Original Article

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Oncology Section

A Cohort Study of Toxicities of Intensity Modulated Radiotherapy in Postoperative Patients of Carcinoma Cervix and Endometrium

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ABSTRACT

Introduction: Conventional Whole Pelvic Radiotherapy (WPRT) is associated with significant morbidity, especially haematological and Gastrointestinal (GI), which increases further with concurrent chemotherapy. Various studies have shown a clinical benefit of pelvic Intensity Modulated Radiotherapy (IMRT) but included a significant number of patients with intact cervix and uterus.

Aim: The primary aim of the study was to record the toxicities of IMRT and the secondary aim was to detect its tolerance.

Materials and Methods: This was a phase 2, single arm cohort study, conducted from August 2015 to October 2018 at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, including a total of 30 patients (23 cervical and seven 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 five 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 Radiation Therapy Oncology Group (RTOG) radiation morbidity criteria. All outcomes were measured from the time of the start of radiotherapy to the time of acute event. Acute and late toxicities were assessed according to RTOG radiation morbidity criteria. Survival analysis was done using the Kaplan-Meier method. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) (IBM Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results: Out of 30 patients, the highest grades of acute toxicities for skin, Lower Gastrointestinal (LGI), Genitourinary (GU), and haematological toxicities were grade 1, 2, 2 and 2, occurring in 11 (36.7%), 9 (30%), 4 (13.4%), and 1 (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 (two distant and three local). At a median follow-up of 35 months, the three 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 haematological toxicities, IMRT is well tolerated and has an acceptable toxicity profile even in the setting of an aggressive trimodality approach.

Keywords: Adverse events, Conformal radiotherapy, Hysterectomy, Malignancy, Pelvis

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 WPRT is associated with significant morbidity, especially haematological and GI, which increases with concurrent chemotherapy [5,6]. An IMRT is a form of highly conformal radiotherapy in which a computer aided optimisation process is used to determine customised 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 tumour control and reduced normal tissue toxicity. Its effectiveness has been validated in several anatomical sites such as head and 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, it is difficult to extrapolate the results from the above studies that have taken a mixed population of patients (both intact and postoperative cases). Although studies are available in literature regarding the same, some ambiguity still exists. The aim of the present study was to evaluate the toxicity and tolerance of IMRT in postoperative patients with carcinoma cervix and endometrium.

MATERIALS AND METHODS

This was a single arm, interventional, cohort study conducted at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, from August 2015 to October 2018 with a sample size of 30 patients who satisfied the eligibility criteria and reported during the specified time frame. The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC Number 42/15) and informed consent was obtained from all patients.

Inclusion criteria: Cervix and endometrial cancer patients who underwent total hysterectomy with or without bilateral salpingo-oophorectomy and lymphadenectomy, having indications of adjuvant pelvic irradiation and The International Federation of Gynaecology and

Obstetrics (FIGO) stage I-IIA (for cancer cervix), I-III (for endometrial cancer) were included in the study [10]. All patients received pelvic IMRT with or without concurrent chemotherapy followed by vaginal brachytherapy.

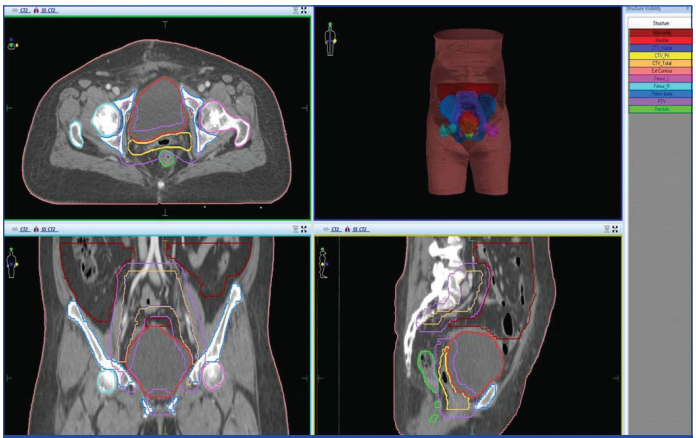
Exclusion criteria: While those having concurrent second malignancy, previous pelvic irradiation, prior chemotherapy, and any histopathology other than squamous or adenocarcinoma, were excluded from the study.

Study Procedure

Radiotherapy (RT) planning: All patients were immobilised in supine position using knee rest followed by contrast-enhanced Computerised Tomography (CT) simulation with 3 mm image acquisition from first lumbar vertebrae to mid thigh. Bladder protocol was followed which entails intake of 500 mL water 30 to 45 minutes 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. The 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 presacral 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) [11].

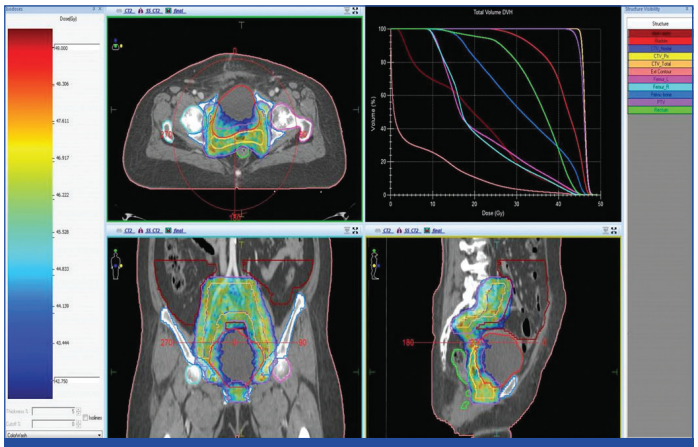
Organs At Risk (OAR) were drawn as per the RTOG guidelines for organ delineation in pelvic radiotherapy which included urinary bladder (inferiorly from its base, and superiorly to the dome), rectum (beginning from the anal verge, moving superiorly till it loses concave shape in the axial plane and connects 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 rectosigmoid junction till 3 cm above the superior most section of the PTV contour) and pelvic bone (bilateral hip bones including sacrum) [Table/Fig-1] [12].



[Table/Fig-1]: A contoured CT slice of a patient depicting target volumes and OARs in axial, coronal and sagittal view (colour legends; bowel bag, maroon; urinary bladder, red; clinical target volume for regional nodes, Persian blue; clinical target volume for primary disease, yellow; combined clinical target volume, honey; external contour, ballerina pink; left femur, purple; right femur, arctic; pelvic bone, azure; PTV, orchid; rectum, light green)

Dosage and planning: A dose of 45-50.4 Gray (Gy) at 1.8-2 Gy per fraction was given as five fractions per week (Monday to Friday) with an Overall Treatment Time (OTT) of 5 to 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, V45 ≤195cc; rectum, V40 ≤50%; bladder, V45 ≤50%; each femur, V40 ≤30% and since no guidelines exist for dose-volume constraints for pelvic bone, hence, V10, V20, V30, and V40 were recorded [13].

Plan evaluation: Plans were evaluated using Dose-volume Histogram (DVH), Planar isodose display, 3-dimensional (3D) isodose display, and modified accordingly. Plans were also evaluated based on the RTOG homogeneity and conformity indices [14]. An IMRT plan with dose colour wash and DVH is depicted in [Table/Fig-2].



[Table/Fig-2]: An IMRT plan of a patient showing dose distribution in axial, coronal and sagittal view with dose-volume histogram curves (colour legends; bowel bag, maroon; urinary bladder, red; clinical target volume for regional nodes, Persian blue; clinical target volume for primary disease, yellow; combined clinical target volume, honey; external contour, ballerina pink; left femur, purple; right femur, arctic; pelvic bone, azure; PTV, orchid; rectum, light green).

Treatment delivery: Treatment was delivered using six or 10 Megavoltage (MV) photons, on the linear accelerator (Agility, Elekta AB, Stockholm, Sweden), having Multileaf 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 three 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 (2D) 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 two to three weeks.

Assessment of patients during the treatment: Patients were assessed at least once weekly during radiation using the following parameters according to the RTOG acute toxicity criteria [Table/Fig-3] [15]: Pelvic skin toxicity, LGI toxicity (diarrhoea), bladder toxicity (frequency of urination, nocturia, dysuria, urgency, haematuria), haematological toxicity (all three cell lines were assessed) and body weight were recorded using standardised weighing machines.

Post-treatment follow-up: The first post-treatment visit was two to three weeks after completion of radiotherapy. Subsequent visits were monthly for the first three months, and then for every two months for the next six months. After this patients were followed-up every three months until one year after treatment. At each visit, the following acute/ late toxicities were assessed as per RTOG toxicity criteria [15]: Skin toxicity, LGI toxicity-diarrhoea, rectal bleeding, bladder toxicity-frequency of urination, nocturia, dysuria, urgency, haematuria, Status of local disease, and regional disease were

Organ		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin		No change over	Follicular, faint or dull erythema/epilation/ dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate oedema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, haemorrhage, necrosis
Lower gastrointestinal		No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholyic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Genitourinary		No change	Frequency of urination or nocturia twice pretreatment/ habit/dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anaesthetic (e.g.,Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross haematuria with/ without clot passage	Haematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
Haematologic	White blood cells (cells/mm^3) (x1000)	≥4.0	3.0-<4.0	2.0-<3.0	2.0-<1.0	<1.0
	Platelets (cells/mm^3) (x1000)	>100	75-<100	50-<75	25-<50	<25 or spontaneous bleeding
	Neutrophils (cells/mm^3) (x1000)	≥1.9	1.5-<1.9	1.0-<1.5	0.5-<1.0	<0.5 or sepsis
	Haemoglobin (gm%)	>11	11-9.5	<9.5-7.5	0.5-<1.0	<0.5 or sepsis
	Haematocrit (%)	≥32	28-<32	<28	Packed cell transfusion required	-

[Table/Fig-3]: Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria.

clinically assessed at each follow-up. Follow-up investigations were performed, if required, as per the clinician's discretion.

STATISTICAL ANALYSIS

All outcomes were measured from the time of the start of radiotherapy to the time of occurrence of an event. Acute and late toxicities were assessed according to RTOG radiation morbidity criteria [15]. Acute toxicity was defined as an adverse event occurring within 90 days from the start of radiotherapy. The 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 [16]. Patients were censored at the date of last follow-up or death. Survival analysis was done using the Kaplan-Meier method. The OTT was calculated from the date of start of radiotherapy to the last fraction of Intravaginal Brachytherapy (IVBT) delivered. Logrank 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

The present study included a total of 30 patients (including 23 with cancer cervix and seven with endometrial cancer) who had undergone a total hysterectomy and required adjuvant pelvic irradiation. 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/Fig-4] [17].

Parameters		Carcinoma cervix n=23 (%)	Carcinoma endometrium n=7 (%)	Overall N=30 (%)
Median age in years (range)		50 (35 to 65)	62 (55 to 75)	56 (35 to 75)
Median karnofsky performance score [17]		90	90	90
FIGO stage	IA	5 (21.7)		5 (16.7)
	IB	10 (43.5)	5 (71.4)	15 (50)
	II	8 (34.8) (IIA)	2 (28.6)	10 (33.3)
	III	0	0	0
Type of surgery	TAH+BSO	14 (60.9)	7 (100)	21 (70)
	Wertheim's hysterectomy	9 (39.1)	0	9 (30)
Lymph node dissection done		8 (34.8)	5 (71.4)	13 (43.3)
Histology	Squamous cell carcinoma	20 (87)	0 (0)	20 (66.7)
	Adenocarcinoma	3 (13)	7 (100)	10 (33.3)
Differentiation	Well differentiated	4 (17.4)	1 (14.3)	5 (16.7)
	Moderately differentiated	16 (69.6)	1 (14.3)	17 (56.6)
	Poorly differentiated	3 (13)	5 (71.4)	8 (26.7)
Margin status	Involved/Close	9 (39.1)	0	9 (30)
	Clear	14 (60.9)	7 (100)	21 (70)

[Table/Fig-4]: Patient characteristics.
N: Number of patients (%); TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy; The International Federation of Gynaecology and Obstetrics (FIGO)

Amongst the 23 patients with cancer cervix, only two patients (due to adverse features such as parametrial invasion, lymphovascular invasion and involved margins) received 50 Gy in 25 fractions at the rate of 2 Gy per fraction, five fractions per week for five weeks, rest all received 45 Gy in 25 fractions at the rate of 1.8 Gy per fraction, five fractions per week for five weeks, followed by vaginal brachytherapy for which 8 Gy per fraction as single fraction per week given for two weeks, was the most common schedule used (in 43.5% cases) while remaining patients (56.5%) received 6 Gy weekly for 2-3 weeks. 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 four and 77.8% of the cases of cancer cervix in the concurrent chemoradiotherapy (CRT) group received greater than four concurrent chemotherapy. Highest grade of acute skin toxicity was grade 1 starting at 3rd week and occurring in 38% of the cases at fifth week. There was no grade 2 or more on-treatment skin toxicity. Highest grade of acute LGI toxicity was grade 2, starting at third week and observed in 31% of the cases at fifth week. Highest grade of acute GU toxicity was grade 2, observed in 14% of the cases at fifth week. Two patients had grade 2 anaemia at the first week which recovered after blood transfusion, although these patients had a lower level of preradiotherapy haemoglobin. No patient had grade 2 anaemia in the third and fourth week while one patient developed grade 2 anaemia 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 summarised in [Table/Fig-5]. 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 V45=24

cc (only two cases exceeding 195 cc) bowel bag while median V40=73.4% for the rectum. The dose coverage of target volumes and OARs are summarised in [Table/Fig-6].

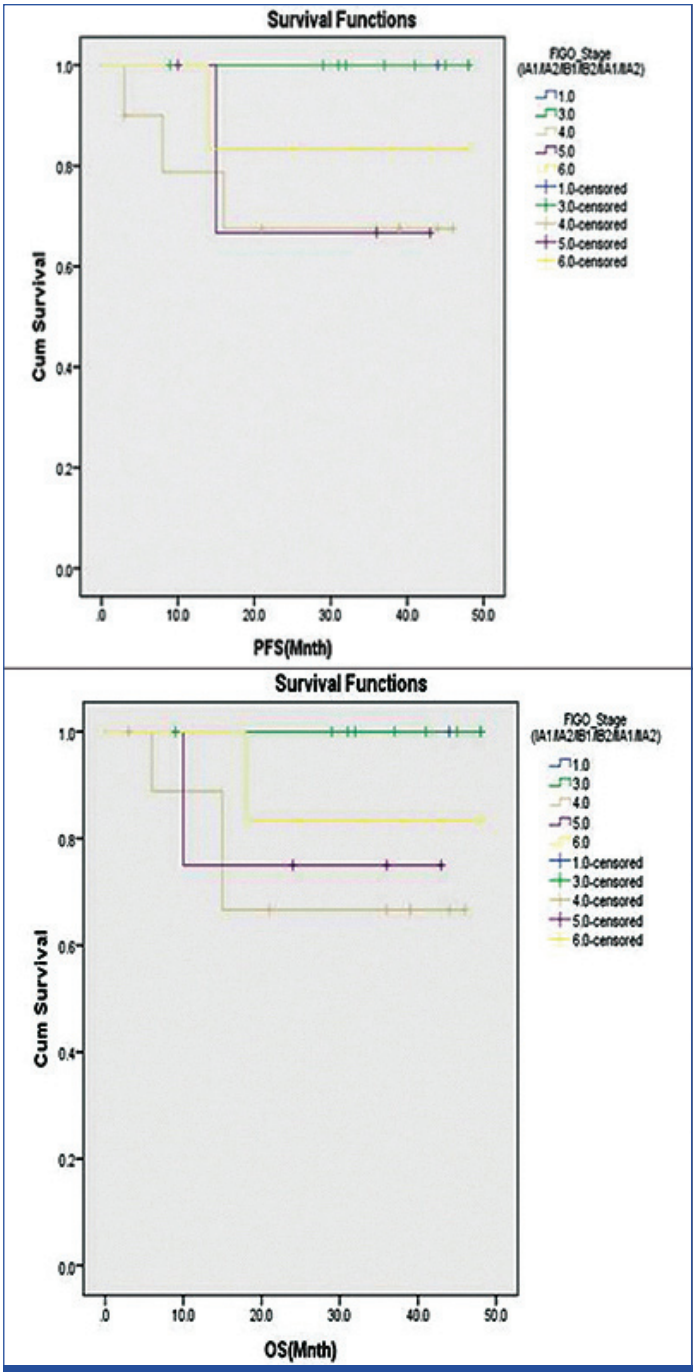
Site	Grade	Week 1 n (%)	Week 2 n (%)	Week 3 n (%)	Week 4 n (%)	Week 5 n (%)
Skin	1	0	0	0	7 (23.4)	11 (36.7)
LGI	1	0	0	10 (33.4)	15 (50)	15 (50)
	2	0	0	1 (3.34)	6 (20)	9 (30)
GU	1	0	5 (16.7)	7 (23.4)	8 (26.7)	9 (30)
	2	0	0	0	0	4 (13.4)
Anaemia	1	2 (6.7)	3 (10)	4 (13.4)	4 (13.4)	6 (20)
	2	2 (6.7)	0	0	1 (3.4)	1 (3.4)
Leukopenia	1	0	2 (6.7)	2 (6.7)	4 (13.4)	2 (6.7)

[Table/Fig-5]: Acute toxicity profile (recorded as per RTOG acute radiation morbidity scoring criteria).
N: Number of patients (%); LGI: Lower gastrointestinal; GU: Genitourinary

Parameters	Acceptable value	Achieved value		
		Median (%)	Mean (%)	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 V45 (cc)	<195	34.53	55.7±49	8.3-208
Rectum V40	≤50	50	50.5±29.4	35-99
Urinary bladder V45	≤50	28	28.5±12.5	3-55
Femur				
Right V40	≤30	3	4.8±4.9	0-21
Left V40	≤30	4	5.2±5.4	0-21
Pelvic bone*				
V10		100	98.8±1.7	94-100
V20		89	87.7±4.6	81-98
V30		60	56.9±7.9	49-88
V40		32	30.4±9.8	21-75

[Table/Fig-6]: Dose coverage for target volumes and dose constraints for organ at risk.
CTV: Clinical target volume; PTV: Planning target volume; *There are no available guidelines for the tolerance dose for pelvic bone

The median follow-up period was 35 months (range 8 to 48 months). Five (out of 30) patients developed treatment failures (one distant and four local), two within six months, and three after 12 months of the start of radiotherapy. A total of five patients died (one due to cardiac event and four due to disease progression) during follow-up period. 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 haemoglobin levels (<10 in all cases of treatment failures). At a median follow-up of 35 months, the three year PFS and OS were 83.3% (all stages included). The Kaplan-Meier curves for PFS and OS are depicted in [Table/Fig-7].



[Table/Fig-7]: Stage wise progression-free survival and overall survival.

DISCUSSION

Selected postoperative 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 [18,19]. The conventional 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 [9,20,21]. Various prospective, randomised 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 postoperative setting [22-28]; however, there is only one phase III trial available, the interim results of which has been published recently but the complete results are still awaited [29].

Dose to OARs and GI/GU toxicities: A study by Yang B et al., suggested that IMRT significantly reduced the average percentage irradiated volume of the rectum resulting from >30 Gy doses and of the small bowel from 45 Gy [21]. Furthermore, in the bladder and bone marrow, the advantages of IMRT over 3DCRT were not significant for any of the radiation doses examined. Sedlis A et al., observed 3 (2.3%) GI and 4 (3.1%) GU grades 3-4 toxicities in 128 patients who received postoperative RT [19]. Hasselle MD 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 1 patient (5%) with grades 3-4 acute GI toxicity and no

acute GU or late grades 3-4 toxicities [30]. Chen MF 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 three 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 [22].

In the present study, we observed no grades 3-4 toxicity, the maximum toxicity observed was grade 2 acute LGI and grade 1 late LGI.

Haematological toxicities: Sedlis A et al., observed grades 3-4 acute haematological toxicity in three (2.3%) patients receiving adjuvant RT [19]; Peters WA et al., observed grades 3-4 haematological toxicities including anaemia in 4 (3.3%) patients, leukopenia in 43 (35.2%), neutropenia in 35 (28.7%), and thrombocytopenia in 1 (0.8%) in the chemoradiation group [31]. Chen MF et al., observed 3 (6%) patients developed acute grades 3-4 haematological toxicities [22]. Mell LK et al., observed grades 3-4 haematological toxicities including anaemia 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 AH et al., observed very low rates of grade 4 or higher haematologic toxicity (zero in the IMRT vs 18% in the conventional group, p=0.002) [24].

In the current study, we observed grade 2 anaemia, leukopenia, neutropenia, and thrombocytopenia in 2 (6.9%), 2 (6.9%), 2 (3.4%), and 0 cases, respectively. All the toxicities observed in the present study were higher in the CRT group as compared to RT alone group which is depicted in [Table/Fig-4].

Survival rates: The gynaecologic oncology group 92 study by Rotman M et al., showed 3 years PFS as 86% and 3 years OS as 88% [32]. Hasselle MD et al., reported three year Disease Free Survival (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 [30]. Chen MF et al., reported three 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 [22]. The RTOG 0418 trial also reported two 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 [24].

With a median follow-up of 35 months in the present study, five patients had treatment failures; of which one was a distant failure (omental metastasis) while the rest four were local failures (at vaginal vault/abdominal wall) and five patients had died till now. The median OTT in the present 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 the present 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 preradiotherapy haemoglobin levels (<10 in all cases of treatment failures).

The first phase 2 trial of postoperative IMRT in gynaecological malignancies (involving cervical and endometrial carcinomas) was launched in 2006 by the RTOG 0418 trial [24]. The primary objective of this trial was to determine the feasibility of postoperative 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 the present study. This trial enrolled 58 patients from 25 different Institutions and 43 were eligible for analysis. In this study, authors enrolled 30 postoperative 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%. 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 QA. The RTOG 1203 was a randomised control trial, published in August 2018, with 278 eligible patients of postoperative 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 diarrhoea (p=0.01), and more patients required anti-diarrhoeal medications in the conventional RT arm versus IMRT arm [33]. The influence of IMRT on survival rates of gynaecological cancers requires further investigation in a phase III trial. Very recently, interim results of a randomised control trial from Tata Memorial Hospital, Mumbai, India, comparing 3DCRT versus IMRT in around 300 patients of postoperative carcinoma cervix, has been published [29]. The results of which were much in favour of IMRT, however, the complete results are still awaited.

Limitation(s)

The present study had inherent limitations of single arm study design, small sample size and a shorter follow-up period. Larger studies with similar cohort of patients and longer follow-up period may help in establishing the accurate role of IMRT in the future.

CONCLUSION(S)

The experience with postoperative pelvic IMRT in patients with cervical and endometrial cancer was favourable in terms of oncologic outcomes, with five patients developing treatment failures at a median follow-up of 35 months. The morbidity profile was also very favourable, 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 the present study as well as that from the RTOG 0418 study highlight the advantages of pelvic IMRT and shows that the technique is well tolerated with an acceptable toxicity profile.

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