Study of toxicities of Intensity Modulated Radiotherapy (IMRT) in post-operative patients of carcinoma cervix and endometrium

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Research

Keywords: Carcinoma cervix, carcinoma endometrium, post-operative patients, Intensity Modulated Radiotherapy (IMRT), toxicity

Posted Date: April 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-403138/v1

Abstract

Background

Various studies have shown a clinical benefit of pelvic IMRT but included a significant number of patients with intact cervix and uterus. Therefore we proposed a prospective study to evaluate the toxicity, feasibility, and tolerance of IMRT in post-operative patients with carcinoma cervix and endometrium.

Methods and Material:

This was a prospective, single-arm study, conducted from August 2015 to October 2018 including a total of 30 patients (23 cervical and 7 endometrial cancer) who had undergone a total hysterectomy and required adjuvant pelvic irradiation. These patients were treated with pelvic IMRT using a dose of 45-50.4 Gray (Gy) at 1.8-2 Gy per fraction given as 5 fractions per week with/without concurrent chemotherapy (using injection cisplatin 35–40 mg/m^2 per week) as per indications. Acute toxicities were recorded at weekly intervals during the treatment followed by the assessment of late toxicities at the time of each follow-up visits using RTOG radiation morbidity criteria.

Results

Maximum on treatment skin, lower gastrointestinal (LGI), genitourinary (GU), and hematological toxicities were grade 1, 2, 2, and 2, occurring in 38%, 31%, 14%, and 3.4% of the cases, respectively. No late skin and GU toxicities were observed. Maximum late LGI toxicity was grade 1, occurring in 6.67% of the cases. Five (out of 30) patients developed treatment failures (2 distant and 3 local). At a median follow-up of 35 months, the 3 year progression free survival (PFS) and overall survival (OS) were 83.3% (all stages included).

Conclusion

Considering acute and late adverse events in the form of skin, LGI, GU, and hematological toxicities, IMRT is well tolerated and has an acceptable toxicity profile even in the setting of an aggressive tri-modality approach.

Introduction:

Malignancies of the female pelvis demonstrate a great variation between the developing and the developed world. The prevalence of carcinoma cervix is lesser in developed countries but it continues to be one of the most common malignancies of women in developing countries while endometrial cancer is more common in developed countries [1–3]. Although these malignancies are highly responsive to treatment allowing better disease control but at the cost of functional morbidities that may impact the

patient's quality of life [4]. Conventional whole pelvic radiotherapy is associated with significant morbidity, especially hematological and gastrointestinal, which increases with concurrent chemotherapy [5, 6]. Intensity-modulated radiotherapy (IMRT) is a form of highly conformal radiotherapy in which a computer-aided optimization process is used to determine customized non-uniform fluence of multiple beamlets and the dose distribution is modified to attain certain specified dosimetric constraints and clinical objectives. The ability to optimally manipulate the intensities of individual rays within each beam permits greatly increased control over the radiation fluence, enabling the custom design of optimum dose distributions which potentially may lead to improved tumor control and reduced normal tissue toxicity. Its effectiveness has been validated in several anatomical sites such as head & neck and prostate cancer treatment [7]. Various clinical and dosimetric studies have suggested the clinical benefit of IMRT [8, 9]. However, a lot of this work has included a mixed population of patients with a significant number of patients with intact cervix and uterus. So we cannot extrapolate the same data for patients in post-operative settings. Therefore we proposed a prospective study to evaluate the toxicity, feasibility, and tolerance of IMRT in postoperative patients with carcinoma cervix and endometrium.

Subjects And Methods:

Study design: This was a prospective, interventional single arm study conducted at a tertiary care centre of one of the largest state of India, conducted from August 2015 to October 2018.

Patients:

Cervix and endometrial cancer patients who underwent total hysterectomy with or without bilateral salpingo-oophorectomy and lymphadenectomy, having indications of adjuvant pelvic irradiation and FIGO stage I-IIA (for cancer cervix), I-III (for endometrial cancer) were included in the study. While those having concurrent second malignancy, previous pelvic irradiation, prior chemotherapy, and any histopathology other than squamous or adenocarcinoma, were excluded. The study protocol was reviewed and approved by the institution and informed consent was obtained from all patients. All patients received pelvic IMRT with or without concurrent chemotherapy followed by vaginal brachytherapy.

Radiotherapy (RT) planning:

All patients were immobilized in supine position using knee rest followed by contrast-enhanced computerized tomography (CT) simulation with 3mm image acquisition from first lumbar vertebrae to mid-thigh. Bladder protocol was followed which entails intake of 500 ml water 30-45 min before simulation and the patient being asked to hold urine until the simulation is complete. A marker was placed at the vaginal vault/introitus/perineum to facilitate delineation. CT data was transferred using a digital imaging and communications in medicine (DICOM) protocol to the Treatment Planning System.

Contouring:

Two Clinical Target Volumes (CTVs) were defined. Primary CTV included vaginal cuff and 3 cm of vagina inferior to the cuff and parametrial/paravaginal tissue from the vaginal cuff to the medial edge of the internal obturator muscle/ischial ramus on each side. Nodal CTV included common iliac, external iliac, internal iliac, and presacral lymph nodes. While delineating nodal CTV, the contours approximated the blood vessels, while covering the complete lymphovascular space, and included any lymphocele (if present). The pre-sacral contour encompassed at least a 1.5-2 cm wide area anterior to the sacrum. The primary and nodal CTVs were subjected to Boolean addition to give rise to the total CTV which was given a 1 cm isotropic margin to give rise to the planning target volume (PTV) [10].

Organs at risk (OAR) were drawn as per the Radiation Therapy Oncology Group (RTOG) guidelines for organ delineation in pelvic radiotherapy which included urinary bladder (inferiorly from its base, and superiorly to the dome, rectum (beginning from the anal verge, moving superiorly till it loses concave shape in the axial plane and connects anteriorly with the sigmoid), femoral heads (including greater and lesser trochanters, up to proximal 1-2 cm of shaft of the femur), bowels/abdominal cavity (from the recto-sigmoid junction till 3 cm above the superior-most section of the PTV contour) and pelvic bone (bilateral hip bones including sacrum) (Fig. 1).

Dosage and Planning:

A dose of 45-50.4 Gray (Gy) at 1.8-2 Gy per fraction was given as 5 fractions per week (Monday to Friday) with an overall treatment time of 5-5.5 weeks. The plan objective was that at least 95% volume of PTV should be covered by a 95% isodose line. The desired dose constraints were as follows: bowel, $V_{40} \leq 30\%$, and $V_{45} \leq 195cc$; rectum, $V_{30} \leq 60\%$; $V_{40} \leq 50\%$; bladder, $V_{45} \leq 50\%$; each femur, $V_{40} \leq 30\%$ and since no guidelines exist for dose-volume constraints for pelvic bone, hence, $V_{10,}$ $V_{20,}$ $V_{30,}$ and V_{40} were recorded.

Plan evaluation:

Plans were evaluated using Dose-volume Histogram (DVH), Planar isodose display, 3-dimensional isodose display, and modified accordingly. Plans were also evaluated based on the RTOG homogeneity and conformity indices. An IMRT plan with dose colour wash and DVH is depicted in Figure 2.

Treatment delivery:

Treatment was delivered using 6 or 10 MV photons, on the linear accelerator (Agility, Elekta AB, Stockholm, Sweden), having multi-leaf collimator (MLC) with a leaf width of 1 cm at isocentre.

Patient set up was verified using CBCT (Cone Beam CT) daily for the first 3 fractions, followed by once-weekly CBCT. Rigorous quality assurance (QA) protocols were followed before commencing the IMRT treatment using an institutional protocol with appropriate phantom and 2-dimensional array matrix, with a gamma index of ±3%.

Concurrent chemotherapy in the form of cisplatin with a dose of 35-40 mg/m^2 was used in the patients with carcinoma cervix as per indications (presence of nodal disease, involved margin or parametrial

invasion). External beam radiotherapy was followed by vaginal brachytherapy using high dose rate (HDR) unit (microSelectron HDR, Elekta AB, Stockholm, Sweden) with Ir-192 source. The dose was given as 6-8 Gy per fraction as single fraction per week given for 2-3 weeks.

On treatment assessment:

Patients were assessed at least once weekly during radiation using the following parameters according to the RTOG acute toxicity criteria: Pelvic skin toxicity, lower gastrointestinal (LGI) toxicity (diarrhea), bladder toxicity (frequency of urination, nocturia, dysuria, urgency, hematuria), haematological toxicity (all three cell lines were assessed) and body weight were recorded using standardized weighing machines.

Post-treatment follow-up:

The first post-treatment visit was 2-3 weeks after completion of radiotherapy. Subsequent visits were monthly for the first 3 months, and then 2 monthly for the next 6 months. After this patients were followed up every 3 months until 1 year after treatment. At each visit, the following acute/late toxicities were assessed as per RTOG toxicity criteria: Skin toxicity, LGI toxicity – diarrhea, rectal bleeding, bladder toxicity – frequency of urination, nocturia, dysuria, urgency, hematuria, Status of local disease, and regional disease were clinically assessed at each follow-up. Follow-up investigations were performed, if required, as per the clinician's discretion.

Statistics:

All outcomes were measured from the time of the start of radiotherapy to the time of that event. Acute and late toxicities were assessed according to RTOG radiation morbidity criteria. Acute toxicity was defined as an adverse event occurring within 90 days from the start of radiotherapy. Overall survival (OS) was defined as the time from the start of radiotherapy to death. Progression-free survival (PFS) was defined as the time to any local, regional, or distant failure. Patients were censored at the date of last follow-up or death. Survival analysis was done using the Kaplan–Meier method. Overall treatment time (OTT) was calculated from the date of start of radiotherapy to the last fraction of intra-vaginal brachytherapy (IVBT) delivered. Log-rank tests and Cox proportional hazards regression models were used for univariate analysis. Statistical analysis was performed using SPSS (IBM Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results:

A total of 30 patients (including 23 with cancer cervix and 7 with endometrial cancer) who had undergone a total hysterectomy and required adjuvant pelvic irradiation, were included in this study from August 2015 to October 2018. All patients completed the treatment and none defaulted during the treatment and complete analysis was done on 30 patients. Patient characteristics are depicted in Table 1.

Amongst the 23 patients with cancer cervix, only 2 patients received 50 Gy in 25 fractions at the rate of 2 Gy per fraction, 5 fractions per week for 5 weeks, rest all received 45 Gy in 25 fractions at the rate of 1.8

Gy per fraction, 5 fractions per week for 5 weeks, followed by vaginal brachytherapy for which 8 Gy per fraction as single fraction per week given for 2 weeks, was the most common schedule used (in 43.5% cases). Out of 23 patients with cancer cervix, 18 patients had high-risk features, received concurrent cisplatin 35 mg/m^2 intravenously once a week. The median number of concurrent chemotherapy cycles was 4 and 77.8% of the cases of cancer cervix in the concurrent chemo-radiotherapy (CRT) group received ≥ 4 concurrent chemotherapy. Maximum on treatment skin toxicity was grade 1 starting at 3rd week and occurring in 38% of the cases at week 5. There was no grade 2 or more on-treatment skin toxicity. Maximum on treatment LGI toxicity was grade 2, starting at week 3 and observed in 31% of the cases at week 5. Maximum on treatment GU toxicity was grade 2, observed in 14% of the cases at week 5. Two patients had grade 2 anemias at the first week which recovered after blood transfusion, although these patients had a lower level of pre-radiotherapy hemoglobin. No patient had grade 2 anemia in the third and fourth week while one patient developed grade 2 anemia in the fifth week. Only one patient developed grade 2 neutropenia and that too at the fifth week and there was no incidence of febrile neutropenia. Acute toxicities are summarized in Table 2. No late skin and GU toxicities were observed. Maximum late LGI toxicity was grade 1, occurring in 6.67% of the cases. The cases that were observed to have grade 2 LGI toxicity had median V_{45} = 24 cc (only 2 cases exceeding 195 cc) bowel bag while median V_{40} = 73.4% for the rectum. The dose coverage of target volumes and OARs are summarized in Table 3.

The median follow-up period was 35 months (range 8–48 months). Five (out of 30) patients developed treatment failures (1 distant and 4 local), 2 within 6 months, and 3 after 12 months of the start of radiotherapy. All the patients with treatment failures received palliative chemotherapy while electron therapy was given in one patient having abdominal wall recurrence. The patients who developed treatment failures had high-risk features such as parametrial invasion (in 50% of the cases), lymphovascular invasion (in 75% of the cases), close or positive margins (in 75% of the cases) and low pre radiotherapy hemoglobin levels (< 10 in all cases of treatment failures). At a median follow-up of 35 months, the 3 year PFS and OS were 83.3% (all stages included). The Kaplan Meier curves for PFS and OS are depicted in Fig. 3.

Discussion:

Selected post-operative patients of early-stage cervical and endometrial cancer are treated with adjuvant RT. The impact of pelvic RT on the survival and morbidity profile of the patient is significant [11, 12]. The conventional whole pelvic radiotherapy (WPRT) technique exposes most of the contents of the true pelvis to radiation and leads to significant acute and late radiation morbidities in the form of skin, haematological, LGI and GU toxicities (acute GI toxicity grade ≥ 2 31.8% versus 63.6% for WPRT and IMRT respectively) [5]. IMRT has been shown in several dosimetric studies to reduce the doses to OARs (bladder, rectum, small bowel), consequently leading to a reduction in toxicities [9, 13, 14]. Various prospective, randomized studies have demonstrated the role of pelvic IMRT in the clinical setting for

intact cervix with promising results [5, 8]. While some studies have evaluated its role in the post-operative setting; [15–21] however, there is no phase III trial available.

A study by Yang et al suggested that IMRT significantly reduced the average percent irradiated volume of the rectum resulting from > 30 Gy doses and of the small bowel from 45 Gy [14]. Furthermore, in the bladder and bone marrow, the advantages of IMRT over 3D-CRT were not significant for any of the radiation doses examined. Sedlis et al. observed 3 (2.3%) gastrointestinal (GI) and 4 (3.1%) GU Grades 3–4 toxicities in 128 patients who received postoperative RT [12]. Hasselle et al. studied 111 patients of cervix cancer having stages I–IVA treated with IMRT. In a subset analysis of 22 patients treated with postoperative RT, of which 12 (55%) received concurrent chemotherapy, they observed one patient (5%) with Grades 3–4 acute GI toxicity and no acute GU or late Grades 3–4 toxicities [22]. Chen et al. studied 54 postoperative patients of cervical cancer treated with adjuvant chemoradiation with a dose of 50.4 Gy using IMRT and intravaginal RT as 6 Gy in 3 fractions. They observed no Grade 3 or more GI or GU acute toxicities and only 1 (1.8%) patient developed late Grade 3 GU toxicity [15]. In our study, we observed no Grades 3–4 toxicity, the maximum toxicity observed was Grade 2 acute LGI and Grade 1 late LGI. Sedlis et al. observed Grades 3–4 acute hematologic toxicity in 3 (2.3%) patients receiving adjuvant RT [12]; Peters et al. observed Grades 3–4 hematologic toxicities including anemia in 4 (3.3%) patients, leukopenia in 43 (35.2%), neutropenia in 35 (28.7%), and thrombocytopenia in one (0.8%) in the chemoradiation group [23]. Chen et al. observed 3 (6%) patients developed acute Grades 3–4 hematologic toxicities [15]. Mell et al. observed Grades 3–4 hematological toxicities including anemia in 3 (8.1%) patients, granulocytopenia in 1 (2.7%) patient, and leukopenia in 4 (10.8%) patients in 37 patients with cervical cancer treated with IMRT and concurrent cisplatin [9]. Klopp et al. observed very low rates of Grade 4 or higher hematologic toxicity (0% in the IMRT vs. 18% in the conventional group, P = .002) [17]. In the current study, we observed Grade 2 anemia, leukopenia, neutropenia, and thrombocytopenia in 2 (6.9%), 2 (6.9%), 1 (3.4%), and 0 (0%) cases respectively. All the toxicities observed in our study were higher in the CRT group as compared to RT alone group which is depicted in Table 4. The GOG 92 study by Rotman et al. showed 3 years PFS as 86% and 3 year OS as 88% [24]. Hasselle et al. reported 3-year DFS and OS rates of 95.2% (95% CI, 86.7–100%) and 100% (95% CI, 80.3–100%) in the subset analysis for the 22 postoperative patients in their cohort with a median follow-up of 27 months [22]. Chen et al. reported 3-year locoregional control rate, DFS, and OS of 93% (95% CI, 86.5–99.5%), 78% (95% CI, 64.7–91.3%), and 98% (95% CI, 94–100%), respectively, in 54 postoperative patients treated with IMRT with a median follow-up of 20 months [15]. RTOG 0418 trial also reported 2-year DFS and OS rates of 86.9% (95% CI, 71.2–94.3%) and 94.6% (95% CI, 80.1–98.6%), respectively with a median follow-up of 32 months [17]. With a median follow-up of 35 months in our study, we reported 5 patients having treatment failures; of which 1 was a distant failure (omental metastasis) while the rest 4 were local failures (at vaginal vault/abdominal wall) and 5 patients had died till now. The median overall treatment time in our study was 55 days, calculated from the day of RT start to the last fraction of vaginal brachytherapy; however, it does not correlate with the recurrence pattern. The patients who developed treatment failures in our study, had high-risk features such as parametrial invasion (in 50% of the cases), lymphovascular invasion (in 75% of the cases), close or

positive margins (in 75% of the cases), and low pre radiotherapy hemoglobin levels (< 10 in all cases of treatment failures).

The first phase II trial of postoperative IMRT in gynecological malignancies (involving cervical and endometrial carcinomas) was launched in 2006 by the Radiation Therapy Oncology Group (RTOG 0418 trial) [17]. The primary objective of this trial was to determine the feasibility of post-operative IMRT in a multi-institutional setting and to establish whether the promising clinical results observed in single-institution studies could be reproduced. The results of this trial may be considered as one of the most relevant references for the discussion of the findings of our study. This trial enrolled 58 patients from 25 different institutions and 43 were eligible for analysis. In our study, we enrolled 30 post-operative patients with the cervix and endometrial cancer. The incidence of acute toxicity (grade 2 or higher) was 28% in the RTOG 0418 trial and 24.1% in our study. The nature and timing of toxicity in these two trials were also similar. Most of the patients were diagnosed in the last week of radiotherapy. The accuracy of CTV and OAR delineation and its reproducibility in the clinical setting is important in IMRT, because of the sharp dose gradients associated with this technique. Even the slightest variation can have a considerable effect on dose distribution and outcome; therefore, the emphasis was placed on quality assurance. RTOG 1203 was a randomized control trial, published in August 2018, with 278 eligible patients of post-operative carcinoma endometrium and cervix taking the acute GI toxicity as its primary endpoint. They observed that 51.9% of women receiving conventional RT and 33.7% receiving IMRT reported frequent diarrhea (P = 0.01), and more patients required anti-diarrheal medications in the conventional RT arm versus IMRT arm [25]. The influence of IMRT on survival rates of gynecological cancers requires further investigation in a phase III trial. Very recently, a randomized control trial from Tata Memorial Hospital, Mumbai, India, comparing 3DCRT versus IMRT in around 300 patients of post-operative carcinoma cervix, has been presented at ASTRO 2020 annual meeting. The results of which are much in favor of IMRT, however, the complete results are yet to be published.

Conclusion:

The present study entitled “Study of toxicities of Intensity Modulated Radiotherapy (IMRT) in post-operative patients of carcinoma cervix and endometrium" is a prospective interventional single-arm study, in which the toxicity and effectiveness of treatment were seen. Post-operative patients with the cervix and endometrial cancer were treated with pelvic IMRT using a linear accelerator. Using established RTOG Acute and Late Morbidity Scoring Criteria, we demonstrated that IMRT is well tolerated considering acute and late toxicities in the form of skin, lower gastrointestinal, genitourinary, and hematological toxicities. We can conclude from our study that the experience with postoperative pelvic IMRT in patients with cervical and endometrial cancer was favorable in terms of oncologic outcomes, with 5 patients developing treatment failures at a median follow-up of 35 months. The morbidity profile was also very favorable, even in the setting of an aggressive trimodality approach. The maximum toxicity seen was grade 2 and no grade 3 or 4 toxicities were observed in any case. Data from our study as well as the data from the RTOG 0418 study highlights the advantages of IMRT in the management of post-operative patients with cervical and endometrial cancer. Although our study had inherent limitations of small

sample size and a shorter follow-up period, it shows that pelvic IMRT is well tolerated with an acceptable toxicity profile. Larger studies with similar cohort of patients and longer follow-up period may help in establishing the accurate role of IMRT in the future.

Declarations

Ethics approval and consent: The study protocol was reviewed and approved by the Institution Ethics Committee (IEC – 42/2015), Dr Ram Manohar Lohia Institute of Medical Sciences, and informed consent was obtained from all patients.

Availability of data and material: Relevant datasets are available from the corresponding author on reasonable requests.

Competing interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding: None to declare

Contribution	Author(s)
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Acknowledgements:

The authors thank all the patients for their participation in this trial and medical physicists, radiotherapy technologists and all other people who were involved in any manner.

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Tables

Table 1

Parameters		Carcinoma cervix N= 23 (%)	Carcinoma endometrium N= 7 (%)	Overall N= 30 (%)
Median age in years (range)		50 (35-65)	62 (55-75)	56 (35-75)
Median Karnofsky Performance Score		90	90	90
FIGO Stage	IA	5 (21.7)		5 (16.6)
	IB	10 (43.4)	5 (71.4)	15 (50)
	II	8 (34.7) [IIA]	2 (28.6)	10 (33.3)
	III	0 (0)	0 (0)	0 (0)
Type of Surgery	TAH+BSO	14 (60.8)	7(100)	21 (70)
	Wertheim's Hysterectomy	9 (39.1)	0 (0)	9 (30)
Lymph Node Dissection done in		8 (34.8)	5 (71.4)	13 (43.3)
Histology	Squamous Cell Carcinoma	20 (86.9)	0 (0)	20 (66.6)
	Adenocarcinoma	3 (13)	7 (100)	10 (33.3)
Differentiation	Well Differentiated	4 (17.4)	1 (14.3)	5 (16.6)
	Moderately Differentiated	16 (69.5)	1 (14.3)	17 (56.6)
	Poorly Differentiated	3 (13)	5 (71.4)	8 (26.6)
Margin status	Involved/Close	9 (30)	0 (0)	9 (23.3)
	Clear	14 (60.8)	7 (100)	21 (70)

Table 2

Site	Grade	Week1	Week2	Week3	Week4	Week5
Skin	Grade 1	0 (0)	0 (0)	0 (0)	7 (23.4)	11 (36.7)
LGI	Grade 1	0 (0)	0 (0)	10 (33.4)	15 (50)	15 (50)
	Grade 2	0 (0)	0 (0)	1 (3.34)	6 (20)	9 (30)
GU	Grade 1	0 (0)	5 (16.7)	7 (23.4)	8 (26.7)	9 (30)
	Grade 2	0 (0)	0 (0)	0 (0)	0 (0)	4 (13.4)
Anemia	Grade 1	2 (6.7)	3 (10)	4 (13.4)	4 (13.4)	6 (20)
	Grade 2	2 (6.7)	0 (0)	0 (0)	1 (3.4)	1 (3.4)
Leukopenia	Grade 1	0 (0)	2 (6.7)	2 (6.7)	4 (13.4)	2 (6.7)

Table 3

Parameters	Acceptable value	Achieved value		
		Median (in %)	Mean (in %)	Range
PTV volume covered by 95% isodose line	≥95	99	98.7±1.03	97-100
CTV volume covered by 95% isodose line	≥95	100	100±0.0	100-100
Bowel bag V_{45} (in cc)	<195	34.53	55.7±49	8.3-208
Rectum V_{40}	≤50	50	50.5±29.4	35-99
Urinary bladder V_{45}	≤50	28	28.5±12.5	3-55
Right Femur V_{40}	≤30	3	4.8±4.9	0-21
Left Femur V_{40}	≤30	4	5.2±5.4	0-21
Pelvic bone V_{10}		100	98.8±1.7	94-100
V_{20}		89	87.7±4.6	81-98
V_{30}		60	56.9±7.9	49-88
V_{40}		32	30.4±9.8	21-75

Table 4

Observed acute toxicities (grade 2)	No. of cases in CRT group N=18(%)	No. of cases in RT alone group N=12(%)	Overall cases N=30(%)
Skin	0(0)	0(0)	0(0)
LGI	7(38.9)	2(16.6)	9(30)
GU	3(16.6)	1(8.3)	4(13.3)
Anemia	1(5.5)	1(8.3)	2(6.6)
Neutropenia	1(5.5)	0(0)	1(3.3)
Thrombocytopenia	0(0)	0(0)	0(0)

Figures

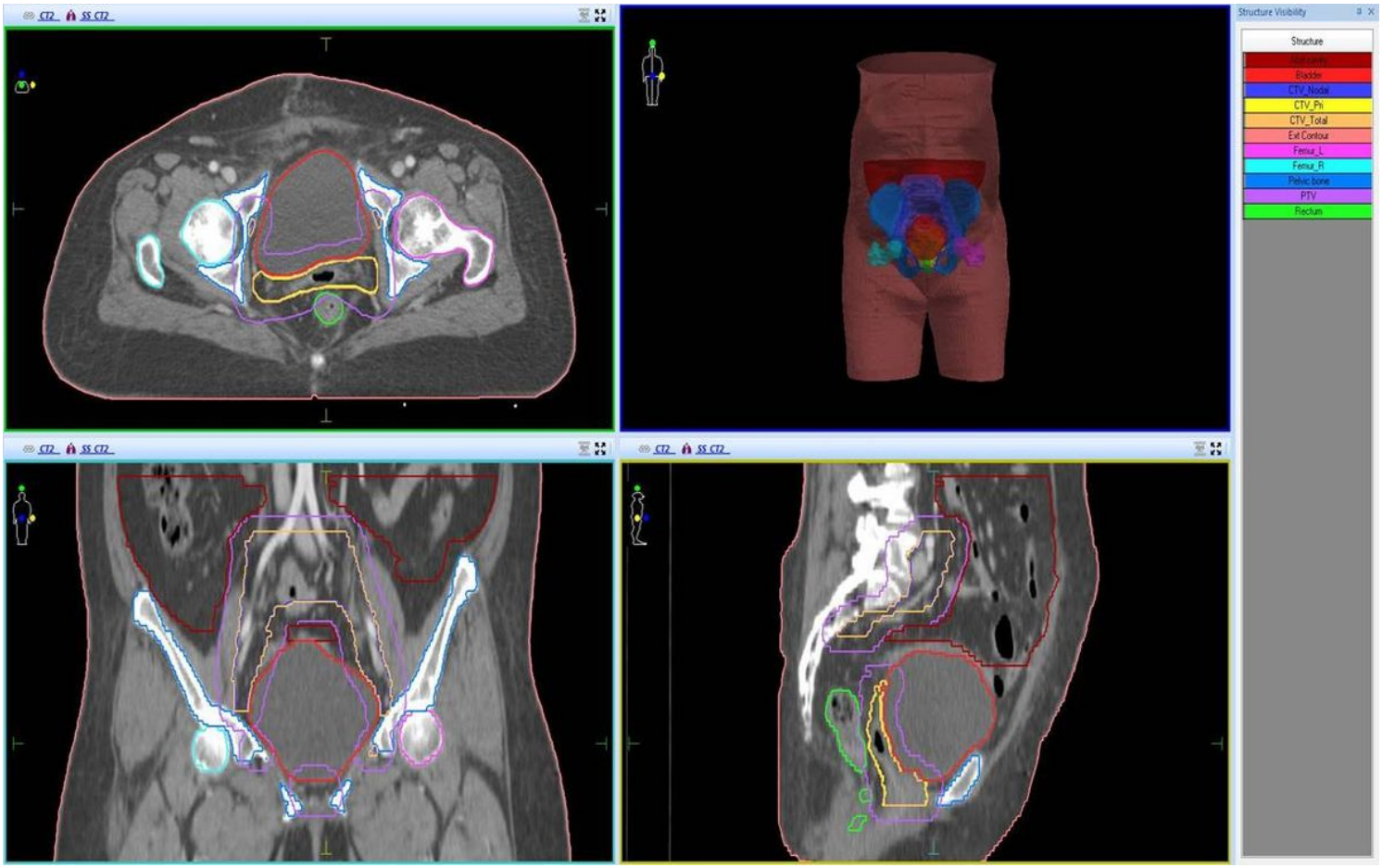

Figure 1

A contoured CT slice of a patient depicting target volumes and OARs in axial, coronal and sagittal view

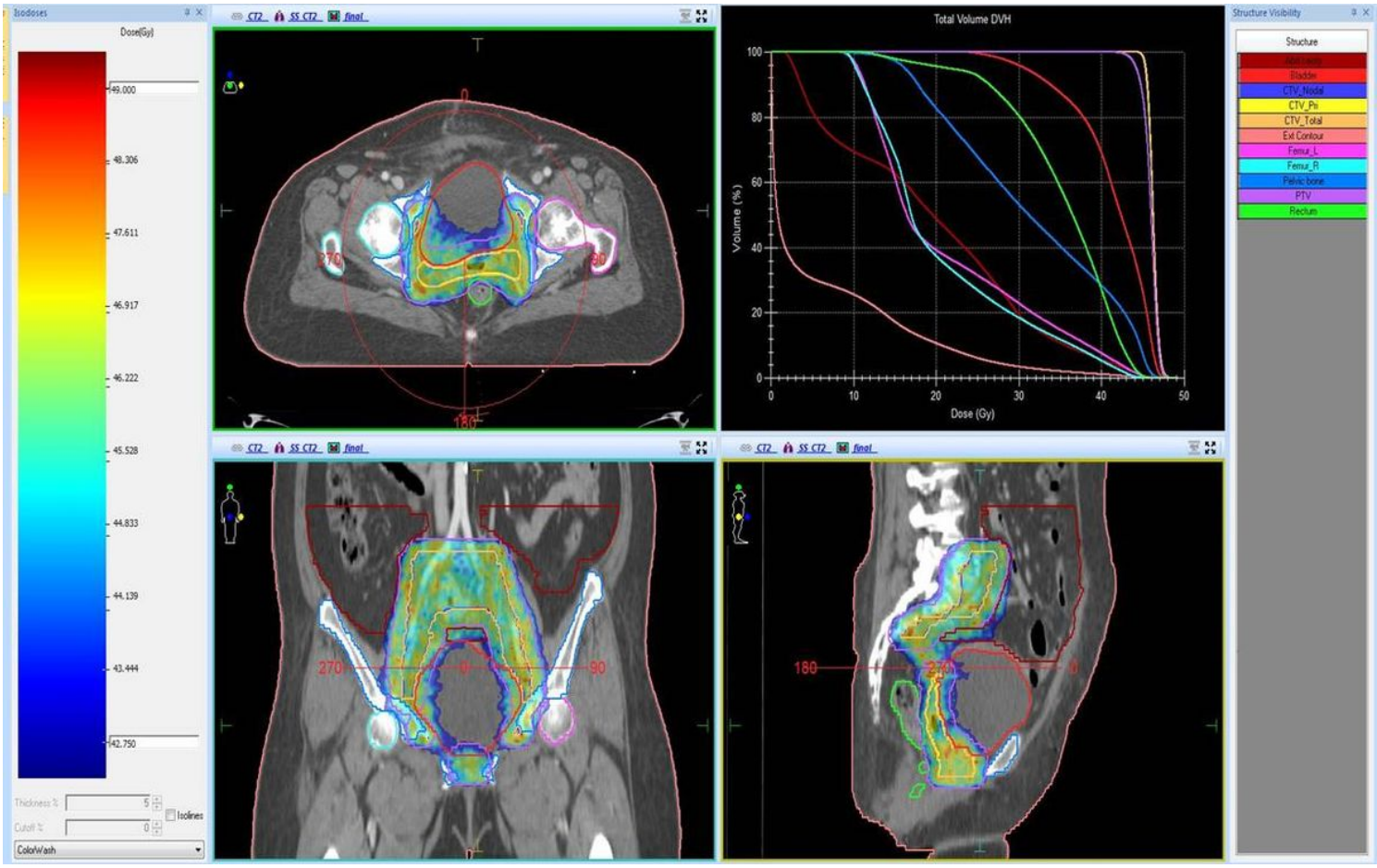

Figure 2

An IMRT plan of a patient showing dose distribution in axial, coronal and sagittal view with DVH curves

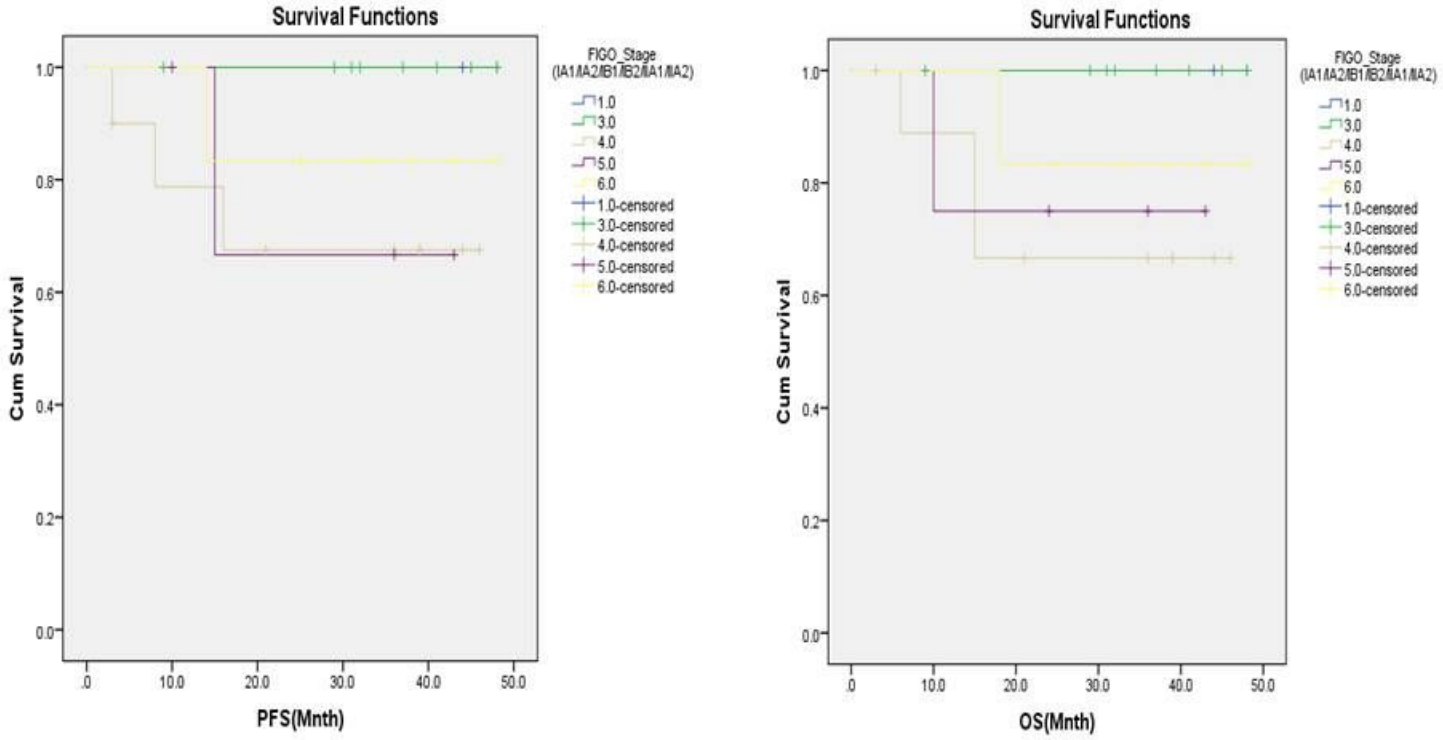

Figure 3

Stage wise progression-free survival and overall survival