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Frequency and severity of acute toxicity of pelvic radiotherapy for gynecological cancer

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ORIGINAL ARTICLE

Frequency and Severity of Acute Toxicity of Pelvic Radiotherapy for Gynecological Cancer

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ABSTRACT

Objective: To determine the frequency and severity of acute toxicity of pelvic radiotherapy for gynecological cancer.
Study Design: A case series.
Place and Duration of Study: Department of Oncology, The Aga Khan University Hospital, Karachi, from March 2011 to June 2012.
Methodology: A total of 99 patients with histologically proven uterine and cervical cancer, receiving radiation therapy, were enrolled into the study after informed consent on justification of inclusion and exclusion criteria. Patients were evaluated for the frequency and severity of pelvic radiotherapy's side effects according to toxicity criteria based on RTOG/EORTC and CTC version 2 criteria at the start, during and at the end of treatment. The data was analyzed by using SPSS version 16.
Results: Out of the 99 enrolled patients, 58 (58.6%) had uterine and 41 (41.4%) had cervical cancer. Mean age was 54.54 ±10.29 years. Thirty-five (35.4%) patients received chemotherapy with RT. Mean RT dose was 60.72 ±7.15 Gy. The most common gastrointestinal adverse effect was diarrhea in 64 (64.6%) followed by proctitis in 55 (55.5%), nausea in 33 (33.3%) and vomiting in 16 (16.2%) patients. Grade (G) 1 was the most frequently observed severity. The most common hematological toxicity was anemia in 37.8% (n=31/82) {(G1=18 (21.9%), G2=11 (13.4%), G3=2 (2.4%)} followed by thrombocytopenia in 22.8% (21/92) {(G1=16 (17.3%), G2=2 (2.1%), G3=3 (3.2%)} and neutropenia in 21 (21.2%) {(G1=12 (12.1%), G2=5 (5%), G3=3 (3%), G4=1 (1%)}. Urinary toxicity was observed in 49 (49.5%) patients. On stratification, chemotherapy and higher RT dose were strong predictor of increased hematological and upper gastrointestinal toxicity ($p < 0.05$) and age > 60 years for diarrhea ($p < 0.05$).
Conclusion: The frequency and severity of acute toxicity of pelvic radiotherapy in women with gynecologic cancers was found intermediate to high.

Key Words: *Gynecological malignancies. Radiotherapy. Chemotherapy. Acute toxicity. Cervical cancer. Endometrial cancer. Hematological toxicity. Gastrointestinal toxicity. Urinary toxicity.*

INTRODUCTION

Gynecological cancer, known to be one of the most common cancers in women, mainly comprises of cervical and uterine cancer. Endometrial cancer is the most common gynecologic malignancy in North America and Europe, with cervical cancer being the second most common amongst women worldwide, especially affecting developing countries.[1] No accurate figures exist for the prevalence and mortality of cancer in Pakistan, however according to Hanif *et al*. cervical and endometrial cancers rank third most frequent malignancy (5.54%) in female which is consistent with the Karachi Cancer Registry data by Bhurgri *et al*.[2,3] Surgery is the recommended modality of treatment for uterine cancer followed by radiotherapy with or without chemotherapy in adjuvant setting in high risk group of patients.[4,5] For cervical cancer, radiotherapy and concurrent cisplatin based chemotherapy is the treatment of choice for FIGO (International Federation of Gynecology and Obstetrics) stage IB and higher,[6,7] surgery is usually reserved for lower stage disease.[8] Post-operative pelvic Radiotherapy (RT) is offered in high risk patients.[9]

Hence radiation to pelvis is an integral part of the curative treatment of gynecologic malignancies. Despite all the precisions and precautions during radiation therapy, the adjacent healthy tissues do get damaged resulting in treatment related toxicity that adversely affects the quality of life; along with being a predictor of late toxicity.[10] Gastrointestinal (GI) and urinary systems are the most frequently observed systems to be affected from pelvic radiotherapy while hematologic toxicity is mainly seen with the addition of chemotherapy. Literature review on early morbidity of pelvic radiotherapy along with chemotherapy has revealed high frequency and severity of varying range. Hematological toxicity has been reported to range from 20 - 74% (Grade 1-2:50-70%, Grade 3 - 4 :< 10%), urinary toxicity as 40 - 74.5% (G1 40%, G2 50.6%) and gastrointestinal toxicity as 40 - 80% (G1 40 - 50%, G2 40 - 60).[10-15] This has resulted in the development and implementation of different scoring systems for its measurement like RTOG/EORTC toxicity criteria for radiation therapy

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induced adverse effects. Secondly, measurement of treatment induced adverse effect is a part of several cancer related clinical trials so that newer cancer treatment options can be evaluated by its impact on patients' Quality of Life (QOL) apart from its efficacy. However, despite its importance there are no local data available that specifically addresses this issue. Hence, incidence of acute toxicity of pelvic radiotherapy treatment in gynecologic cancer patients is unknown in our population.

The aim of this study was to determine the frequency and severity of acute toxicity of pelvic radiotherapy for gynecological cancers in our population so that a comparison could be made with the West in this regard which would help us in developing appropriate strategies for its prevention and better management.

METHODOLOGY

This observational study was carried out at the Department of Oncology Section of Radiation Oncology, The Aga Khan University Hospital, Karachi, from March 2011 to June 2012 for a period of 15 months. The sample size was calculated in an empirical way, based on frequency and severity of toxicity as mentioned in recent literature, assuming a power of 80% with 95% confidence level and bound on error of 10% for sample estimation. Patients who were referred for radiotherapy by gynecologist were enrolled into the study on justification of strict inclusion and exclusion criteria after informed consent. Non-probability sampling technique was used.

Inclusion criteria were histologically proven uterine or cervical cancer and age more than 18 years. Patients with ovarian, fallopian tube, vaginal and vulvar cancer, on palliative treatment, previous history of pelvic radiotherapy, history of inflammatory bowel disease and fistula were excluded from the study.

All patients received radiation therapy with a minimum dose of 45 Gray (Gy) in 25 fractions through External Beam Radiotherapy (EBRT) and a minimum dose of 10Gy in 2 fractions *via* brachytherapy. Decision regarding addition of concurrent chemotherapy during radiation to patients was made by medical oncologist at the time of referral according to hospital standards. Patients were assessed before commencement of radiotherapy, during and at the end of treatment for frequency and severity of side effects. Gastrointestinal and urinary toxicities were assessed according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system (RTOG/EORTC), and Common Toxicity Criteria version 2.0 (CTC version 2.0) was used for hemato-logical toxicity and recorded in study proforma.[16,17] Patients, who had changes in laboratory values or clinical complaints that might be mistaken for acute side effects before beginning of radiation, were excluded from the assessment of one type of toxicity.

All the data were analyzed through Statistical Package for Social Sciences (SPSS) version 16. All quantitative variables were presented as mean and standard deviation while qualitative variables were presented as frequency and percentages. Chi-square test or Fisher's exact test was used to evaluate the statistical difference. A p-value < 0.05 was considered significant.

RESULTS

A total of 99 patients were recruited in the study, their demographic characteristics and treatment specifications are presented in the Table I. Uterine to cervix sub sites ratio was 1.4. In uterine cancer mean age of presentation was 56. 25 ±9.07 years, endometroid adenocarcinoma was the most frequently observed histology, i.e. 93% (n=54/58) and majority of the patients had early stage disease, i.e. stage I 55% (32/58). In cervical cancer mean age of presentation was 52.12 ±11.48 years, most frequently observed histology was squamous cell carcinoma 85% (35/41) and majority 73% (30/41) had locally advanced stage II and above disease. Mean radiation therapy dose was 60.7 ±7.15 Gray (Gy). All patients received external beam radiotherapy (mean dose 46.76 ±2.78 Gy) as well as brachytherapy (13.94 ±6 Gy). On initial evaluation, 17 patients were found to have hemoglobin level < 11 gm/dl so they were excluded from anemia analysis, similarly 7 patients were excluded from thrombocytopenia analysis

Table I: Characteristics of patients (n=99).

Characteristics	Number of patients (%)	
Age in years , Mean ±S.D (range)	54.54 ±10.24 (24-75)	
Sites		
Uterus	58 (58.6%)	
Cervix	41 (41.4%)	
Surgery		
Yes	74 (74.7%)	
No	25 (25.3%)	
FIGO Stage	Uterus	Cervix
IA	11 (11.1%)	0
IB	21 (21.2%)	11
IIA	(11.1%)	-
IIB	6 (6.1%)	2 (2%)
IIIA	5 (5%)	16
IIIB	(16.2%)	-
IIIC	9 (9.1%)	0
IVA	1 (1%)	7
	(7.1%)	-
	5 (5.1%)	0
	0 (5.1%)	5
Chemotherapy		
Yes	35 (35.4%)	
No	64 (64.6%)	
Radiotherapy dose in Gray (Gy)		
Mean ±S.D (range)*	60.7 ±7.15 (55-83.4)	

**External Beam Radiotherapy +Brachytherapy*

as they had platelet counts < 150 x 10^9/L at the start of the treatment.

The most frequently observed hematological toxicity was anemia in 37.8% (n=31/82) followed by thrombocytopenia in 22.8% (21/92) and neutropenia in 21.2% (21/99). Majority had grade 1 or 2 severity (17 - 34%), whereas only one patient developed grade 4 neutropenia. Diarrhea was the most frequently observed gastrointestinal toxicity in 64.6% (64/99) followed by proctitis in 55.5% (55/99). Only grade 1 or 2 gastrointestinal toxicity was observed. Almost half of the patients 49.5% (49/99) developed grade 1 or 2 cystitis as shown in Table II.

Table III shows the stratification of the outcome with the patients' demographic and treatment characteristics. Chemotherapy was found to have strong association with the acute hematological and upper gastrointestinal (GI) toxicities when compared with non-chemotherapy group. Anemia in 67.7% (n=21/31) vs. 19.6% (10/51), neutropenia in 51.4% (18/35) vs. 4.6% (3/64), thrombocytopenia in 55.8% (19/34) vs. 3.4% (2/58), nausea in 57.1% (20/35) vs. 20.3% (13/64), vomiting in 31.4% (11/35) vs. 7.8% (5/64) were observed respectively with statistical significance of p < 0.001. In locally advanced disease, anemia was detected in 51% (24/47), neutropenia in 30.3% (17/56), thrombo-cytopenia in 35.2% (18/51) and vomiting in 25% (14/56). In early diseases, anemia was observed in 20% (7/35), neutropenia in 9.3% (4/43), thrombocytopenia in 7.3% (3/41) and vomiting in 4.6% (2/43) that was statistically significant (p < 0.05).

A radiation dose of > 60 Gy as compared to < 60 Gy also showed strong association with hematological toxicities of anemia in 56.7% (21/37) vs. 22.2% (10/45), neutropenia in 42.2% (19/45) vs. 3.7% (2/54), thrombocytopenia in 47.6% (20/42) vs. 2% (1/50), and vomiting in 24.4% (11/45) vs. 9.2% (5/54) respectively (p < 0.05). Diarrhea was more frequently observed in patients of age > 60 years (76.2%, 32/42) as compared to patients < 60 years (56.1%, 32/57) with statistical significance (p < 0.03). The proportion of cystitis was higher in the group of patients with radiation dose of > 60 Gy (60%, 27/45) than patients having radiation dose < 60 Gy (40.7%, 22/54) with marginal statistical significance (p=0.056).

Table II: Frequency and severity of acute toxicity (n=99).

Toxicity	Frequency n (%)	
	Yes	No
Anemia*	31 (37.8) G1=18 (21.95), G2=11 (13.41), G3=2 (2.44)	51 (62.2)
Neutropenia	21 (21.21) G1=12 (12.12), G2=5 (5.05), G3=3 (3.03), G4=1 (1.01)	78 (78.79)
Thrombocytopenia**	21 (22.83) G1=16 (17.39), G2=2 (2.17), G3=3 (3.26)	71 (77.17)
Nausea	33(33.33) G1=32 (32.32), G2=1 (1.01)	66 (66.67)
Vomiting	16(16.16) G1=14 (14.14), G2=2 (2.02)	83 (83.84)
Diarrhea	64(64.65) G1=60(60.61), G2=4 (4.04)	35 (35.35)
Proctitis	55 (55.56) G1=52 (52.52), G2=3 (3.03)	44 (44.44)
Cystitis	49 (49.49) G1=45 (45.45), G2=4 (4.04)	50 (50.51)

** 17 patients from anemia and **7 patients from thrombocytopenia were excluded for the analysis (see text).*

DISCUSSION

Radiation doses required for tumor eradication in the management of uterine and cervical cancer usually exceed the tolerance of the normal structures that surround the tumor, leading to toxicity both acute as well as late that affects patient's quality of life. Therefore, evaluation of the toxicity has been a part of good clinical trials. There have been trials that specifically focused on toxicity as a result of radiotherapy. Vaz *et al*. reported the incidence of acute toxicity as high as 93.5% in women with gynecological cancers who underwent pelvic radiotherapy.[11] In this study, most common acute reactions (75% - 87%) occurred in the gastrointestinal system with 23% having grade 1 and 64% grade 2 toxicity.[11] This study also showed gastrointestinal toxicities especially diarrhea (64.6%) and proctitis (55.5%) as most frequently observed toxicities. Jereczek-Fossa *et al*. also reported that gastrointestinal symptoms were the most common complaints, i.e. 76% in pelvic radiotherapy for endometrial cancer.[15]

Table III: Stratification of toxicities by the patients demographic and treatment characteristics.

Toxicity	Sites		Chemotherapy		Surgery		Stage		RT dose		Age			p-value
	Uterus	Cervix	Yes	No	Yes	No	Early	LA[a]	<60Gy	> 60Gy	<60 years	>60 years	p	
	n=58	n=41	n=35	n=64	n=74	n=25	n=43	n=56	n=54	n=45	n=57	n=42		
Anemia**	9	22	21	10	14	17	7	24	10	21	17	14	P=0.4	<0.001
Neutropenia	3	18	18	3	3	18	4	17	2	19	14	7	P=0.4	<0.001
Thrombocytopenia*	1	20	19	2	3	18	3	18	1	20	13	8	P=0.4	<0.001
Nausea	13	20	20	13	17	16	11	22 (p=0.15)	14	19 (p=0.09)	20	13	P=0.67	<0.001
Vomiting	5	11	11	5	8	8	2	14	5	11	11	5	P=0.0	<0.05
Diarrhea	37	27	24	40	44	20	24	40	32	32	32	32	P=0.03	NS ***
Proctitis	32	23	22	33	39	16	21	34	27	28	36	19		NS
Cystitis	27	22	19	30	37	12	22	27	22	27	P=0.0	28	21	NS

** 7 patients from thrombocytopenia and **17 patients from anemia were excluded for the analysis (see text), *** NS=p >0.05; [a] Locally advanced(FIGO stage > II).*

Peters *et al*. found similar results, in patients with cervical cancer who underwent pelvic radiotherapy, diarrhea in 55% (G1-2:48%, G3-4:6%), nausea in 29.5% (G1-2:27.7%, G3:1.8%) and vomiting in 12.5% (G1-2: 10.7%, G3:1.8%).[9] However, in this study no grade 3 or 4 toxicity was observed.

The second most common toxicity in this study was urinary toxicity, i.e. 49.5%, (45.5% grade 1 and 4.04% grade 2). Jereczek-Fossa *et al*.[15] reported urinary toxicity to be 41.3% (21% grade 1 and 20% grade 2) that is consistent with the present finding. However, Vaz *et al*. reported higher frequency of urinary toxicity, i.e. 78% (26.5% grade 1 and 50.6% grade II) however; but reason for that was not defined.[11] Another phase III trial of pelvic RT after surgery by Keys reported 30% urinary toxicity (26% G1 and 8% G2).[18]

Kirwan *et al*. in a systematic review reported incidence of hematological toxicity in radiotherapy alone arm, anemia in 33% (29% grade 1 - 2 and 4% grade 3 - 4), neutropenia in 47.9% (40% grade 1 - 2 and 7.9% grade 3 - 4) and thrombocytopenia in 10.4% (Grade 1 - 2:10%, G3-4:0.4%).[14] However, the authors here observed lower hematological toxicity in radiotherapy alone arm, anemia in 19.6%, neutropenia in 4.6% and thrombocytopenia in 3.4% that might be due to less radiation dose in the postoperative group to which majority of the patients belonged.

Introduction of concurrent chemotherapy with radiation in the management of cervical cancer resulted in improved disease outcome.[6] However, these benefits are achieved at the expense of increased acute as well as late toxicity. Roberts *et al*. reported the interim result of a phase III trial in which patients with cervical cancer were randomized to concurrent chemoradiotherapy versus radiotherapy alone. He found that chemoradiotherapy was associated with increased toxicity leucopenia 44 - 82%, nausea/vomiting from 36.6% to 46.2%, respectively.[19] The authors also observed same finding in this study in which patients, who were treated with definitive intent, had cervical cancer and in advanced stage developed more toxicity because of the use of chemotherapy along with RT in their management. However, Farrukh *et al*. shared experience of combined modality in cervical cancer management from single institution. He reported acceptable toxicity (diarrhea 33%, vomiting 12.5%, cystitis 12.5-29% and proctitis 8%).[20] Moreover, in this study, acute and late side effects were not separated. A Cochrane review showed that addition of chemotherapy to RT significantly increased the rate of grade 1 and 2 hematological, gastrointestinal and genitourinary toxicity. It resulted in 29% increase in the risk of leucopenia (OR = 1.29, 95% CI 1.08-1.53, p=0.004) up to a greater than 3-fold increase in the risk of nausea and vomiting (OR=3.09, 95% CI 2.27-4.21, p < 0.00001).[21]

Radiotherapy in patients who had abdominopelvic surgery has increased risk of acute as well as late toxicity. This might be due to the postoperative anatomical changes such as increased volume of intestine in the pelvis, adhesion of the bowel to the surrounding structures resulting in reduced motility, therefore, more exposure to radiotherapy. Also approximation of bowel and urinary bladder to the radioactive source during brachytherapy increases the risk. Likewise, typical post-surgery complications like bladder dysfunctions and infection can confound the evaluation of post RT bladder toxicity.[22] Keys *et al*. reported the acute toxicity of pelvic RT after surgery in endometrial cancer patients. The incidence of hematological, gastrointestinal and urinary toxicity were found to be 35.3% (G1-2=35%, G3=0.5%), 68% (G1-2=63%, G3 and 4=5%) and 30% (G1-2=30%, G3=0%) respectively as compared to RT alone as 9.9% (G1-2=9.9%, G3=0.9%), 7% (G1=5%, G2=2%), 7.9% (G1=4.5%, G2=3.4%) respectively with statistical significance (p < 0.001).[18] However, the authors did not find surgery to be a predictor of increase acute toxicity in the present study which is consistent with the finding of Jereczek-Fossa *et al*.[15]

Age is an important predictor of acute RT induced morbidity although literature appears to be divided regarding toxicity profile in elderly patients. Various studies like those of Mitchell *et al*. and Sakuria *et al*. reported an equivalent overall outcome as compared to younger patients with acceptable toxicity in selected elderly patients.[23] Laurentius *et al*. found worse tolerance of CCRT in elderly patients > 60 years requiring intensive monitoring and treatment protocol amendment due to severe acute toxicity.[24] This study also showed similar trends of increased toxicity in women aged > 60 years, however, it was limited to lower gastrointestinal system (diarrhea and proctitis) only.

Jereczek-Fossa *et al*. also found that higher radiotherapy dose and age were important determinant of acute normal tissue reactions both in univariate as well as multivariate analysis.[15] Whereas, FIGO stage failed to show any relation. In this study, the authors observed increased toxicity by increasing the RT dose. Moreover, as the FIGO stage advances it translates into increased toxicity which might be due to the increased RT dose and addition of chemotherapy.

Recent advancement in radiotherapy techniques such as 3D-conformal radiotherapy, improved immobilization devices, treatment verification with portal imaging and IMRT (intensity modulated radiation therapy) show promising result, in reducing RT induced toxicity. However, certain investigator have reservation against IMRT use due to inhomogeneity and higher integral dose.[25]

There are certain limitations of this study. Firstly, accurate comparison of radiotherapy complications from literature is difficult because of various reporting methods along with difference in radiotherapy and

chemotherapy schedules and doses. Secondly, this was only a single tertiary care center study so the results may differ from the centers with limited resources.

CONCLUSION

The frequency and severity of acute toxicity of pelvic radiotherapy in women with gynecological cancer was found intermediate to high. Gastrointestinal toxicity was the most frequently observed toxicity followed by urinary and hematologic toxicity.

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