Original Article

Treatment Related Toxicity in Gynecological Malignancies after Conventional Radiotherapy

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ABSTRACT

Objective: To determine treatment related toxicity in gynecological malignancies after conventional radiotherapy.
Study Design: Descriptive study
Place and Duration of Study: This study was conducted at the Department of Radiation Oncology, Atomic Energy Medical Centre, Jinnah Post Graduate Medical Centre, Karachi from January 2017 to December 2018.
Materials and Methods: The study includes Patients who received chemotherapy, assessed before commencement of radiotherapy, during and at the end of treatment for frequency and severity of sides effects and evaluated according to toxicity proforma, based on RTOG/EORTC and CTC version 4 criteria.
Results: Total 97 patients with mean age 48.55±8.44 years. The adjunctive treatment was given to 57patients and definitive treatment to 40 patients. The results of comparison of gastrointestinal and urinary toxicity with age and marital status showing statistically significant difference between the nausea condition with age. i.e p-value=0.001 and between the nausea condition with marital status of the patients i. e p-value=0.025. Comparison of gastrointestinal and urinary toxicity with stages of cancer showing p-value=0.370, 0.144, 0.969 & 0.863 respectively. Statistically significant difference between the Proctitis with stages of cancer i.e. p-value=0.007. Dermatological and hematological toxicity with chemotherapy showing statistically significant difference between the chemotherapy with neutropenic patients i.e p-value=0.011.
Conclusion: Study concluded that nausea is associated with age and marital status however neutropenia is more prevalent in patients received chemotherapy. Women with advanced gynecological cancers receiving radiotherapy are more prone to develop proctitis than early stage gynecological cancers interestingly stage of cancer is not associated with dermatological and hematological toxicity.

Key Words: Gynecological cancer, Pelvic Radiotherapy, Gastrointestinal

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INTRODUCTION

Gynecological cancers, known to be one of the most common cancers in women in developing and developed world, comprise of endometrial, cervical and vaginal cancers[1,2]. Endometrial cancer is the most common gynecologic malignancy and cervical cancer is the second most common amongst women worldwide, especially affecting developing and underdeveloped countries. Vaginal cancers are rarely seen and comprises of 1-2 % of gynecological malignancies.

For Endometrial cancer surgery is a recommended treatment but in inoperable cases radiotherapy has been used as an effective treatment for loco-regional control and long term progression free survival. Adjuvant radiotherapy and chemotherapy is recommended for high risk group.

For cervical cancer treatment surgery is usually reserved for lower stage disease. Postoperative pelvic radiotherapy with chemotherapy and brachytherapy is offered to high risk patients.[3]

For vaginal cancers treatment depends on stage of disease, in early stage vaginal cancer surgery is recommended, radiotherapy is offered to high risk group, while in advanced stages pelvic radiotherapy and vaginal brachytherapy is recommended. Cisplatin based concurrent chemotherapy may be added to radiotherapy

Radiation to pelvic region is an integral part of the curative treatment of gynecologic malignancies. In spite of all the precisions and precautions during radiation therapy, the adjacent healthy tissues do get radiation induced damage resulting in treatment related toxicity that affect the quality of life; along with being a predictor of late toxicity[4]. The skin, urinary and gastrointestinal systems are the main sites of radiation induced pelvic complication while hematologic for chemotherapy. Literature review on early morbidity

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after both radiotherapy and chemotherapy has shown frequency and severity of acute hematological, urinary and gastrointestinal toxicity.

Grade 1 and 2 skin reactions are common in gynecologic radiotherapy with an incidence of 10-50%. This has resulted in the development and implementation of scoring systems designed for radiotherapy, like the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system (RTOG/EORTC), and chemotherapy, Common Toxicity Criteria version 4.0 (CTC version 4.0). In our study, grading used for toxicity is derived from both toxicity criteria system.

Intensity Modulated Radiotherapy (IMRT) is an attractive option as compared with traditional 2D of 3D radiotherapy in treatment of gynecological cancers[5]. It significantly reduces the volume of rectal wall, bladder and bowel irradiated in gynecologic patients. As shown by the study done by Kunogi H, patients with preexisting renal dysfunction IMRT should be considered with IMRT standard dose of radiation could be given to even elderly patients (70 years and older) with minimum toxicity (grade 2 toxicity 68%)[6].

In western countries incidence and severity of acute dermatological, hematologic, urinary and gastrointestinal toxicity is as high as 40-80% in gynecological cancer patients undergoing pelvic radiotherapy. We aimed to determine the frequency and severity of acute dermatological, hematological, gastrointestinal and urinary toxicity in pelvic radiotherapy in our population as there is no local data available that specifically addresses it therefore help us to decide whether frequency and pattern of severity of acute toxicity in our patient is same as in west or not so that appropriate strategies could be developed for prevention and management of these toxicities. Effective strategies and Treatment planning with IMRT optimization may decrease the risk of toxicity.

Weekly blood counts are routinely obtained. Chemotherapy is typically held when the neutrophil count decreases below 1500/μL. RT is typically held when the neutrophil count approaches 500/μL to 1000/μL. Radiation therapy is typically continued until the counts fall below 40,000/μL. Despite uncertainty, the standard recommendation for patients with cervical cancer is to transfuse to maintain a hemoglobin level above 10 mg/dL for patient quality of life and treatment tolerance in addition to the potential impact on outcomes[7].

MATERIALS AND METHODS

A descriptive study done at Department of Radiation Oncology, Atomic Energy Medical Centre, Jinnah Post Graduate Medical Centre, Karachi from January 2017 to December 2018 after permission from Ethical review committee with ERC no. 3(131)12013.

Taking the minimum value of severity 40%[11] to get maximum sample size, with a bound on error of 0.10 (10%) with a power of 0.8, an alpha significance level of 0.05 with a 95% Cis, a sample of at least 97 will require. Therefore, a sample of 97 patients will be targeted to cover both the objectives with Non probability consecutive sampling.

Patients with uterine, cervical cancer of any site (body, fundus, anterior and posterior lips)and vaginal cancers (primary not secondary) and size of 2cm or more planned for radical (with curative intent) radiotherapy, of FIGO stage I-IVA, with a minimum dose of 45 Gray in 25 fractions through external beam +/- brachytherapy dose 5-8 Gy in 3 or more fraction in adjuvant (after surgery) or definitive (without surgery as primary modality of treatment) setting with or without chemotherapy (decided by medical oncologist).

Patients with Histopathologically proven Ovary, Fallopian tube, and Vulvar cancer, on palliative treatment (complete cure of diseases not possible), history of prior radiotherapy in the same region, History of inflammatory Bowel Diseases (increase the toxicity of gastrointestinal toxicity) and Fistula (Rectal, Urinary) and patients with Age less than 35 years or more than 65 years were excluded from the study. All analyses were conducted by using the statistical package for social science SPSS.

RESULTS

In our study total 97 patients with mean age was 48.55±8.44 years (Age range 35-65 years). The married patients were 87(89.7%) and unmarried patients were 10(10.3%). 10(10.31%) patients were with no parity, the patients with parity one were 24(24.74%), the patients with parity two were 23(23.71%), parity three patients were 18(18.56%) and the parity four patients were 22(22.68%). the uterine cancer was diagnosed in 33(34%) patients, cervical cancer was diagnosed in 39(40.2%) and the vaginal cancer diagnosed in 25(25.8%) patients. The study results showed that the stage I patients were 25(25.8%), stage II patients were 26(26.8%), stage III & IV patients were 23(23.7%). In this study the adjunctive treatment was given to 57(58.8%) patients and definitive treatment was given to 40(41.2%) patients. In this study the chemotherapy was given to 44(45.36%) patients and it was not given to 53(54.64%) patients. The mean value of radiotherapy of the patients was 72.32±16.96.

In our study, frequency distribution of Toxicity seen as Dry skin in 43(44.3%) patients, maculo popular rash in 46(47.4%) patients, anemia 54(55.7%) patients, neutropenia 49(50.5%) patients and cystitis in 48(49.5%) patients.

The frequency distribution of gastrointestinal toxicity shows nausea in 55(56.7%) patients, vomiting in 54(55.7%) patients, diarrhea in 47(48.5%) patients and the proctitis was noted in 57(58.8%) patients.

When comparison of dermatological and hematological toxicity with age done, it showed Dry skin patients were 43 [≤ 50 years=26, >50 years=17], macular rash patients were 46 [≤ 50 years=25, >50 years=21], Anemic patients were 54[≤ 50 years=29, >50 years=25] and the neutropenic patients were 49 [≤ 50 years=30, >50 years=19]. Statistically insignificant difference was found between the dermatological and hematological toxicity with age. i. e p-value=0.504, 0.657, 0.504 & 0.364 respectively.

The results of comparison of gastrointestinal and urinary toxicity with age and marital status respectively showing statistically significant difference between the nausea condition with age. i. e p-value=0.001 and between the nausea condition with marital status of the patients. i. e p-value=0.025

Table No.1: Comparison of gastrointestinal and urinary toxicity with stages of cancer

		Stages		Total	p-value
		Stage I	>stage I		
Nausea	Yes	11	44	55	0.137
	No	14	28	42	
Vomiting	Yes	13	41	54	0.668
	No	12	31	43	
Diarrhea	Yes	10	37	47	0.326
	No	15	35	50	
Proctitis	Yes	9	48	57	0.007
	No	16	24	40	
Cystitis	Yes	12	36	48	0.863
	No	13	36	49	

Table No.2: Comparison of dermatological and hematological toxicity with chemotherapy

		Chemotherapy		Total	p-value
		Yes	No		
Dry skin	Yes	22	21	43	0.306
	No	22	32	54	
Maculo rash	Yes	19	27	46	0.446
	No	25	26	51	
Anemia	Yes	20	34	54	0.065
	No	24	19	43	
Neutropenia	Yes	16	33	49	0.011
	No	28	20	48	

However the comparison of dermatological and hematological toxicity with stages of cancer showed Statistically insignificant difference found between the dermatological and hematological toxicity with stages of cancer i. e p-value=0.370, 0.144, 0.969 & 0.863 respectively. Table#1 shows comparison of gastrointestinal and urinary toxicity with stages of cancer showing p-value=0.370, 0.144, 0.969 & 0.863 respectively. Statistically significant difference between the Proctitis with stages of cancer i.e. p-value=0.007. Similarly Table#2 shows comparison of dermatological and hematological toxicity with chemotherapy showing Statistically significant difference between the chemotherapy with neutropenic patients i. e p-value=0.011. Table#3 shows comparison of gastrointestinal and urinary toxicity with chemotherapy. Statistically insignificant difference was found between the gastrointestinal and urinary toxicity with treatment. i.e. p-value=0.665, 0.836, 0.781, 0.086 & 0.258 respectively.

Table No.3: Comparison of gastrointestinal and urinary toxicity with chemotherapy

		Chemotherapy		Total	p-value
		Yes	No		
Nausea	Yes	26	29	55	0.665
	No	18	24	42	
Vomiting	Yes	25	29	54	0.836
	No	19	24	43	
Diarrhea	Yes	22	25	47	0.781
	No	22	28	50	
Proctitis	Yes	30	27	57	0.086
	No	14	26	40	
Cystitis	Yes	19	29	48	0.258
	No	25	24	49	

DISCUSSION

This study was done to determine the frequency and severity of acute dermatological hematological, urinary and gastrointestinal toxicity of pelvic radiotherapy in women with gynecological cancer. Approximately 94,890 women will be diagnosed with gynecologic cancer in the United States in 2014. Although multimodality therapy may be curative, morbidity because of treatment presents a significant concern to patients, health care providers, and society[9]. In 2010, the American Cancer Society (ACS) has estimated that 12,200 cases of uterine cervical cancer will be diagnosed and 4210 deaths will occur from the disease in the United States[10].

In our study the dermatological toxicity like dry skin was noted in 43(44.3%) patients, maculo popular rash was noted in 46(47.4%) patients. Hematological toxicity like anemia and neutropenia was noted in 54(55.7%) & 49(50.5%) patients respectively. urinary toxicity cystitis was found in 48(49.5%) patients. Similarly gastrointestinal toxicity like nausea, vomiting and diarrhea was noted in 55(56.7%), 54(55.7%) & 47(48.5%) patients respectively. One prospective trial demonstrated that approximately 30% of postoperative patients with endometrial cancer who received radiation therapy (RT) experienced acute diarrhea, which persisted in approximately 10% of patients up to 5 years after treatment[11].

Another study on cancer[12] studied cancer incidence by age group and gender for the population of Karachi Division by analyzing the Karachi Cancer Registry data of 2017-19 and found corpus uteri malignancy more common than Cervical cancer in females.

Literature review on early morbidity after both radiotherapy and chemotherapy has shown frequency and severity of acute hematological toxicity anemia 40% (Grade1 50%, Grade2 40%), neutropenia 40-74%(Grade1 42%, Grade2 40-49.5%), urinary 40-74.5%(Grade1 40%, Grade2 50.6%) and gastrointestinal toxicity nausea 60-70%(Grade1 45%, Grade2 42%), vomiting 70%(Grade1 39.6%, Grade2 42.9%), diarrhea 67-80%(Grade1 54%, Grade2 43-64%) and proctitis 40-76%(Grade1 40%, Grade2 43-57%)[13,14,15].

Severe urinary tract toxicity is relatively rare during treatment (range, 2%-5%). In particular, when adjuvant therapy is given with IMRT technique, the urinary tract complaints are less frequent.

The reported rates of major urologic complications (grades 3-4) after RT for cervical cancer range from 1.3% to 14.5% at 3 years and most commonly include ureteral stricture and hemorrhagic cystitis. Hemorrhagic cystitis may be treated with laser fulguration of ectatic vessels, intravesical alum or formalin, or hyperbaric oxygen[16].

Late toxicities are less common Ranjan N et al[17] found that CTCAE grade 3 diarrhea ranges from 0·23 to 2·13.

CONCLUSION

Our study concludes that nausea is associated with age and marital status in gynecological cancer patients receiving conventional radiotherapy however neutropenia is more prevalent in those who receive chemotherapy too. Women with advanced gynecological cancers receiving conventional radiotherapy are more prone to develop proctitis than early stage gynecological cancers, Interestingly, stage of cancer is not associated with dermatological and hematological toxicity.

Author's Contribution:

Concept & Design of Study:	Uzma Gul
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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