ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

ORIGINAL RESEARCH

Evaluation of normal tissue toxicities and tolerability of chemo-radiotherapy in patients of Carcinoma Cervix

[1]Dr Jaspinder Kaur, [2]Dr Parneet Singh, [3]Dr Jaineet Patil

[1]Consultant, Radiation Oncology, CCA-SPS Hospitals, Ludhiana, Punjab, India
[2]Consultant, Radiation Oncology, Paras Hospitals, Panchkula, Haryana, India
[3]Professor, Radiation Oncology, CMC, Ludhiana, Punjab, India

Correspondence:
Dr Jaspinder Kaur
Consultant, Radiation Oncology, CCA-SPS Hospitals, Ludhiana, Punjab, India
Email: drjaspinderkaur13@gmail.com

Abstract
Carcinoma Uterine cervix is the second most common cancer among women and the primary cause of cancer related mortality in developing countries. India has the second highest incidence rate after breast cancer in the rest of the PBCR. Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria (1987) (RTOG/ARMSC),which reports acute toxicity related to radiation. The present study aimed to evaluate the normal tissuetoxicities of chemo-radiotherapy in patients of Carcinoma Cervix. This prospective and randomized study included 26 patients that were histologically proven cases of carcinoma uterine cervix. Patients were divided into two study groups : IMRT and 3DCRT groups, using a web generated randomized plan. Higher number of patients developed grade2 bladder toxicity in 3DCRT arm than IMRT. Onset of UGI toxicity was earlier in 3DCRT arm and one patient even had graded 2 toxicity from week 1 itself while grade 2 toxicity appeared only in week 4 in IMRT group. It was concluded that IMRT was well tolerated with considerable sparing of surrounding normal tissues and lesser tissue toxicity.

Introduction

Carcinoma Uterine cervix is the second most common cancer among women and theprimarycauseofcancerrelatedmortalityindevelopingcountries.Cervicalcanceristheleading cancer among women in terms of incidence rates in 2 out of the 12 Population Based Cancer Registries (PBCRs) in India, and has the second highest incidence rate after breast cancer in the rest of the PBCRs. [1]

Every year cervical cancer is diagnosed in about 500,000 women globally, of which 443,000 are in the Developing countries and is responsible for more than 280,000deaths annually. It is one of the most common cancer among women in the developingcountries.[2] Surgery and radiotherapy are main treatment options for the treatment of early disease(Stage I-IIA) but chemoradiation is generally considered as the standard treatment of choice in more advanced stages of disease(IIB-IVA). Chemoradiotherapy is the standard of care and all patients with advanced tumors should receive concurrent chemotherapy with radiotherapy unless medically contraindicated[3]. Compelling evidence of survival benefit (10-15%)

With concurrent cisplatin chemotherapy has been established by five randomized phase III trial so radical RT alone versus concurrent cisplatin based chemotherapy and RT.[4-7]

Cisplatin, is an inorganic complex, cell cycle non- specific compound and bears are semblance to the bifunctional alkylating agents. Cisplatin is one of them cytotoxic agents in advanced, metastatic recurrent squamous cell carcinoma of the uterine cervix.[8] NCI has

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

recommended that concurrent cisplatin based chemotherapy with radiation therapy should be incorporated in the management of women who require radiation therapy for treatment of cervical cancer especially in early stage disease.[9]

The majority of the effects of radiation therapy on normal tissues can be attributed to cell killing. The two main toxicity scoring systems for side effect are the Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria(1987) (RTOG/ARMSC),which reports acute toxicity related to radiation, and the National Cancer Institute/Common Toxicity Criteria (1988)(NCICTC), anelaboration of the World Health Organization (WHO) scale originally developed for chemotherapy toxicity, both of which have been adopted by major cooperative groups.Although several investigator shave highlighted the importance of recording combined therapy toxicity, it is only since 1998 combined toxicity system has been available.[10] Acute skin reactions associated with radiation include erythema, dry desquamation ,hyper pigmentation, and moist desquamation. In pelvic radiation these changes are commonly seen in the perineum, inter-gluteal folds and groin folds. All patients do not experience all acute skin reactions. However, there may be a combination of reactions occurring simultaneously in the radiation treatment field.[11,12] Acute injury to the small intestine after radiation is a common event and is dose dependent. Multi field and conformal radiationtherapy, as well as patient positioning techniques, reduce the volume of small bowel exposed to radiation and can decrease the potentialtoxicity.[12] Chenetal. Investigated treatment out comes and toxicity of intensity-modulated radiotherapy (IMRT) with concurrent chemotherapy for patients with locally advancedcervical cancer. 109 patients with stage IB2-IVA cervical carcinoma treated with IMRT and concurrent cisplatin-based chemotherapy were evaluated retrospectively. Three (2.7%) patients developed grade 3 or greater acute gastrointestinal (GI) toxicity and 26(23.9%) patients developed grade3 or greater hematological toxicity. Five (4.6%) patients developed grade3 orgreater chronic GI toxicity and 7(6.4%)patients developed grade 3 or greater genitor-urinary system toxicity.[13] so the present study aimed to evaluate the normal tissue toxicity and tolerability of chemo-radiotherapy in patients of Carcinoma Cervix

Material and methods

This prospective and randomized study was carried out in Department of Radiotherapy, Christian Medical College and Hospital,Ludhiana from 1stNovember2012to31stOctober2013 in all histologically proven cases of carcinoma uterine cervix. A total of 26 patients were enrolled in this study. Patients who had undergone any surgical intervention or received any chemotherapy prior to the treatment were excluded from the study.

Pre- Treatment Evaluation

A complete detailed history and physical examination was done and patients were staged according to FIGO staging (APPENDIXII).[14]Patientsunderwentbloodinvestigations like CBC, RFT and viral markers. Patients underwent metastatic workup: ChestX-ray, USG Abdomen & Pelvis and MRI pelvis. After an informed consent patients were taken up for a planning CT scan.

Patients were divided into two groups – IMRT group and 3D-CRT group by using web based randomization. Both groups also received weekly chemotherapy with injection Cisplatin 40mg/m^2 with adequate hydration and premedication. A computed tomography (CT)scan of each patient .The scan parameters consisted of largefield-of-viewpelvicprotocolwitha3-mm slice thickness for 3DCRT and IMRT. The CT scans were obtained from the T12vertebral body to 5-cm below the ischial tuberosities. Oral contrast and Intravenous contrast(CONTRAPAQUE) were administered total patient before CT scan. These images were then transferred to treatment planning system CMS Xio and after that tumor and normal

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

tissue delineation done. Three targets were delineated in all the patients based on ICRU50: Gross tumour volume(GTV),Clinical target volume(CTV), Planning target volume(PTV). For organ at risk deteremination- the rectum and bladder were contoured for each patient. Entire rectum and bladder were contoured. The rectum was defined from the level of the sacral promontory to the ischial tuberosities. The peritoneal cavity (excluding the rectum and bladder) from the level of aortic bifurcation (L4-5) was used to define the small bowel region (SBR). The individual loop of small bowel were not separately contoured. The3D-CRT and IMRT plans were generated using Treatment Planning SystemCMSXiO4.6. The prescribed total dose was 50.4Gy in 28 fractions. All patients were followed up weekly during treatment. Portal imaging was done weekly to ensure proper treatment delivery. 12outof total 26 patients were included in IMRT group and 14 out of total 26 patient in 3DCRTgroup based on web randomization table. Patients were treated with 6 MV Elekta linear accelerator equipped with a multi- leaf collimator. Treatment was delivered in the step and shoot mode. The accuracy of the setup was verified on the first day of treatment by matching the DRR(digitally reconstructed radiograph) with EPID (electronic portal imaging device) and then weekly with EPID. These films were checked before treatment. Patients were followed up monthly and response was assessed. All patients were followed up for a minimum period of six months. At each visit, the clinical history was updated and a complete physical examination including pelvic examination was done. Basic Laboratory tests were performed. Chest X-ray and USG abdomen /pelvis was repeated every three months. Pap smear was done at six months.

Statistical Analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%).

Chi-square test and Student T- test has been used to find the significance of study parameters on categorical scale between two or more groups. Parameters of dose distribution and incidence of skin, gastrointestinal, genitourinary and bone marrow toxicities were compared using paired and unpaired T tests, Chi Square test and other tests of statistical significance.

Results and observations

A total of 43 patients of Carcinoma cervix presented to Radiotherapy OPD in the 1 year study period. Out of these, only 26 patients could be included in the study. Rest 17patients were either post-op, had already received treatment outside, had metastatic disease at presentation or were not deemed fit for concurrent chemotherapy. Patients were divided into two study groups : IMRT and 3DCRT groups, using a web generated randomized plan. Out of the total 26 patients included in this study,12 patients were in IMRT group and 14 pts were in 3DCRT group. Patients were examined and clinical staging was done by FIGO, underwent metastatic work up and investigations according to protocol.

Toxicity analysis

Toxicity analysis was done for both the study groups and toxicity profiles were compared for acute tissue reactions for: skin, upper gastrointestinal, lower gastrointestinal, genitourinary and heamatological toxicity

Table 1: Comparison Of Various Organs Toxicity In Both Groups

GRADE	Bladder Toxicity Analysis				
	IMRT(%)		3DCRT(%)		
0	3	25.00	4	28.57	
1	5	41.67	3	21.43	

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

2	**4**	**33.33**	**7**	**50.00**	**PVALUE**
TOTAL	**12**	**100.00**	**14**	**100.00**	**.518**
GRADE	**Skin Toxicity Analysis**				
	IMRT(%)		**3DCRT(%)**		
0	**10**	**83.33**	**8**	**57.14**	
1	**1**	**8.33**	**1**	**7.14**	
2	**1**	**8.33**	**2**	**14.29**	
3	**0**	**0.00**	**3**	**21.43**	**PVALUE**
TOTAL	**12**	**100.00**	**14**	**100.00**	**.331**
GRADE	**Upper Gastro- intestinal Toxicity Analysis**				
	Imrt(%)		**3DCRT(%)**		
0	4	33.33	2	14.29	
1	5	41.67	9	64.29	
2	3	25.00	3	21.43	PVALUE
Total	12	100.00	14	100.00	.435
GRADE	**Lower Gastrointestinal Toxicity**				
	IMRT(%)		**3DCRT(%)**		**PVALUE**
0	1	8.33	1	7.14	
1	5	41.67	5	35.71	
2	6	50.00	8	57.14	.936
Total	12	100.00	14	100.00	

In our study, it was seen that 25% had no bladder toxicity in IMRT group while 28.57% in 3DCRT group had no bladder toxicity. Grade 1 toxicity was observed in 41.47% in IMRT group as compared to 21.43% in 3DCRT group but grade 2 toxicity was higher in 3DCRT arm (50%) as compared to 33.33% in IMRT arm(p=0.518).Though the results were statistically in significant In our study, we found that 83.33% had no acute skin toxicity in IMRT group while it was 57.14% in 3DCRT group. Grade 1 toxicity was seen in 8.33% pts in IMRT group while7.14%hadgrade 1toxicityin3DCRT group. In our study, grade 2 lower GI toxicity was observed in 8.33% pts in IMRT group whereas it was seen in 14.29% in 3DCRT group. No Grade 3 toxicity was seen in IMRT group while it was as higher 21.43%in3DCRTgroup. These results were statistically not significant (p=0.331).. In our study, we found that 33.33% had no upper GI toxicity in IMRT group while 14.29% had no toxicity in 3DCRT group. 41.67% had grade1 toxicity in IMRT arm whereas 64.29%had grade 1toxicity in 3DCRTgroup. Grade2 toxicity was found in 25% in IMRT group as compared to 21.43% in 3DCRT group. No grade 3 toxicity was seen in either group.It was observed that 8.33% had no toxicity in IMRT group while 7.14% had no toxicity in3DCRT group. Grade 1 toxicity was seen in 41.67% in IMRT group whereas it was seen35.71% pts in 3DCRT group. Grade 2 toxicity was observed in 50% pts in IMRT as compared to 57.14% in 3DCRT group. No grade 3 toxicity was seen in either group. In our study, it was seen that no patient developed any toxicity in wk 1in IMRT or 3DCRT group. In our study, it was seen that no patient developed any toxicity in wk1 in IMRT or 3DCRTgroup. In week 2,25% pt developed grade1 toxicity in IMRT group while 71% had grade 1 toxicity in 3DCRTgroup. During wk3, 25% had grade1 toxicity in IMRT no grade 2or3 toxicity was seen in wk2. In comparison, grade 2 and grade 3 toxicities appeared in3DCRT group in wk3 with 14.3% having grade 1, 21.4% having grade 2 and 7.1% having grade 3 toxicity. In wk4, 33.3% had grade 1 and 8.35 had grade 2 toxicity in IMRT group whereas 14.3% had grade1, 28.6% had grade2 and 21.4% had grade3 toxicity in 3DCRT group. In wk5 , 16.7% pts had grade 1 toxicity and 33.3% had grade 2 toxicity in IMRT group while in 3DCRT group,21.4%had grade1,35.7% had grade 2 and 14.3% had grade 3 toxicity. No grade 3 toxicity was seen in

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

IMRT group at all. In our study, we observed that grade 1 toxicity developed in wk1 in 25% pts in IMRT group as compared to 28.6% in 3DCRT group. In wk2, 33.3% had grade 1 toxicity while50% had grade 1 toxicity in 3DCRT group. In wk3, 66.7% developed grade 1 toxicity in IMRT group while in 3DCRT group,35.7%had grade1and14.3%had grade 2 toxicity. In wk4 , 50% had grade 1 toxicity in IMRT arm while in 3DCRT arm, 28.6%had grade 1toxicity and 7.1% had grade 2toxicity. Grade 2 toxicity appeared in IMRT group duringwk5 with 58.6% having grade 1 and 8.3% developing grade 2 toxicity in wk5. In 3DCRTarm, 28.6% had grade 1 and 42.9% had grade 2 toxicity in week 5. Results show that no grade 3 toxicity was seen in either of the study groups.

Discussion

This was a prospective randomized study was under taken in Department of Radiotherapy at Christian Medical College, Ludhiana to compare the two techniques IMRTand3DCRTinterms of acute toxicity. In our study, 26 patients with histologically proven Carcinoma Uterine cervix were randomized in to two study groups: IMRT and 3DCRT.The dose of EBRT delivered was 50.4 Gy in 28 fractions in both groups. All patients received concurrent chemotherapy with Inj.Cisplatin 40mg/m^2weekly as a radio-sensitizer. All patients received HDR intra-cavitary brachytherapy after completion of EBRT either to a dose of 7Gy / 3 fractions or9Gy/2fractions. All patients underwent baseline investigations before starting treatment. Patients in both the study groups underwent weekly haematological and bio-chemical investigations to assess toxicities. The patients were also assessed for skin, gastro-intestinalandgenito-urinarytoxicitiesweeklyduringtreatmentperiod.

Rose et al carried out a 3 arm randomized trial of RT in combination with 3 differentchemotherapyregimesi.e.cisplatinalone,cisplatin+5FU+hydroxyurea,orhydroxyurea alone. This analysis included 526 patients. Treatment with cisplatin alonewas less toxic than treatment with 3 drug regimen. They recommended cisplatin as a standard for a concomitant protocol in locally advanced cervical cancer. The highest combined frequency of grade 3 (moderate) and grade 4 (severe) adverse effects was associated with treatment with radiotherapy and the three-drug regimen; the frequency in the other two groups was similar. RT with Cisplatin arm had combined grade 3 and 4GItoxicity6.7%andGU toxicity2.8%.[6]

Erpolat OP et al. compared the incidence of HT between 3DCRT and IMRT planning in total of 127 patients with cervical cancer receiving concomitant pelvic radiotherapy (RT) and cisplatin. Grade2 or greater acute anemia, leucopenia, neutropenia ,thrombocytopenia was observed in 2%, 41.5%, 12% ,and 0% in IMRT group and in 27%,53%, 24.5%, and 4.5% in 3DCRT group, respectively. Grade 2 or greater chronic anemia, leukopenia, neutropenia, and thrombocytopenia was observed in 11%, 10%, 6%, and 0%in3DCRTgroupandin11%,9%,4.5%,and0%inIMRTgroup,respectively.LS-V30,40;IL-V10,20,30,40;LP-V10,20,40;P-V10,20,30,40,andTP-V10,20,30,40 were significantly reduced with IMRT planning compared to 3DCRTplanning.[15] Bhavaraju et al conducted a study to assesst the acute toxicity of concomitant treatment of chemo radiation with single agent cisplatin in patients with carcinoma of the cervix. Thirty-five patients with carcinoma of the cervix at all stages were treated for 4 - 6weekswith weekly infusion of Cisplatin (40mg/m2) and external beam radiotherapy. The major adverse toxic responses identified were hematologicaltoxicity(anemia62.9%,neutropenia51.4%,andthrombocytopenia17.1%),gastroin testinaltoxicity (nausea and vomiting 65.7% and diarrhea (54.4%). Grade I and II skin reactions were evident in two patients, oneineachgrade.[16]

J.HMaduro et al in their review summarized the acute and long-term toxicity of radiotherapy given with or without chemotherapy for cervical cancer. Acute toxicity (allgrades) of radiotherapy is reported in 61% of the patients in the recto-sigmoid, in 27%asurological, in 27% as skin and in 20% as gynaecological toxicity. Moderate and severe morbidity consists

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

of 5% to 7% gastrointestinal and 1% to 4% genitourinary toxicity. Adding chemotherapy to radiotherapy increases acute haematological toxicity to 5% to37%ofthe patientsandnauseaandvomitingin12%to14%.[125] Saibish kumar et al studied the effect of concurrent chemoradiation in locally advanced Carcinoma cervix. Overall 18 patients (31.6 %) had severe acute toxicities (>= grade 3according to RTOG criteria) in CRT protocol. Grade 3 skin reactions in perineum andgluteal region in 2 patients (3.5 %), grade 3 lower gastrointestinal (GI) toxicity in 5patients (8.8%), grade3 hematological toxicity in 3patients(5.3%),grade4hematological toxicity in 1patient (1.8 %) and grade 3 upper GI toxicity in 7 patients(12.3%).[17]

Conclusion

Presents study concluded that Skin toxicity appeared later in the IMRT group and none of the patients had grade 3toxicityatthecompletionofthe treatment. Higher number of patients developed grade2 bladder toxicity in 3DCRT arm than IMRT (50%vs33.3%) (p = 0.518) Grade1 toxicity in bladder started in wk2 in both the study groups but higher no. of patients had grade 2 toxicity in 3DCRT arm and none of the patients developed grade3 toxicity in both groups. UGI toxicity was higher in 3DCRT group vs IMRT group (gd1in64.29%vs41.67%) not statistically significant. Onset of UGI toxicity was earlier in 3DCRT arm and one patient even had gd 2 toxicity from week 1 itself while grade 2 toxicity appeared only in week 4 in IMRT group. No grade3toxicitywas seen in both the groups. Grade 2 lower GI toxicity was higher in 3DCRT arm vs IMRT arm. Equal number of patients had grade 1 lower GI toxicity in both the groups (notsignificant). In the lower GItoo,the onset of grade1toxicity was seen in week1itself in 3DCRTarm whereas it started in wk2 in IMRT arm. Also higher no. of patients had grade 2 toxicity at the endof treatment in3DCRT group. Therefore IMRT was well tolerated with excellent PTV coverage, considerable sparing of surrounding or maltissues, no treatment breaks,better compliance.

References

1. National Cancer Registry Programme (NCRP,ICMR). Time trends in cancer incidence ates:1982-2005.Bangalore:NCRP2009.
2. Nandakumar A, Ramnath T, Chaturvedi M. The magnitude of Carcinoma cervix inIndia.IndianJMedRes2009;130:219-21.
3. BarillotI,HoriotJC,PigneuxJ,SchraubS,PourquierH,DalyNetal.Carcinomaoftheintact uterine cervix treated with radiotherapy alone: a French cooperative study:updateandmultivariateanalysisofprognosticsfactors.IntJRadiatOncolBiolPhys1997;15:969–78.
4. WhitneyCW,SauseW,BundyBN,MalfetanoJH,HanniganEV,FowlerWCetal.Randomized comparison of Fluorouracil plus Cisplatin versus Hydroxyurea as anadjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negativepara-aortic lymph nodes: a Gynecologic Oncology Group and Southwest OncologyGroupstudy.Journalofclinicaloncology1999;17:1339–48.
5. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. New England Journal of Medicine1999;340:1137–43.
6. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G MM. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer.NewEnglandJournalofMedicine1999;340:1144-53.
7. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE SC. Cisplatin, radiationand adjuvant hysterectomy compared with radiation and adjuvant hysterectomy forbulkystageIbcervicalcarcinoma.NewEnglandJournalofMedicine.1999;340:1154–61.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

8. ThigpenT,ShingletonH,HomesleyH,LagasseL,Blessing. Cisplatin treatment of advanced or recurrent squamous cell carcinoma of cervix. Annals ofOncology1981;48:899.
9. National Cancer Institute Clinical Announcement: Concurrent chemoradiation for cervical cancer.WashingtonDC1999:1-5.
10. Kirwan J M, Symonds P, Green J A, Fresco L, Collingwood M, Tierney J et al. Asystematic review of acute and late toxicity of concomitant chemoradiation forcervicalcancer.RadiotherOncol2003;68:217-26.
11. PerezCA,KavanaghBD. Uterinecervix .In:Halper inEC ,PerezCA, BradyLW, editors. Perezand Brady's Principles and Practice of Radiation Oncology.5th ed.Philadelphia,PA:LippincottWilliamsandWilkins2008:p.1532-600.
12. Rosen S. Radiation toxicity. In: Small W, Woloschal G, editors. Radiation Toxicity :A practical medicalguide.Springer2006;X:160-87.
13. ChenMF, TsengCJ, TsengCC ,KuoYC, YuCY, ChenWC. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. IntJRadiatOncolBiolPhys 2007;67:1438–44.
14. PecorelliS,ZiglianiL,OdicinoF.RevisedFIGOstagingforcarcinomaofthecervix.IntJGynecol Obstet2009;105:107-8.
15. Erpolat OP, Alco G, Caglar HB, Igdem S, Saran A, Dagoglu N et al. Comparison of hematologic toxicity between 3DCRT and IMRTplanning in cervical cancer patients after concurrent chemoradiotherapy :anational multi-center study. EurJ GynaecolOncol 2014;35:62-6.
16. BhavarajuVKM,ReedNS. Acute toxicity of concomitant treatment of chemoradiation with single agent cisplatin in patients with carcinoma of the cervix. Thai Journal of Physiological Sciences 2004;17:90–7.
17. Saibishkumar EP, Patel FD, Sharma SC. Results of a phase II trial of concurrentchemoradiationin the treatment of locally advanced carcinoma of uterine cervix:anexperiencefromIndia.BullCancer2005;92:7-12.