Original Article

Indian Journal of Cancer Education and Research
Volume 5 Number 2, July - December 2017
DOI: http://dx.doi.org/10.21088/ijcer.2321.9815.5217.10

Comparison of Volumetric Modulated ARC Therapy (VMAT) to Conventional Intensity Modulated Radiation Therapy for Carcinoma Cervix

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Received on 01.07.2017, **Accepted on** 11.07 .2017

Abstract

Introduction: Cervical cancer is the second most common cancer in women worldwide and in India, the fifth most common cancer in humans. Two new techniques of radiation therapy in cervical cancer have been widely shown interest in treatment, i.e., IMRT and VMAT. VMAT has proven superiority over conventional radiotherapy with regard to dose conformity and organ sparing. *Aim*: In this present study, we propose to compare VMAT with IMRT in terms of target coverage (homogeneity and conformity indices) and dose to organs at risk (OARs) by means of dosimetric studies in patients of cervical cancer. *Materials and Methods:* The present study was conducted in Inlaks & Budhrani hospital, a state of art cancer institute from September 2013 to February 2015 to compare the technique of VMAT to IMRT. All the cervical cancer patients as per inclusion and exclusion criteria who opted for either VMAT or IMRT were included in our Study, Thus a total of 63 patients were recruited of which 33 opted for IMRT and 30 opted for VMAT. *Results:* 98% of the patients included in our study were in the age group of 40-69yrs. Age didn't show to affect the results of the acute or chronic toxicities during our study period. 76% of VMAT patients and 67% of IMRT patients were of Stage IIB. Stage IIB was the most common stage of presentation in our study. After it, 23% of VMAT patients and 27% of IMRT patients were of Stage IIIB. FIGO stage is an established prognostic factor for survival. Both the techniques have almost similar number of patients of same stage of disease. Squamous cell carcinoma was the most common histopathological diagnosis in 89% of the patients combined..

VMAT proved to be better than IMRT when it comes to mean dose to bladder and rectum, and it was statistically significant. VMAT failed to show superiority over IMRT in mean dose to bowel bag, right and left femoral head. VMAT and IMRT reported similar target coverage. Uniformity index, heterogeneity index and conformity index between the treatment techniques didn't show any difference. VMAT didn't prove to be superior over IMRT when it comes to acute and chronic toxicities of gastrointestinal, genitourinary or hematological systems. *Conclusion:* Within limitations of the present study we found no significant difference between IMRT and VMAT was observed except VMAT showed superiority to IMRT only in minimizing dose to bladder and rectum

Keywords: Cervical Cancer; VMAT; IMRT.

Introduction

Cervical cancer is the second most common cancer in women worldwide and in India, the fifth most common cancer in humans. It is the most common cancer causing death in the developing countries [1]. 2nd most common female cancer in women aged 15 to 44 years in India [2]. According to the latest estimates approximately 1,32,000 new cases of cervical cancer are diagnosed and 74,000 deaths are seen annually in India, responsible for nearly 1/3rd of the worldwide cervical cancer deaths [3].

Cervical cancer thus becomes a priority of women health. Cervical cancer has long lag period and the disease course goes through premalignant states to carcinoma over a period of 10-12 yrs. Thus it is feasible for screening and optimal intervention. The treatment for cervical cancer has improved tremendously over the last decade especially with advent of newer techniques of radiotherapy.

Radiation therapy plays an important role in both definitive and adjuvant (i.e. Post hysterectomy) treatment settings.

Definitive radiation therapy is the standard of care for early stage patients not suitable for surgical resection and consists of a combination of external beam radiotherapy and brachytherapy; including brachytherapy as an integral part of definitive radiation therapy for cervical cancer has shown to improve overall survival [4]. It is integrated with concurrent cisplatin chemotherapy for patients with node positive or locally advanced tumours > 4 cm. It also has been established as standard of care in locally advanced disease following the publication of 5 randomized trials, which led to NCI recommendation in February 1999 [5-9].

Two new techniques of radiation therapy in cervical cancer have been widely shown interest in treatment, i.e., IMRT and VMAT.

Intensity modulated radiation therapy (IMRT) techniques use multiple radiation beams of variable intensities leading to the construction of highly conformal dose distributions. This is accomplished by subdividing each radiation beam into smaller radiation beamlets and varying the individual intensities of these beamlets [10,11]. IMRT has potential to improve the therapeutic ratio of external beam radiotherapy. It can potentially mitigate adverse effects as well as allow dose escalation to optimize tumour control.

Volumetric modulated arc therapy was first introduced in 2007 and it was described as a novel radiation technique that allowed the simultaneous variation of three parameters during treatment delivery, i.e. gantry rotation speed, treatment aperture shape by the help of movement of multileaf collimator (MLC) leaves and dose rate [12]. Arc therapies thus have the ability to achieve highly conformal dose distribution. The major advantage of VMAT over IMRT is shorter treatment delivery time and reduction in monitor unit (MU) usage leading to lesser integral dose which is associated with increased risk of radiation induced malignancy. Volumetric modulated arc therapy (VMAT) is essentially an alternative form of IMRT.

Statement of Problem

VMAT has proven superiority over conventional radiotherapy with regard to dose conformity and organ sparing. However the distinction between VMAT and IMRT is not established in terms of dosimetric parameters and there is a lack of clinically significant data.

Rationale

In this present study, we propose to compare VMAT with IMRT in terms of target coverage (homogeneity and conformity indices) and dose to organs at risk (OARs) by means of dosimetric studies in patients of cervical cancer.

Hypothesis

This study is a comparison of volumetric modulated arc therapy (VMAT) using single or multiple arcs to Conventional Intensity modulated radiation therapy for carcinoma cervix in terms of target coverage (homogeneity and conformity indices) and to measure the dose to Organs at risk (OARs) such as bladder, rectum and bowel bag by means of dosimetric studies done on MONACO TPS and toxicities in both the plans. Purpose of the study is to measure whether there is actually a superiority of volumetric modulated arc therapy (VMAT) over Intensity modulated radiation therapy or not.

Aims and Objectives

Aim

To evaluate and compare the techniques of VMAT to IMRT in patients with carcinoma cervix.

Primary Objective

Compare VMAT to IMRT technique for dosimetry (target coverage, conformity index, heterogeneity index and dose to OARs) and toxicities (acute and chronic).

Secondary Objective

Analyze the MU and integral dose pattern in IMRT and VMAT plans.

Materials and Methods

This study was conducted in department of radiation oncology, Inlaks & Budhrani hospital from Sept 2013 to Feb 2015. Total of 63 patients were taken in the study of which 33 patients opted for IMRT and 30 patients for VMAT.

At first visit of the patient a careful history was taken and patient underwent thorough systemic & pelvic examination. Before starting the therapy, every patient was completely investigated for complete haemogram, urine examination, blood grouping and

Rh typing, blood urea and blood sugar levels, cervical biopsy, X ray- chest, abdominal and pelvic ultrasound.

Study Site: Radiation oncology department, Inlaks & Budhrani hospital in Pune.

Study Population: Patients coming to OPD during the study period.

Study Design: Prospective Observational Study.

Time Frame of Study: September 2013 to February 2015.

Sample Size: Statistical software available with "Primer of Biostatistics" was used for sample size calculation [13].

The following inputs were used to estimate sample size using the above software:

(a) Type 1 or alpha error = 0.05

(b) Type 2 or beta error = 0.20 (power of study 80%)

(c) Effect size = 1.5 units (mean difference in the two groups to be detected).

(d) Standard Deviation (SD) within the groups = 2.

With the above inputs the sample size calculated using the above software comes to 29 in each group.

Rounding off to a minimum of 30 subjects in each group was included in this study.

Inclusion Criteria

- Invasive Cancer Cervix at different stages of presentation. (FIGO IB – IV A)
- Age limit: More than 18 years to less than 70 years.
- All patients willing to give written consent to participate in the study
- Histopathological diagnosis of Squamous cell carcinoma and Adenocarcinoma
- Patient planned for radical radiotherapy with or without chemotherapy
- Reasonable Medical fitness to undergo radical radiotherapy according to ECOG Grade.

Exclusion Criteria

- Cancer cervix post operated cases
- Cancer cervix metastatic cases (IV– B) and IA stage.
- Patient with history of neo-adjuvant chemotherapy
- History of radiotherapy to the pelvis
- Immune-compromised patients

Methodology

- Informed written consent was taken from all patients enrolled in this study for CT Simulation.
- All patients were immobilized with Vac-lok cushions.
- CT Simulation and treatment planning were done according to standard departmental procedures.
- The acquired contrast enhanced CT scans included 5mm axial slices through D10 to mid thigh.

Treatment Planning

All treatment planning was done in Monaco® (Elekta Medical Systems, Crawley, UK) treatment planning system (TPS). The TPS automatically scales the Hounsfield units (HU) from the CT image set to relative electron density (RED) for in homogeneity correction. Radiobiological cost functions were used to achieve the dose-volume constraints prescribed for both target(s) and OARs. The dose-volume constraints prescribed were same for both IMRT and VMAT plans and beam energy of 6 MV was used in all plans. Seven to nine beams were used for the IMRT plans whereas double full arcs (One clockwise and one counter-clockwise) were used for the VMAT plans. The dose-volume constraints for target(s) and OARs were compared using Monte Carlo dose calculation, which was considered as gold standard in radiotherapy. Dose calculations were used for both VMAT and IMRT with a variance of 1% per plan with a dose calculation grid size of 3mm.

Treatment Delivery

- External beam radiotherapy was delivered on a Elekta Synergy Linear Accelerator.
- It was followed by Brachytherapy using Varian GammaMediX (24 channels).
- External Beam RT: 50.4 Gy/28 #/5.5 weeks. (1.8Gy/ Fraction)
- Brachytherapy (ICRT): 7 Gy to point A x 3 sessions.
- Concurrent weekly Cisplatin based chemotherapy depending upon medical fitness.

Stastical Analysis

Data entry was done using M.S. Excel and it was statistically analysed using Statistical package for social sciences (SPSS Version 20) for M.S.Windows.

Descriptive statistical analysis was carried out to explore the distribution of several categorical and quantitative variables. Categorical variables were

summarized with n (%), while quantitative variables were summarized by mean± S.D. All results were also presented in tabular form and are also shown graphically using bar diagram or pie diagram as appropriate.

Inferential Statistics: The difference in the two groups were tested for Statistical Significance using Parametric tests such as Unpaired T test for quantitative variables and Chi-Square test for categorical variables. P-value less than 0.05 were considered to be statistically significant.

Results

The present study conducted in Department of Radiation Oncology, Inlaks & Budhrani hospital, a total of 63 patients were enrolled as per inclusion and exclusion criteria's. Of which 30 opted for VMAT and 33 for IMRT. These patients were studied for both dosimetric results as well as their clinical outcomes. The results are as follows:

Out of a total 63 patients, 98% of the patients belong to 40-69 yr age group. Maximum i.e., 36.66% of the VMAT arm come under 50-59 yrs group followed by 33.34% in 40-49 yrs group and 26.66% of them were under 60-69yrs. whereas in IMRT arm 42.42% patients were under 60-69 yrs, while 30% of the patients were under 50-59 yrs and 27% of them belong to 40-49 yrs group.

Table 2 Shows stage wise distribution: Stage II-B was the most common; includes 76% of VMAT and 66% of IMRT patients while Stage III-B, was presented in 23% of VMAT and 27% of IMRT patients.

Table 3 describes Per Vaginal bleeding was the most common complaint, accounting for 83% of VMAT patients and 90% of IMRT patients. Hypertension happens to be the most common morbidity seen in the patients, accounting for 27%, i.e., 36% of VMAT patients and in 18% of IMRT patients.

Table 1: Distribution of Age groups in VMAT and IMRT

Age Group	Treatment Technique		Total cases (n=63)
	VMAT % (n=30)	IMRT % (n=33)	
≤39 yrs	1 (3.34%)	0	1 (1.58%)
40-49 yrs	10 (33.34%)	9 (27.27%)	19 (30.15%)
50-59 yrs	11 (36.66%)	10 (30.30%)	21(33.34%)
60-69 yrs	8 (26.66%)	14(42.42%)	22 (34.92%)

Table 2: Distribution of stage of disease in VMAT and IMRT

Stage group	Treatment Technique		Total Cases (n=63)
	VMAT % (n=30)	IMRT % (n=33)	
Stage II-B	23 (76.67%)	22 (66.67%)	45 (71.42%)
Stage III-A	0	1 (3.03%)	1(1.58%)
Stage III-B	7 (23.34%)	9 (27.27%)	16(25.39%)
Stage IV-A	0	1 (3.03%)	1(1.58%)

Table 3: Distribution of patients according to chief complaints in VMAT and IMRT

Chief Complaint	Treatment Technique		Total
	VMAT % (n=30)	IMRT % (n=33)	
P/V Bleeding	25/30 (83.34%)	30/33 (90.90%)	55/63 (87.30%)
Abdominal Pain	12/30 (40%)	16/33 (48.48%)	28/63 (44.44%)
P/V Discharge	15/30 (50%)	15/33 (45.45%)	30/63 (47.61%)

Table 4: Distribution of Associated Co morbidities in VMAT and IMRT

Past History (Co morbidity)	Treatment Technique		TOTAL (n=63)
	VMAT % (n=30)	IMRT % (n=33)	
HTN (Hypertension)	11(36.66%)	6 (18.18%)	17(26.98%)
DM (Diabetes Mellitus)	5(16.66%)	2 (6.06%)	7(11.12%)
Others (Asthma, IHD)	1(3.34%)	2(6.06%)	3(4.76%)

Table 5: Distribution of patients according to Histopathology in VMAT and IMRT

Histo-Pathology	Treatment Technique		Total cases (n=63)
	VMAT % (n=30)	IMRT % (n=33)	
Well Diff SCC	3 (10%)	8 (24.24%)	11 (17.46%)
Mod Diff SCC	17 (56.66%)	15 (45.45%)	32 (50.79%)
Poorly Diff SCC	6 (20%)	7 (21.21%)	13 (20.63%)
Adeno-Squamous ca	0	1(3.03%)	1 (1.58%)
Mod Diff Adeno Ca	4 (13.33%)	2 (6.06%)	6 (9.52%)

Table 6: Distribution of Mean Dose to OAR in VMAT and IMRT

OAR – Mean Dose	Treatment Technique		Mean Difference	95% Confidence interval	P value Unpaired T test
	VMAT (mean + SD) GY (n=30	IMRT (mean + SD) GY (n=33)			
Bladder	41.24±4.28	43.24 ± 3.04	2.00	-3.85 to -0.14	0.04
Rectum	43.76±3.95	45.53 ± 1.71	1.77	-3.27 to -0.26	0.02
Bowel Bag	26.48±3.34	26.19±2.65	-0.29	-1.80 to 1.22	0.70
(R) Femur	20.83±2.30	20.53±2.21	-0.30	-1.4 to 0.83	0.59
(L) Femur	21.56±3.13	21.31±2.88	-0.25	-1.76 to 1.26	0.73

Table 7: Distribution of PTV in VMAT and IMRT

PTV	Treatment Technique		Mean Difference	95% Confidence interval	P VALUE Unpaired T Test
	VMAT (Mean ± SD) GY (n=30	IMRT (Mean ± SD) GY (n=33)			
D_{MAX}	54.80±0.76	54.62±0.85	-0.18	-0.58 to 0.22	0.37
D_{MEAN}	51.27±0.77	51.18±0.55	-0.09	-0.42 to 0.24	0.62
D_{95}	49.39±0.73	49.18±0.60	-0.21	-0.54 to 0.12	0.22

Table 8: Distribution of other indices in VMAT and IMRT

INDICES	TREATMENT TECHNIQUE		Mean Difference	95% Confidence Interval	P VALUE Unpaired T Test
	VMAT (Mean ± SD) n=30	IMRT (Mean ± SD) (n=33)			
Uniformity Index	3.55±0.76	3.50±0.54	-0.05	-0.37 to 0.27	0.95
Heterogene-Ity Index	1.06±0.01	1.07±0.01	0.01	0.004 to 0.01	0.74
Conformity Index	1.36±0.09	1.35±0.08	-0.01	-0.05 to 0.03	0.59
Integral Dose	3.13±0.62	3.19±0.74	0.06	-0.28 to 0.40	0.72
Total MU/Fraction	942.31±236.73	799.32±152.25	-143	-242 to -43.9	0.006

Table 5 describes that Squamous cell carcinoma was the most common pathological type, of which moderately differentiating SCC accounts for 50% of the patients; 56% of VMAT patients and 45% of IMRT patients were of Mod diff SCC.

Table 6 describes the mean doses received by different Organs at Risk under VMAT and IMRT, with its significance. Mean Dose received by Bladder in VMAT was less than that of IMRT and it was statistically Significant. P value was 0.04. Mean Dose received by Rectum in VMAT was less than that of IMRT and P Value was 0.02 which was statistically significant.

While the Mean Doses received by Bowel, (R) Femur and (L) Femur in both VMAT and IMRT didn't show much variation. P values were also not found significant.

Table 7 Shows Mean dose values received by PTV in VMAT and IMRT and its significance.

Mean Dose received by PTV didn't show major changes between the two arms, the mean difference between VMAT and IMRT was very less. P value for D_{MAX}, D_{MEAN} and D_{95} were not statistically significant.

Table 8 describes the mean doses received by various indices in VMAT and IMRT and its significance.

VMAT and IMRT showed similar results when it comes to uniformity index, heterogeneity index, Conformity index and Integral Dose. (Integral dose was calculated as $\times 10^5$ Gycm^3). P values were calculated using Unpaired T test and P values for these Indices were not statistically significant.

Total MU/ Fraction by VMAT and IMRT show difference; the calculated P value using the test was 0.006 and it was statistically significant.

Table 9: Acute gastro-intestinal toxicities in VMAT and IMRT

Grade	Treatment Technique		Total (n=63)
	VMAT (n=30)	IMRT (n=33)	
GRADE- 0	6 (20%)	3(9.09%)	9 (14.28%)
GRADE – I	18(60%)	25(75.75%)	43 (68.25%)
GRADE- II	6(20%)	5(15.15%)	11 (17.46%)
GRADE- III	0	0	-
GRADE- IV	0	0	-

Chi square = 2.092 with 2 degrees of freedom; P Value= 0.351

Table 10: Acute genito-urinary toxicities in VMAT and IMRT

GRADE	Treatment Technique		Total (n=63)
	VMAT (n=30)	IMRT (n=33)	
GRADE- 0	13(43.34%)	14(42.42%)	27 (42.85%)
GRADE – I	15(50%)	15(45.45%)	30 (47.61%)
GRADE- II	2(6.67%)	4(12.12%)	6 (9.5%)
GRADE- III	0	0	-
GRADE- IV	0	0	-

Chi Square = 0.562 with 2 degrees of freedom; P Value = 0.755

Table 11: Acute haematological toxicities in VMAT and IMRT

GRADE	Treatment Technique		Total (n=63)
	VMAT (n=30)	IMRT (n=33)	
GRADE- 0	4(13.34%)	6(18.18%)	10 (15.87%)
GRADE – I	24(80%)	24(72.72%)	48 (76.19%)
GRADE- II	2(6.66%)	3(9.09%)	5 (7.9%)
GRADE- III	0	0	0
GRADE- IV	0	0	0

Chi Square: 0.458 with 2 degrees of freedom; P Value = 0.795

Out of the total patients, 80% of the patients under VMAT experienced grade I / grade II gastrointestinal toxicities, of which 60% of them had grade I toxicities and 20% of them had grade II during the treatment course. While in IMRT patients, 90% of them had grade I or grade II gastrointestinal toxicities, of which 75% of them had grade I toxicities and 15% of them had grade II toxicities. 20% of the VMAT patients didn't experience any acute GI toxicity and 9% of the IMRT patient didn't have any. Similar toxicities were seen in both the arms. P value by chi square test was 0.351, not statistically significant.

Out of 63 patients, 56% of VMAT patients experienced either grade I or grade II acute genitourinary toxicities during the course of radiation therapy, while in IMRT 57% of the patients experienced grade I / grade II side effects during the treatment. 43% of the patients in VMAT and 42% of patients in IMRT didn't experience any genitourinary side effects. Thus either of the treatment techniques did not prove to be different. P value was 0.755, not statistically significant.

82% of IMRT patients and 86% of VMAT patients experienced Grade I / Grade II toxicities during the treatment course. Of which in IMRT, 73% patients Grade I and 9% experienced grade II toxicities and in VMAT, 80% patients grade I and 6% experienced grade II acute toxicities. 18% of IMRT patients and 13% of VMAT patients didn't experience any acute haematological toxicity. Thus similar results were seen in both the arms. P Value was 0.795, not statistically significant.

Table 12: Chronic gastrointestinal toxicities associated with VMAT and IMRT

Grade	Treatment Technique		Total (n=30)
	VMAT (n=17)	IMRT (n=13)	
Grade 0	7 (41.1%)	8 (61.5%)	15 (50%)
Grade I	7 (41.1%)	4 (30.7%)	11 (36.67%)
Grade II	3 (17.6%)	1 (7%)	4 (13.33%)
Grade III	0	0	0
Grade IV	0	0	0

Chi Square = 1.376 with 2 degrees of freedom; P Value = 0.503

Table 13: Chronic genitourinary toxicities associated with VMAT and IMRT

Grade	Treatment Technique		Total (n=30)
	VMAT (n=17)	IMRT (n=13)	
Grade 0	14 (82.3%)	10 (77%)	24 (80%)
Grade I	1 (5.8%)	3 (23%)	4 (13.33%)
Grade II	2 (11.7%)	0	2 (6.67%)
Grade III	0	0	0
Grade IV	0	0	0

Chi Square= 3.190 with 2 degrees of freedom; P Value = 0.203

30 patients out of 63 patients were evaluated for their chronic toxicities as only these patients had a minimum follow up of 3 months; others were too early for follow up or defaulted for follow up. In these 30 patients, In VMAT arm 41% didn't experience any toxicity, 41% experienced grade I and 18% experienced grade II toxicities. In IMRT arm, 61% didn't experience any toxicity, 31% patients experienced grade I and 7% experienced grade II toxicities. Both the techniques showed similar results. P value was 0.503, not statistically significant.

In the 30 patients studied for chronic toxicities, 3 patients of IMRT and 3 patients in VMAT arm experienced grade I / grade II toxicities post treatment. In IMRT arm, grade I toxicity was seen in 3 patients i.e., 23% of the patients. In VMAT arm, grade I toxicity was noted in 1 patient and grade II toxicities were noted in 2 patients i.e., 6% and 12% of the patients. Both the techniques had similar results. P value was 0.203, not statistically significant.

Discussion

In this study conducted in Department of Radiation Oncology, Inlaks & Budhrani Hospital, during the study period, a total of 63 patients after meeting the inclusion and exclusion criteria's were selected, of which 33 opted for IMRT and 30 for VMAT.

Distribution of Patients according to the Age

Out of a total 63 patients, 98% of the patients belong to 40-69 yr age group. Maximum i.e., 36.66% of the VMAT arm come under 50-59 yrs group followed by 33.34% in 40-49 yrs group and 26.66% of them were under 60-69yrs. whereas in IMRT arm 42.42% patients were under 60-69 yrs, while 30% of the patients were under 50-59 yrs and 27% of them belong to 40-49 yrs group. In the present Study 68% of the patients belonged to 50-69yrs age groups. Age as a major prognostic criterion is not established.

In the study conducted by Akiko Loka et al the relative 5-year survival for cervical cancer has been reported to be lower in older women in Japan. Lower survival among older women was caused mainly by the presence of more advanced disease at diagnosis [14].

Brewster et al reported that there is no overall difference in survival in women diagnosed with cervical cancer in young age and old age [15].

As per studies, the peak age of cancer cervix is 55-65 yrs [3].

Distribution of Patients according to Stage of Disease

71.42% of the patients in both arms belonged to Stage II B and 25.39% belonged to Stage IIIB as a whole. 76.67% of the VMAT patients belonged to stage IIB patients and 23.24% of stage IIIB patients. While 66.67% of the IMRT patients belongs to stage IIB and 27.27% of them belongs to stage IIIB. Most of the Patients in our study in either of the groups belonged to stage IIB. There was no comparative study to show the outcome of stage of the disease in VMAT and IMRT. But as a whole stage of the disease is a prognostic criterion for the outcome of the treatment and survival.

A study conducted by Geetakumari et al to evaluate prognostic factors in cervical cancer, also states that most of the cancers belonged to Stage II B to Stage III B i.e., 70% [16].

Viladiu et al [17] identified clinical stage as the only independent prognostic factor. The survival rate of advanced stage patients is less. Longest survival was for patients with early stage disease [16,17].

Distribution of Pathological Staging in VMAT and IMRT

Squamous cell carcinoma was the most common histo-pathological finding accounting for 89%. In VMAT arm 86% belongs to Squamous cell carcinoma and rest of them to adenocarcinoma. And 91% of the Patients in IMRT arm have Squamous cell carcinoma, remaining 9% to adeno carcinoma. Of the Squamous cell variant, moderately differentiating Squamous cell

carcinoma accounts for the maximum in both the arms combined and around 17% patients have well differentiated type. As in both the arms maximum of the patients are of squamous cell type, the histopathology causing the treatment variation is very minimal.

In Studies done by Wang et al and Bray et al, it shows that the incidence of Squamous cell carcinoma of the cervix has been falling for some time, although that of adenocarcinoma of the cervix is now rising [18,19].

Vinh-hung et al stated that small cell carcinoma and adenocarcinoma were associated with poorer survival [20].

Geethakumari et al, a retrospective study has shown that the most common histopathological type is Squamous cell carcinoma [16].

Incidence of Squamous cell carcinoma might be fast declining in the west, but squamous cell type is still the most common type in countries like India [16] and adenocarcinoma is associated with poorer survival [21].

Distribution of doses to OAR

VMAT achieved lesser mean dose to IMRT when it comes to bladder. Mean dose to bladder in VMAT arm was 41.24Gy with a standard deviation of 4.28Gy. While in IMRT bladder mean dose was 43.24Gy with a standard deviation of 3.04Gy. P value was 0.04 which is considered significant.

Mean dose to Rectum in VMAT arm was 43.76Gy with standard deviation of 3.95Gy and mean dose in IMRT arm was 45.53Gy with a standard deviation of 1.71Gy. P value obtained was 0.02 that is considered significant.

Whereas there was not much change in the mean dose attained by bowel bag and femoral heads both right and left in VMAT and IMRT.

Mean dose received by bowel bag in VMAT arm was 26.48 Gy with a standard deviation of 3.34 Gy while in IMRT it was 26.19 Gy with standard deviation of 2.65 Gy. P value was 0.70, not significant.

Mean dose received by right femur in VMAT arm was 20.83Gy with standard deviation of 2.30 Gy and in IMRT arm it was 20.53 Gy with standard deviation of 2.21 Gy. P value was 0.59, not significant. Mean dose received by left femur in VMAT arm was 21.56 Gy with a standard deviation of 3.13 Gy, while in IMRT it was 21.31 Gy with a standard deviation of 2.88 Gy. P value was 0.73 considered not significant.

The dosimetric studies conducted by Cozzi et al showed that the dose received by OAR (bladder, rectum, bowel bag and right femur) was comparatively less in RapidArc than IMRT. Mean dose was reduced by about 6 Gy in RapidArc to IMRT, bladder mean reduced to 4-6Gy in RapidArc to IMRT and similar trends were seen in bowel bag and right femur [22].

Study conducted by Luis Oy et al showed it the other way in dosimetric study conducted on patients of cancer prostate, wherein IMRT proved to be better organ preserving than that of RapidArc. IMRT showed statistically significant dose reduction in rectum, bilateral femoral heads. Mean dose received by rectum in IMRT arm is ~ 2 Gy lesser than in RapidArc and ~ 4Gy lesser mean dose is achieved by bilateral femoral heads in IMRT arm compared to RapidArc [23]

Both of these were dosimetric studies done on the same subset of patients, when it comes to organ sparing, Similar to Cozzi et al [22], our study achieved 2Gy lesser dose to bladder in VMAT arm than IMRT and dose of 2.23 Gy lesser mean dose to rectum in VMAT arm than IMRT. But the doses to bowel bag, right and left femur were not statistically significant.

Distribution of PTV dose in VMAT and IMRT

Both the arms showed similar target coverage by comparing PTVMax, PTV Mean and PTV D95. The doses achieved by VMAT: PTVMax PTV Mean and PTV D95 with Standard deviation were 54.80± 0.76Gy, 51.27±0.77Gy and 49.39±0.73Gy.

While dose achieved by IMRT were 54.62±0.85, 51.18 ±0.88 and 49.18 ± 0.60Gy. P values for PTVMax, PTV Mean and PTV D95 were 0.37, 0.62 and 0.22. No statistical significance was observed in the PTV coverage.

Both Cozzi et al [22] and Lui Oy et al [23] showed PTV coverage to be similar in both RapidArc and IMRT in their studies. Statistical significance was not noted.

Distribution of other indices in VMAT and IMRT

Uniformity index, Heterogeneity index and Conformity index of both VMAT and IMRT were similar. Uniformity Index (D5-D95%) in VMAT was 3.55 with standard deviation of 0.76 and IMRT achieved 3.50 with standard deviation of 0.54. P value was 0.95, not significant.

Conformity index (CI 95%) of VMAT was 1.36 with standard deviation of 0.09 and IMRT achieved 1.35 with standard deviation of 0.08. P value was 0.59,

not statistically significant. Both the plans are highly conformal.

As regards to Heterogeneity index (HI), both the plans achieved similar results. VMAT achieved 1.06 with standard deviation of 0.01 and IMRT achieved 1.07 with standard deviation of 0.01.

Integral dose pattern/ Integral dose distribution (Dose integral - $\times 10^5$) of VMAT and IMRT didn't show statistical significance. Integral dose by VMAT was 3.13 $Gycm^3$ with standard deviation of 0.62 and IMRT was 3.19 $Gycm^3$ with standard deviation of 0.74. VMAT achieved marginally less dose than IMRT, P value was 0.72.

Total MU / fraction of VMAT arm were 942.31 with standard deviation of 236.73 and in IMRT arm it was 799.32 with standard deviation of 152.25. P value was 0.006, statistically significant. IMRT achieved less total MU/ fraction than VMAT.

In the study conducted by Cozzi et al [22] RapidArc achieved better conformity index, Integral dose (Dose integral) and MU/Gy than IMRT and these were statistically significant. Lui Oy et al [23] also showed that RapidArc achieved better homogeneity index and conformity index than IMRT.

As the plans of the same patient are utilized for both IMRT and Rapidarc, this statistical significant P value was seen, while our Study used two different sets of patients for planning and treatment. The patient's morphologies were different and this can affect the results.

Distribution of Acute Gastrointestinal toxicities by VMAT and IMRT

Out of the total patients, 80% of the patients under VMAT experienced grade I / grade II gastrointestinal toxicities, of which 60% of them had grade I toxicities and 20% of them had grade II during the treatment course. While in IMRT patients, 90% of them had grade I or grade II gastrointestinal toxicities, of which 75% of them had grade I toxicities and 15% of them had grade II toxicities. 20% of the VMAT patients didn't experience any acute GI toxicity and 9% of the IMRT patient didn't have any. Similar toxicities were seen in both the arms. P value by chi square test was 0.351, not statistically significant.

Zhang et al [24] conducted a study in which patients received extended field intensity modulated radiation therapy with concurrent cisplatin and observed the acute toxicities. In his study only 3 patients out of 45 patients developed grade III acute gastrointestinal toxicities, 28 patients developed grade II and 5 patients experienced grade I toxicities. These patients experienced more grade II toxicities than our study, and even grade III toxicities were seen, which were not seen in ours. Possible reason could be the extended field radiation therapy.

In the study conducted by Gerszten K et al, who received IMRT with concurrent cisplatin, none of the patients out of 22 experienced grade III or IV acute gastrointestinal and genitourinary toxicities. Similar to our study none of the patients had grade ≥ III toxicities [25].

Beriwal et al conducted a study clinical outcome with concurrent cisplatin and extended field intensity modulated radiation therapy (EF-IMRT) concluded that only 1 patient i.e., 2.8% experienced grade ≥ III, 25 patients i.e., 69% had grade II and 8 patients i.e., 22% had grade I acute gastrointestinal toxicities [26]. Compared to our study toxicities were higher with respect to grade II and III, as patients were treated with extended field radiation therapy. Grade I toxicities were higher in our study in both VMAT and IMRT arms.

Jensen et al conducted a study to evaluate toxicities in patients of cervical cancer treated with EF-IMRT and concurrent cisplatin. It is noted that 4 patients i.e., 19% had grade III acute gastrointestinal toxicities, 4 patients i.e., 19% grade II and 8 patients i.e., 38% had grade I diarrhoea out of 21 patients studied [27]. Results of this study were almost similar to our study with similar number of patients experiencing grade I and II toxicities. Grade III toxicities were seen in 4 patients which were not seen in ours.

Gandhi et al conducted a clinical outcome and toxicity study in advanced cervix carcinoma in patients treated with IMRT. Of 22 patients who received whole pelvic IMRT, grade ≥ II acute gastrointestinal toxicities were seen in 31.8% and grade ≥ III toxicities in 4.5% patients [29]. Similar number of patients in our study had grade II toxicities, none of our patients had grade III toxicities., while only 1 patient had grade ≥ III toxicities in this study.

Grade I toxicities were higher in our patients than these studies quoted above, as patients in other studies had greater grade II/III toxicities.

Distribution of Acute genitourinary toxicities by VMAT and IMRT

Out of 63 patients, 56% of VMAT patients experienced either grade I or grade II acute genitourinary toxicities during the course of radiation therapy, while in IMRT 57% of the patients experienced grade I / grade II side effects during the treatment. 43% of the patients in VMAT and 42% of

patients in IMRT didn't experience any genitourinary side effects. Thus either of the treatment techniques did not prove to be different. P value was 0.755, not statistically significant.

Zhang et al reported that only 1 patient experienced grade III toxicity, 24 patients grade II and 1 patient grade I acute genitourinary toxicities out of 45 patients [24]. Compared to this study our patients experienced lesser grade II and none had grade III toxicities. Most of the toxicities experienced by our patients in both the arms were of grade I. Possible reason could be extended field radiation therapy.

As already mentioned Gerszten K et al reported that none of their patients experience grade III or more acute toxicities [25]. Similar results were seen in our study.

Beriwal et al reported that only 1 patient i.e., 3% experienced grade III toxicities, 7 patients i.e., 19% had grade II and 16 patients i.e., 44% had grade I acute genitourinary toxicities [26]. Our study results closely correlate with this study.

Jensen et al stated that none of the patients had grade III, 2 patients i.e., 9.5% had grade II and 4 patients i.e., 19% grade I acute genitourinary toxicities [27]. Similar to this study none of ours had grade III and similar grade II toxicities. Our study had greater grade I toxicities to this study. Overall toxicities were lesser in this study compared to ours.

Distribution of Acute haematological toxicities by VMAT and IMRT

82% of IMRT patients and 86% of VMAT patients experienced Grade I / Grade II toxicities during the treatment course. Of which in IMRT, 73% patients Grade I and 9% experienced grade II toxicities and in VMAT, 80% patients grade I and 6% experienced grade II acute toxicities. 18% of IMRT patients and 13% of VMAT patients didn't experience any acute haematological toxicity. Thus similar results were seen in both the arms. P Value was 0.795, not statistically significant.

Study by Zhang et al reported that 60% of their patients experienced either Grade I/ II or III toxicities following extended field radiation therapy. Of which 20% had grade III, 31% grade II and 9% had grade I toxicities [24]. Compared to this study, our patients had greater grade I and overall acute haematological toxicities possible reason could be as our patients had border line complete blood count values at the start of the treatment, which is a common scenario in Indian population.

Beriwal et al stated that 10 patients i.e., 28% developed grade III, 13 patients i.e., 36% had grade II and 7 patients i.e., 19% had grade I acute haematological toxicities out of 36 patients studied [26]. Compared to this study, 83% patients had grade I/II/III toxicities which is similar to our study, but we had greater grade I toxicities while these patients had greater grade II/III toxicities possible reason could be extended field treatment in their study.

Hui et al conducted a haematological toxicities study in patients who had undergone IMRT concurrent with cisplatin. It was seen that none of them had grade III neutropenia, grade II neutropenia was seen in 40% patients i.e., 8 patients and grade I neutropenia in 20% i.e., 4 patients out of 20 patients studied [29]. Similar to our study, none of them had grade III toxicities, we had greater grade I and lesser grade II toxicities in comparison to this study, as our patients have borderline blood counts as mentioned previously.

Jensen et al quoted that 12 patients i.e., 57% had grade ≥ III toxicities, 33% i.e., 7 patients had grade II and 9.5% i.e., 2 patients had grade I leukopenia out of 21 patients studied [27]. In this study more number of patients had grade II/III toxicities than our study. We had a high grade I toxicities in both the arms possibly because of low blood counts.

Distribution of Chronic gastrointestinal toxicities by VMAT and IMRT:

30 patients out of 63 patients were evaluated for their chronic toxicities as only these patients had a minimum follow up of 3 months; others were too early for follow up or defaulted for follow up. In these 30 patients, In VMAT arm 41% didn't experience any toxicity, 41% experienced grade I and 18% experienced grade II toxicities. In IMRT arm, 61% didn't experience any toxicity, 31% patients experienced grade I and 7% experienced grade II toxicities. Both the techniques showed similar results. P value was 0.503, not statistically significant.

Zhang et al reported that only 3 patients in his study had late grade III toxicities i.e., 6% and only 2 patients i.e., 5% had grade II toxicities [24]. Our study had similar grade II toxicities i.e., 1-3 patients. Grade III toxicities were not experienced by our patients, while only 3 patients had these in this study, possible reason could be extended fields used for their treatment.

Wang X et al also reported that only 6 patients out of 80 reported either had grade I or grade II late toxicities [30]. Similar results were seen in the IMRT arm of our study and none of our patients had grade III toxicities in both the arms.

In Beriwal et al study, 2 patients i.e., 6% had late grade III toxicities. None of their patients had grade IV toxicities [26]. While in our study none had grade III toxicities.

As per Jensen et al study none had grade III late gastrointestinal toxicities, 3 patients i.e., 14.3% had grade II and 1 patient i.e., 4.8% had grade I late gastrointestinal toxicities [27]. Over all grade I/II toxicities were similar in our study and none had grade III toxicities.

Gandhi et al reported that only 13.6% of their patients had grade I/II/III late gastrointestinal toxicities [28]. Over all toxicities were higher in our study compared to this but most of our toxicities were grade I. More of VMAT patients had grade I/II toxicities in comparison to IMRT, as most of our patients had mild to moderate diarrhoea/cramping complaints post treatment.

Distribution of Chronic genitourinary toxicities by VMAT and IMRT

In the 30 patients studied for chronic toxicities, 3 patients of IMRT and 3 patients in VMAT arm experienced grade I / grade II toxicities post treatment. In IMRT arm, grade I toxicity was seen in 3 patients i.e., 23% of the patients. In VMAT arm, grade I toxicity was noted in 1 patient and grade II toxicities were noted in 2 patients i.e., 6% and 12% of the patients. Both the techniques had similar results. P value was 0.203, not statistically significant.

Zhang et al [24] reported only 1 patient out of 45 developed grade II toxicity. Genitourinary fistula was reported. Similar results were seen in our study, none of our patients had grade III and only 3 patients in each arm had grade I/II toxicities.

Wang X et al reported that only 4 patients out of 80 reported either had grade I or grade II late genitourinary toxicities [30]. Similar results were seen with respect to toxicities in our study as well.

Beriwal et al concluded that none of their patients had grade ≥ III late genitourinary toxicities [26]. Compared to this study, none of our patients had the above toxicities.

Jensen et al reported that only 2 patients i.e., 9.5% had grade III, 1 patient i.e., 5% grade II and 1 patient had grade I late genitourinary toxicities [27]. Similar number of our patients had grade I/II toxicities compared to this study, while none of ours had grade III toxicities.

Patients in our study had intermittent macroscopic or microscopic hematuria by urine routine examination.

No clinical outcome study results were found in patients of carcinoma cervix who have undergone VMAT plan.

Conclusion

Many comparative dosimetric studies were done between IMRT and volumetric modulated arc therapy/ RapidArc. In Cervical cancer, comparative dosimetric studies showed RapidArc to be better than IMRT but these were not followed by clinical studies, Our aim was to find the superiority of VMAT to IMRT in two different subset of patients.

VMAT showed superiority to IMRT only in minimizing dose to bladder and rectum, P values proved statistical significance ($P < 0.05$) while other organs received similar mean doses under both the techniques. Target coverage including uniformity, heterogeneity, conformity and integral dose pattern also are similar and data and P values prove that VMAT was not superior to IMRT in these parameters. While contrastingly IMRT received lesser Total MU/ fraction than VMAT, obvious reason could be two different subset of patients. Acute and chronic toxicity profile between VMAT and IMRT were similar. VMAT didn't show statistically significant results to IMRT.

Thus VMAT, the latest treatment modality being rapidly practised in recent times didn't show major advantage to IMRT in treating patients.

Limitations

1. Treatment offered in both VMAT and IMRT patients varied in body surface area.
2. Minimum follow up time was 3 months.
3. Double Arc usage in VMAT caused increased Total MU/ Fraction.

Recommendations

1. Target coverage and dose to Organs at risk improved with IMRT and VMAT but larger randomized studies are required.
2. Longer follow up period must be considered, to see the chronic effect of the treatments.
3. Clinical outcomes and toxicities need to be kept in mind before advocating VMAT superiority.
4. More long term studies need to be designed to show superiority of IMRT and VMAT in cervical cancer.
5. Effect of Integral dose because of IMRT and VMAT leading to secondary malignancies should be extensively studied.

References

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007 Sep 14;370(9590):890-907.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5): E359-86.
3. Kaarthigeyan K. Cervical cancer in India and HPV vaccination. Indian J Med Pediatr Oncol: official journal of Indian Society of Medical & Paediatric Oncology. 2012 Jan;33(1):7-12.
4. Montana GS, Hanlon AL, Brickner TJ, Owen JB, Hanks GE, Ling CC et al. Carcinoma of the cervix: patterns of care studies: review of 1978, 1983, and 1988–1989 surveys. Int J Radiat Oncol Biol Phys. 1995 Jul 30;32(5):1481-6.
5. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999 Apr 15;340(15): 1154-61.
6. 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. N Engl J Med. 1999 Apr 15;340(15):1137-43.
7. Peters WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, Berek JS et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol. 2000 Apr 1;18(8):1606-13.
8. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999 Apr 15;340(15):1144-53.
9. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler Jr WC et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol. 1999 May 1;17(5):1339-48.
10. Khan FM. The Physics of Radiation Therapy. 4th ed. Baltimore: Lippincott Williams & Wilkins; 2010.
11. Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol. 2011;84(1007):967-96.
12. Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. Med Phys. 2008 Jan 1;35(1):310-7.
13. Glantz SA. Primer of Biostatistics. 7 th ed. New York: McGraw Hill Medical; 2012.p.1-306.
14. Ioka A, Tsukuma H, Ajiki W, Oshima A. Influence of age on cervical cancer survival in Japan. Jpn J Clin Oncol. 2005 Aug 1;35(8):464-9.
15. Brewster WR, DiSaia PJ, Monk BJ, Ziogas A, Yamada SD, Anton-Culver H. Young age as a prognostic factor in cervical cancer: results of a population-based study. Am J Obstet Gynecol. 1999 Jun 30;180(6):1464-7.
16. Kumari KG, Sudhakar G, Ramesh M, Kalpana VL, Paddaiah G. Prognostic Factors in Cervical Cancer: A Hospital-based Retrospective Study from Visakhapatnam City, Andhra Pradesh. J Life Sci. 2010;2(2):99-105.
17. Viladiu P, Bosch FX, Castellsague X, Munoz N, Escriba JM, Hamsikova E et al. Human papillomavirus DNA and antibodies to human papillomaviruses 16 E2, L2, and E7 peptides as predictors of survival in patients with squamous cell cervical cancer. J Clin Oncol. 1997 Feb 1;15(2):610-9.
18. Bray F, Carstensen B, Moller H, Zappa M, Zakelj MP, Lawrence G et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev. 2005 Sep 1;14(9):2191-9.
19. Wang SS, Sherman ME, Hildesheim A, Lacey JV, Devesa S. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976–2000. Cancer. 2004 Mar 1;100(5):1035-44.
20. Vinh-Hung V, Bourgain C, Vlastos G, Cserni G, De Ridder M, Storme G et al. Prognostic value of histopathology and trends in cervical cancer: a SEER population study. BMC cancer. 2007 Aug 23;7(1):164.
21. Eifel PJ, Burke TW, Morris M, Smith TL. Adenocarcinoma as an independent risk factor for disease recurrence in patients with stage IB cervical carcinoma. Gynecol Oncol. 1995 Oct;59(1):38-44.
22. Cozzi L, Dinshaw KA, Shrivastava SK, Mahantshetty U, Engineer R, Deshpande DD et al. A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. Radiother Oncol. 2008 Nov 30;89(2): 180-91.
23. Lui OY, Li WK, Lock KM, Chow CF, Lo HY, Lam YF et al. Dosimetric comparison between RapidArc and conventional intensity modulated radiotherapy for prostate cancer. Biomed Imaging Interv J. 2013 Sep 19;9(3): e17.
24. Zhang G, He F, Fu C, Zhang Y, Yang Q, Wang J et al. Definitive extended field intensity-modulated radiotherapy and concurrent cisplatin chemosensitization in the treatment of IB2-IIIB cervical cancer. J Gynecol Oncol. 2014 Jan 1;25(1): 14-21.
25. Gerszten K, Colonello K, Heron DE, Lalonde RJ, Fitian ID, Comerci JT et al. Feasibility of concurrent cisplatin and extended field radiation therapy (EFRT) using intensity-modulated radiotherapy (IMRT) for

carcinoma of the cervix. Gynecol Oncol. 2006 Aug 31;102(2):182-8.

26. Beriwal S, Gan GN, Heron DE, Selvaraj RN, Kim H, Lalonde R et al. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys. 2007 May 1;68(1):166-71.
27. Jensen LG, Hasselle MD, Rose BS, Nath SK, Hasan Y, Scanderbeg DJ et al. Outcomes for patients with cervical cancer treated with extended-field intensity-modulated radiation therapy and concurrent cisplatin. Int J Gynecol Cancer. 2013 Jan 1;23(1):119-25.
28. Gandhi AK, Sharma DN, Rath GK, Julka PK, Subramani V, Sharma S et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. Int J Radiat Oncol Biol Phy. 2013 Nov 1;87(3):542-8.
29. Hui B, Zhang Y, Shi F, Wang J, Wang T, Wang J et al. Association between bone marrow dosimetric parameters and acute hematologic toxicity in cervical cancer patients undergoing concurrent chemoradiotherapy: comparison of three-dimensional conformal radiotherapy and intensity-modulated radiation therapy. Int J Gynecol Cancer. 2014 Nov;24(9):1648.
30. Wang X, Zhao Y, Shen Y, Shu P, Li Z, Bai S et al. Long-term follow-up results of simultaneous integrated or late course accelerated boost with external beam radiotherapy to vaginal cuff for high risk cervical cancer patients after radical hysterectomy. BMC cancer. 2015 Apr 11;15(1):257.