ACUTE TOXICITY PROFILE OF CERVICAL AND UTERINE CANCER PATIENTS TREATED WITH CHEMORADIATION: A 10-YEAR REVIEW

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ABSTRACT

Background: Radiation therapy is integral to treating many gynaecologic cancers.
Objective: We sought to determine the frequency and severity of acute toxicity in patients who had pelvic radiotherapy for cervical and uterine cancers.
Methods: A retrospective study of all women who had pelvic radiation for cervical and uterine cancers at Usmanu Danfodiyo University Teaching Hospital, Sokoto, Nigeria, from January 2010 to December 2019.

All cases of cervical and uterine cancers that met the inclusion criteria were studied. A structured pro forma was used to extract relevant data from patients' case files and treatment cards. Information obtained included biodata, site and size of tumour, dose of radiation prescribed to the pelvis, date of completion of external beam radiotherapy (EBRT) as well as dose of radiation received from EBRT, cycles of chemotherapy, the cytotoxics used and dose, interval between both therapies, side effects during and after EBRT (follow-up), disease status on follow-up period. Toxicity profile was recorded based on Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) Late Radiation Morbidity Scoring Scheme.

Result: Most patients seen in the study were of the age group 41-50 years, with cervical cancer being by far the commoner of the two (2) gynaecological cancers treated with chemoradiation in this study. Majority of the cases were diagnosed at stage IIIA. The most prescribed radiation dose from EBRT was 50Gy in 25 fractions. The study showed that acute toxicity had a similar pattern as compared to studies conducted in other regions of the world.

The acute toxicity profile of pelvic radiotherapy in women with cervical and endometrial cancer was found to be mainly mild to moderate. Gastrointestinal toxicity was the most frequently observed toxicity, followed by urinary and hematologic toxicity. In this study, most common acute reactions (64.9%) occurred in the gastrointestinal system, with 60.6% having grade 1 and 4.3% grade 2 toxicity for cervical cancer patients, while those with endometrial cancer recorded 50% grade 1 and 3% grade 2 toxicity.

Conclusion: The frequency and severity of acute toxicity of pelvic radiotherapy in women with gynaecologic cancers were found to be mild to moderate.

Keywords: Gynaecological malignancies, Radiotherapy, Chemotherapy, Acute toxicity, Cervical cancer, Endometrial cancer, Haematological toxicity, Gastrointestinal toxicity, Urinary toxicity

INTRODUCTION

Gynaecological cancers, one of the most prevalent cancers in women, mostly consist of uterine and cervical cancers and continually remain a significant public health burden worldwide. Other cancers that make up this group of malignancies include: Ovarian/ fallopian/ vulvo-vaginal cancers.[1,2] Similar to malignancies in other anatomical sites, the majority of women with cervical and uterine cancers in underdeveloped countries typically present with locally advanced disease for a variety of reasons.[3] Over the years, the treatment for locally advanced cervical and endometrial malignancies has gradually advanced from External Beam Radiotherapy (EBRT) alone to EBRT plus brachytherapy boost to EBRT and brachytherapy with concomitant cytotoxic chemotherapy.[4]

Pelvic radiation is thereby a crucial component of the curative management of gynaecologic cancers, either alone or in combination with surgery and/or chemotherapy. Despite all the improved precision and safety measures used during radiation therapy planning, nearby healthy tissues do get harmed by the toxic effect of radiation, leading to treatment- related toxicity that has a significant impact on the patient's quality of life, treatment outcome and overall survival. Understanding the frequency and severity of these toxicities is crucial for informed decision-making amongst patients and providers, optimising treatment planning and developing effective mitigation strategies. These toxicities may be acute or chronic. Acute radiation toxicity is defined as adverse effects occurring during or within three months of exposure to radiation, and chronic side effects are defined as those occurring beyond 3 months.[5] However, despite the importance of this topic, there is paucity of data in Nigeria, more especially in the Northern part. Because of this, the

prevalence of acute toxicity is not well understood in our population.[1]

The aim of this study was to determine the acute toxicity profile of pelvic radiotherapy in patients treated for cervical and uterine cancers in our population.

MATERIALS AND METHODS

This is a retrospective study in which all patients aged 18 to 65 years with histologically confirmed cervical and uterine cancers treated with at least 50Gy of external beam radiotherapy, irrespective of other treatment status, were included over a ten-year period from January 2010 to December 2019. Despite Brachytherapy being an integral part of the treatment for these cancers (without which the treatment is deemed incomplete), toxicities from brachytherapy were not included because all the patients were referred to other centres. Ethical approval was obtained from the hospital's ethics and research committee before commencement. Information was obtained from all case files and radiation treatment cards and entered into a structured proforma. The study was completed within 3 months.

Data cleaning, entry, processing and analysis were done using IBM Statistical Package for the Social Sciences Version 21.0 statistical software. Quantitative variables were analysed using appropriate measures of central tendency and dispersion, such as mean and standard deviation. Categorical variables, such as the occupation of respondents, were summarised using frequencies and percentages.

RESULTS

A total of three hundred and ninety (390) patients were treated with chemoradiation for various gynaecological cancers over the period of ten years at the Radiotherapy and Oncology Department of Usmanu Danfodiyo University Teaching Hospital, Sokoto. Three hundred and fifty-one (351) patients were eligible for the study.

Table 1: Socio-demography of patients who had chemoradiation at Usmanu Danfodiyo University Teaching Hospital, Sokoto, January 2010 to December 2019

Variables	Frequency (%)	Percentage (%)
Age		
<40	98	27.9
41-50	168	47.5
51-60	82	23.4
>60	3	0.9
Ethnicity		
Hausa/Fulani	171	48.7
Yoruba	47	13.4
Igbo	107	30.5
Others	26	7.4
Occupation		
Civil Servant	54	15.4
Self Employed	26	7.4
Housewife	145	41.3
Trading	126	35.9
Marital Status		
Single	28	8.0
Married	152	43.3
Divorced/Separated	153	43.6
Widowed	18	5.1
Parity		
<4	108	30.8
>4	243	69.2
Highest Level of Education		
No Formal Education	9	2.6
Arabic	36	10.3
Primary	18	5.1
Secondary	190	54.1
Tertiary	98	27.9
Age (Years), Mean ± Sd: 45.3 ± 6.3		

Most of the patients seen in the study were in the age group 41-50 years. Majority of the cases were diagnosed at stage IIIA. Cervical cancer accounted for 85.5% of cases. It was by far the commoner of the two (2) gynaecological cancers treated with chemoradiation in this study. The most prescribed radiation dose from EBRT was 50Gy in 25 fractions. The distribution of initial symptoms of the endometrial and cervical cancer patients is shown in Figures 1 and 2, respectively.

Table 2: Prevalence of acute toxicities at six weeks post-treatment in patients who had chemoradiation at Usmanu Danfodiyo University Teaching Hospital, Sokoto, January 2010 to December 2019

Variables	Cervical (n=300) Frequency (%)	Endometrial (n=51) Frequency (%)
White Blood Cells (x 10^9/ L)		
Normal	188(62.7)	80(62.5)
3-<4	67(22.3)	14(27.5)
2-3	30(10)	3(5)
1-2	15(5)	3(5)
Platelets		
Normal	255(85)	43(91.5)
Mild	30(10)	5(2.5)
Moderate	6(2)	2(4)
Severe	9(3)	1(2)
Neutrophils		
1.5-<1.9	45(15.0)	9(17.6)
1-<1.5	15(5)	1.53(3)
0.5-1	6(2)	1.02(2)
Haemoglobin (G/Dl)		
Normal	237(79)	11(79.4)
9.5-11	45(15.0)	9(17.6)
<9.5-7.5	12(4)	1.02(2)
<7.5-5	6(2)	0.51(1)
SKIN		
None	218(72.7)	35(68.6)
Mild	82(27.3)	16(31.4)
Gastrointestinal		
Diarrhea		
None	154(51.3)	23(47)
Mild	136(45.3)	26(50)
Moderate	10(3.3)	2(3)
NAUSEA		
None	250(83.3)	40(78.4)

Mild	40(13.3)	6(11.7)
Moderate	10(3.3)	5(9.8)
VOMITING		
None	270(90)	40(78)
Mild	20(7)	7(14)
Moderate	10(3)	4(8)
ABDOMINAL PAIN		
None	222(74)	35(68)
Mild	50(17)	12(24)
Moderate	28(9)	4(8)
PROCTITIS		
None	250(83.3)	40(78)
Mild	45(15)	10(20)
Moderate	5(1.7)	1(2)
URINARY		
None	131(43.9)	39(78.07)
Mild	125(41.5)	10(20.4)
Moderate	4(2.4)	2(1.53)

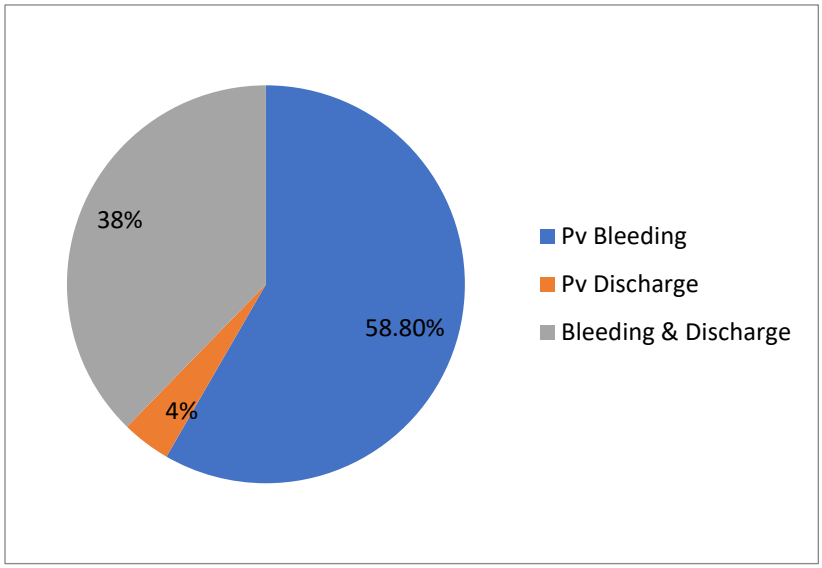

Figure 1: Pie Chart Showing the Distribution of Symptoms at Diagnosis of Endometrial Cancer

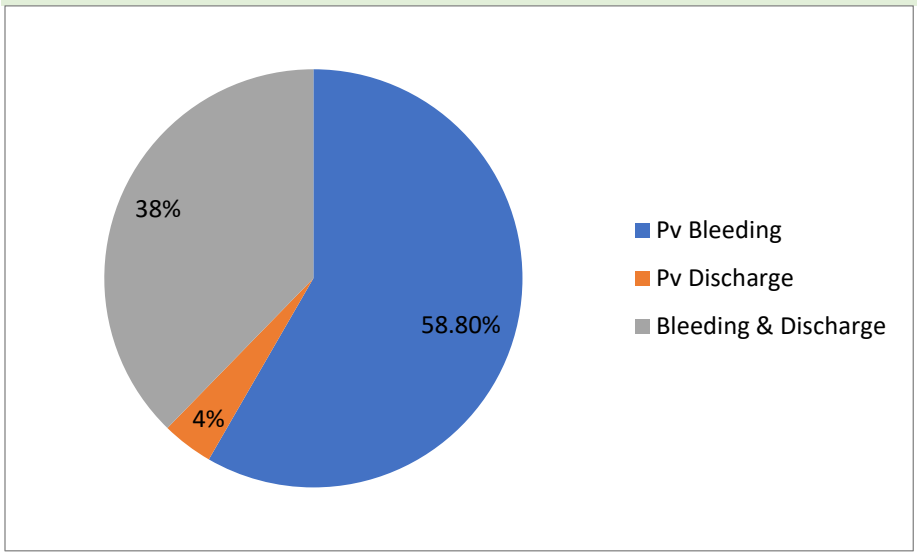

Figure 2: Pie Chart Showing the Distribution of Symptoms at Diagnosis of Cervical Cancer

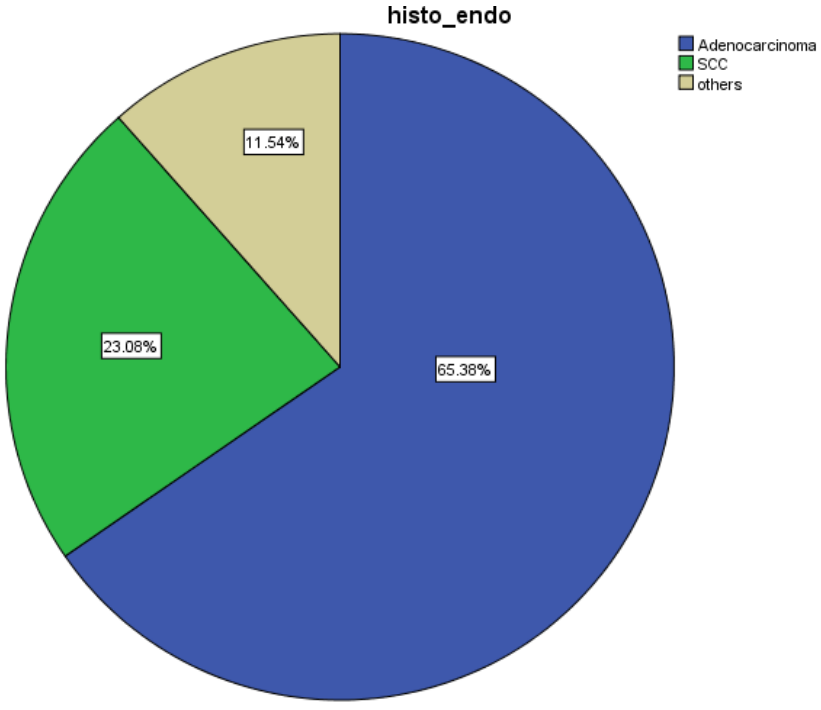

Figure 3: Pie Chart showing the histologic pattern of endometrial cancer

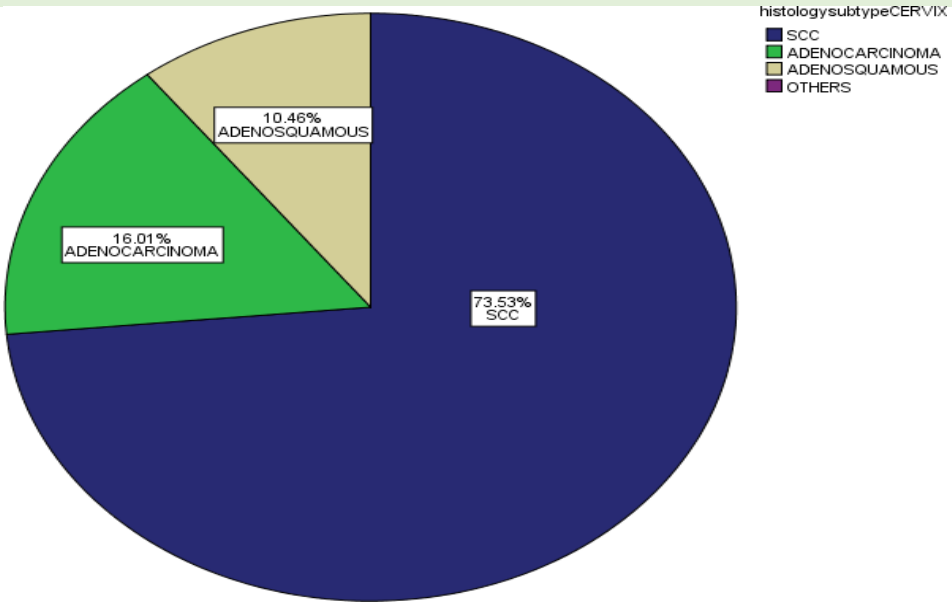

Figure 4: Pie Chart showing histologic patterns of cervical cancer patients

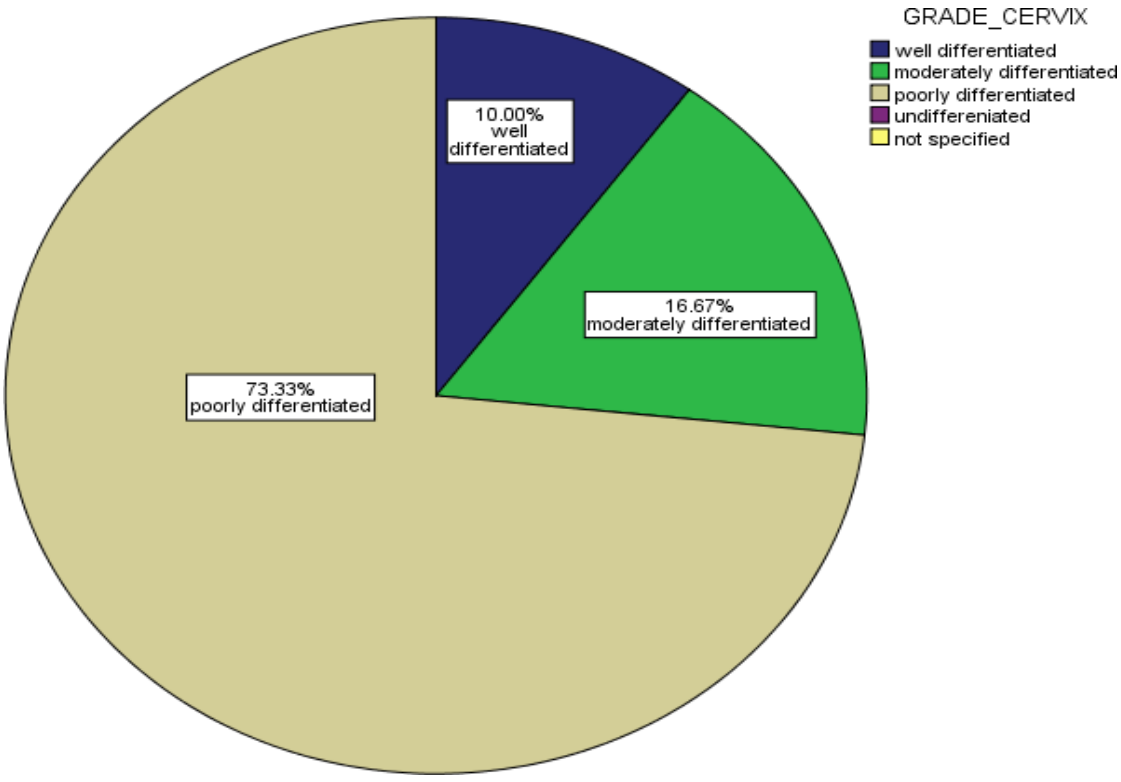

Figure 5: Pie Chart Showing the Grade of Cervical Cancer

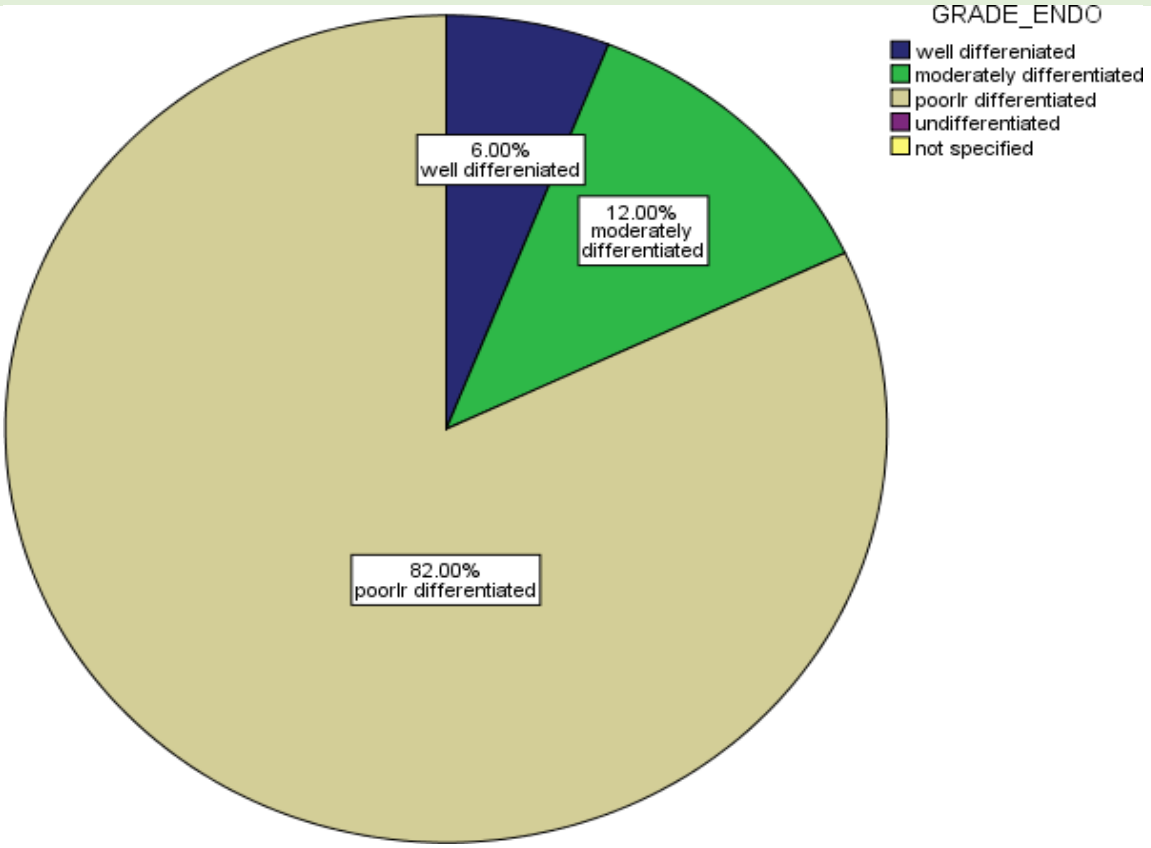

Figure 6: Pie Chart showing levels of differentiation for endometrial cancer

The frequency and severity of acute toxicity of pelvic radiotherapy in women with cervical and endometrial cancer were found to be mild to moderate. Gastrointestinal toxicity was the most frequently observed toxicity, followed by urinary and hematologic toxicity. In this study, most common acute reactions (64.9%) occurred in the gastrointestinal system, with 60.6% having grades 1 and 4.3% grade 2 toxicity for cervical cancer patients, while those with endometrial cancer recorded 50% grades 1 and 3% grade 2 toxicity. Diarrhea was seen in 45% (G1-2:48%), nausea in 29.5% (G1-2: 27.9%, G3:1.6%) and vomiting in 10.5% (G1-2: 8.7%, G3:1.8%). This is depicted in Table 2.

The histological subtypes of the patients are shown in Figures 3 and 4.

Poorly differentiated adenocarcinoma was seen in 82% of endometrial cancer patients, while 73.3% of cervical cancer patients had poorly differentiated squamous cell carcinoma. This is shown in Figures 5 and 6, respectively.

DISCUSSION

The commonest age group was 41-50 years, which constituted 47.9% of the total patients, with a mean age of 45.3±6.3 years. This is in keeping with most epidemiological studies on gynaecological cancers in Nigeria.[6] Several other socio-demographic studies on various

cancers in North-western Nigeria have shown the commonest age range diagnosed with malignancies to be 50-59 years.[6] Also, according to cancer registry data, the mean age of cancer diagnosis in Nigeria was 51.1 years.[7] Majority of the patients were multiparous, with a frequency of 69.2%. This was similar to data from other published studies in Nigeria that showed cervical cancers, vaginal and endometrial cancers to be far commoner in multiparous women.[8] A total of 45 patients, representing 11.6% of all the patients studied, had no formal education. This is in keeping with the already established educational status of majority of the patients in Northern Nigeria who do not have any level of formal education.[9]

The commonest organ affected by a tumour in this study was the cervix, as seen in 85.4% of the cases. This is in keeping with all the epidemiological studies on gynaecological malignancies in Nigeria, which showed cervical cancer to be the commonest gynaecological malignancy.[10, 11] Malignancies of epithelial cell origin are the most common forms of cancer seen in the genital tract.[12,13] Squamous cell carcinoma was the commonest histological type seen in the majority (73.5% of cervical cancer cases) of the cervical cancer patients in this study. This was followed by adenocarcinoma in 11.76% of the cases. This finding also corresponds with most other studies in this regard.[14] In a study conducted by Afro JS et al. 86.56% of the patients had squamous cell carcinoma and the remaining 13.43% had adenocarcinoma respectively which was in keeping with findings of Munoz et al.[8] In this index study, adenocarcinoma was seen to be the commonest histologic subtype in endometrial cancer, accounting for 65.38% while squamous cell carcinoma and other subtypes were seen in 23.08% and 11.54% respectively. This is in keeping with a study conducted by Banas et al, where adenocarcinoma was by far the most prevalent histology in the uterine body, accounting for 60–70% of all cancers found in the organ.[15] Majority of our cases had a poorly differentiated pattern, as seen in 74.64% of the patients. This was also the predominant histological pattern seen in the study by Matsuo et al, in which they demonstrated that poorly differentiated histologies were the commonest and also had prognostic significance.[16]

The most prevailing presenting complaints in this study were those of vaginal bleeding, which was recorded in 58% of patients with cervical and 58.8% of endometrial cancers; this was closely followed by vaginal discharge, with figures of 38% in both cervical and endometrial cancers. The presenting complaints were essentially similar to the reports in the study conducted by JN Eze et al. at Federal Teaching Hospital Abakaliki, which showed that the incidence of abnormal vaginal bleeding was marginally higher than the 55.9%–84.0% reported in literature, thus affirming that abnormal vaginal bleeding is an important sign in cervical cancer.[17]

In this study, most common acute reactions (64.9%) occurred in the gastrointestinal system, with 60.6% having grade 1 and 4.3% had grade 2 toxicity for cervical cancer patients, while those with endometrial cancer recorded 50% grade 1 and 3% grade 2 toxicity. Diarrhea was seen in 45% (G1-2:48%), nausea in 29.5% (G1-2: 27.9%, G3:1.6%) and vomiting in 10.5% (G1-2: 8.7%, G3:1.8%).

Jereczek-Fossa et al. also reported that gastrointestinal symptoms were the most common complaints, i.e. 76% in pelvic radiotherapy for endometrial cancer.[18] This is also in agreement with a study conducted by Asim et al. were most common acute reactions (75% - 87%) occurred in the gastrointestinal system, with 23% having grade 1 and 64% grade 2 toxicity.[1] Peters et al. found similar results, in patients with cervical cancer who underwent pelvic radiotherapy, diarrhoea 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%).[19] However, in this study, no grade 3 or 4 toxicity was observed. The second most common toxicity in this study was urinary toxicity, seen in 35% of the study population (41.5% grade 1 and 2.4% grade 2 in cervical cancer, while 20.4% grade 1 and 1.53% grade 2 in endometrial cancer). Asim et al. in their study reported urinary toxicity, i.e., 49.5%, (45.5% grade 1 and 4.04% grade 2), which was consistent with the present finding. Jereczek- Fossa et al. reported urinary toxicity to be 41.3% (21% grade 1 and 20% grade 2), which was consistent with the present finding.[18]

There are certain limitations of this study, being a retrospective study, some information could not be obtained from patients' case files and records. Since some of the patients were seen based on referral from other institutions, follow-up of such patients was erratic.

CONCLUSION

The frequency and severity of acute toxicity of pelvic radiotherapy in women with gynaecological cancer in UDUTH were found to be mild to moderate. Gastrointestinal toxicity was the most frequently observed toxicity, followed by urinary and hematologic toxicity.

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