNA protein synthesis.

Dose: 40 mg/m^2 weekly 4-6 hours before radiation. Hydration is required to minimise the nephrotoxicity. Pre-treatment hydration with 1-2 liters of fluid infused 8-12 hours prior to cisplatin dose. Side effects-Ototoxicity (31%), Tinnitus (9%), Myelosuppression (25-30%), Delayed nausea and vomiting (>90%), Electrolyte imbalance and Nephrotoxicity (28-36%).

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/m2 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 >10gm% 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 Saturday 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 assessment of 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 urethra 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}

EQD^2 = 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 inter space, inferiorly at the bottom of obturator foramen or 2-3cm below the lower extent of the disease and 1.5-2cm lateral to lateral margin of true pelvis[13,14].

Chemotherapy: Cisplatin[15] 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

All the patients were assessed for acute toxicities of concurrent chemoradiation, both during and after the treatment according to R.T.O.G. toxicity criteria. Treatment was well tolerated without delay and delay in some cases was due to the mechanical errors that occurred in the machines. As expected, Genitourinary toxicities were higher in patients followed by Gastrointestinal and Haematological toxicities all categorized under acute toxicities. The most frequently reported adverse events included burning micturition, abdominal pain, nausea and vomiting, diarrhoea and anaemia. Late toxicities such as cystitis and proctitis were also reported. Only 1 (2%) of the case study patients showed skin toxicities. After 1 month follow up, 4 (8%) patients showed Grade I and 1 (2%) patient showed Grade II Gastrointestinal toxicities; 8 (16%) patients showed Grade I and 2 (4%) patients showed Grade II haematological toxicities. After 3 months follow up, 2 (4%) patients showed Grade I and 1(2%) patient showed Grade II Gastrointestinal toxicities; 2 (4%) patients showed Grade I and 2 (4%) patients showed Grade II Genitourinary toxicities. After 6 months follow up, 9 (18%) patients showed Grade I and 1 (2%) patient showed haematological toxicity; 5 (10%) patients showed Bladder toxicity and 8 (16%) of the total patients showed rectal toxicities.

Toxicities Observed During 1st Week of Treatment: None of the patients showed skin toxicity. 9 (18%) patients showed gastrointestinal toxicities, 4 (8%) patients showed haematological toxicities and 18 (36%) patients showed genitourinary toxicities.

Toxicities Observed During 2nd Week of Treatment: None of the patients showed skin toxicity. 9 (18%)

Table 1: Toxicities Observed During 4th week of Treatment

Toxicities	Grade	No. of patients	Percentage
Skin	I	0	0
Gastrointestinal	I	2	4
Haematological	I	4	8
Genitourinary	I	17	34

Table 2: Toxicities Observed During 5th Week of Treatment

Toxicities	Grade	No. of patients	Percentage
Skin	I	0	0
Gastrointestinal	I	5	10
Haematological	I	7	14
Genitourinary	I	19	38

Table 3: Toxicities Observed During 6th Week of Treatment

Toxicities	Grade	No. of patients	Percentage
Skin	I	0	0
Gastrointestinal	I	2	4
Haematological	I	4	8
Genitourinary	I	14	28

Table 4: Toxicities Observed After 1 Month of Completion of Treatment

Toxicities	Grade	No. of patients	Percentage
Skin	I	1	2
Gastrointestinal	I	4	8
	II	1	2
Haematological	I	8	16
	II	2	4
Genitourinary	I	7	14

Table 5: Toxicities Observed After 3 Months of Completion of Treatment

Toxicities	Grade	No. of patients	Percentage
Skin	I	0	0
Gastrointestinal	I	2	4
	II	1	2
Haematological	I	1	2
Genitourinary	I	2	4
	II	2	4

Table 6: Toxicities Observed After 6 Months of Completion of Treatment

Toxicities	Grade	No. of patients	Percentage
Skin	I	0	0
Haematological	I	9	18
	II	1	2
Bladder	I	4	8
Rectal	I	8	16

patients showed gastrointestinal toxicities, 1 (2%) patient showed haematological toxicities and 16 (32%) patients showed genitourinary toxicities.

Toxicities Observed During 3rd Week of Treatment: None of the patients showed skin tonicity. 6 (12%) patients showed gastrointestinal toxicities, 3 (6%) patients showed haematological toxicities and 21 (42%) patients showed genitourinary toxicities. None of the patients showed skin toxicity. 5 (10%) patients showed gastrointestinal toxicities, 7 (14%) patients showed haematological toxicities and 19 (38%) patients showed genitourinary toxicities. None of the patients showed skin toxicity. 2 (4%) patient showed gastrointestinal toxicities, 4 (8%) patients showed haematological toxicities and 14 (28%) patients showed genitourinary toxicities. 1 (2%) patient showed skin toxicity, 5 (10%) patients showed gastrointestinal toxicities, 10 (20%) patients showed haematological toxicities and 7 (14%) patients showed genitourinary toxicities. None of the patients showed skin toxicities. 3 (6%) patients showed gastrointestinal toxicities, 1 (2%) patient showed haematological toxicities and 4 (8%) patients showed genitourinary toxicities. None of the patients showed skin toxicity. 10 (20%) patients showed haematological toxicities, 4 (8%) patients showed bladder toxicity and 8 (16%) patients showed rectal toxicity. In this study, toxicities were observed at different points during and after the treatment.

Toxicities Observed During 1st Week: None of the patients showed skin toxicity. 9 (18%) patients showed gastrointestinal toxicities, 4 (8%) patients showed haematological toxicities and 18 (36%) patients showed genitourinary toxicities.

Toxicities Observed During 2nd Week: None of the patients showed skin toxicity. 9 (18%) patients showed gastrointestinal toxicities, 1 (2%) patient showed haematological toxicities and 16 (32%) patients showed genitourinary toxicities.

Toxicities Observed During 3rd Week: None of the patients showed skin toxicity. 6 (12%) patients showed gastrointestinal toxicities, 3 (6%) patients showed haematological toxicities and 21 (42%) patients showed genitourinary toxicities.

Toxicities Observed During 4th Week: None of the patients showed skin toxicity. 2 (4%) patients showed

gastrointestinal toxicities, 4 (8%) patients showed haematological toxicities and 17 (34%) patients showed genitourinary toxicities.

Toxicities Observed During 5th Week: None of the patients showed skin toxicity. 5 (10%) patients showed gastrointestinal toxicities, 7 (14%) patients showed haematological toxicities and 19 (38%) patients showed genitourinary toxicities.

Toxicities Observed During 6th Week: None of the patients showed skin toxicity. 2 (4%) patient showed gastrointestinal toxicities, 4 (8%) patients showed haematological toxicities and 14 (28%) patients showed genitourinary toxicities. Toxicities observed after 1 month of completion of treatment: 1 (2%) patient showed skin toxicity, 5 (10%) patients showed gastrointestinal toxicities, 10 (20%) patients showed haematological toxicities and 7 (14%) patients showed genitourinary toxicities. Toxicities observed after 3 months of completion of treatment: None of the patients showed skin toxicities. 3 (6%) patients showed gastrointestinal toxicities, 1 (2%) patient showed haematological toxicities and 4 (8%) patients showed genitourinary toxicities. Toxicities observed after 6 months of completion of treatment: None of the patients showed skin toxicity. 10 (20%) patients showed haematological toxicities, 4 (8%) patients showed bladder toxicity and 8 (16%) patients showed rectal toxicity. In this study, early toxicities such as skin toxicities, diarrhoea, vomiting, burning micturition, pain during defecation, anaemia, neutropenia occurred which were well manageable. Rubinsak *et al.* Int J. Gynecol cancer 2019-170 patients were taken, 21.2% had acute toxicity, 17.3% had severe GI toxicity, 10% had severe genitourinary toxicity. Main duration of follow up was 37 months. Most patients (84.1%) received 3D CRT and 15.9% received IMRT. Factorassociated with AT were lower body mass index (24.9 vs 28.3, p = 0.043), white race (63.2% vs 44%, p = 0.035).

Efiel *et al.* In 1784 patients with stage IB carcinoma of cervix noted that the greatest risk of sequelae is in the first 3 years after therapy. The risk of rectal complications declined after the first 2 years of follow up to 0.6% per year, whereas the risk of major urinary tract complications for survivors continued at 0.3% per year, with a 20 year actuarial risk of major complications of 14.4%. Montana *et al*, Pourquier *et al.* and Perez *et al.* Greater incidence of complications with higher doses of irradiation. Doses <75-80 Gy delivered to limited volumes, grade 2 and Grade 3 complications in the urinary tract and recto sigmoid were approximately 5%. Doses >60 Gy were also correlated with a greater incidence of small bowel injury. The same analysis shows patient who experienced sequelae of therapy had slightly better survival rate than patients without any complications. This was related to improved tumor control with higher doses of irradiation.

CONCLUSION

Acute toxicities were noted, 0.28% patient developed grade I skin toxicities , 10.85% patients developed grade I and II gastrointestinal toxicities (nausea ,vomiting , abdominal pain, diarrhoea), 9.43% patients developed grade I and II haematological toxicities(anemia , neutropenia) and 32% patients developed grade I and II genitourinary toxicities(burning micturition, increased frequency of urination) according to R.T.O.G. toxicity criteria. Late toxicities were noted, 11% patients developed grade I and IIhaematological toxicities (anemia and neutropenia), 11% patients developed grade I and II gastrointestinal toxicities (abdominal pain, anorhexia, nausea, vomiting, diarrhoea, pain during defecation and rectal bleeding) and 9% patients developed grade I and II genitourinary toxicities (dysuria and hematuria) according to R.T.O.G. toxicity criteria.

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