Case Study

Adverse Effect after Radiation Therapy

Healthcare

Keywords: Urinary toxicity, adverse effects RTOG, pelvic radiotherapy.

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Abstract

Introduction: The objective of the study is to evaluate and analyze acute and late toxicity of GU genito-urinary tract, estimating GFR as a marker of kidney function, and investigate adverse effect of treatment according RTOG scoring system at the at 3-rd and 6-th month of treatment. Material and methods: This study is done at Clinical Center of Kosovo, Oncology Department. 75 patients are evaluated where several variables have been investigated: sex, age, type of primary malignancy, Median TD (tumor dose) evidence over 50 and above 50 Gy. At the beginning, at 3rd and 6th of the treatment patient have been followed by fulfilling in the questioner according RTOG scoring system. Chemotherapy have been employed based on primary tumor site concurrently with radiotherapi Median follow up (FU) have take 6 months. Excluding criteria: Patients with PGUM (Pre Treatment GenitoUrinary Morbidity). G0 of RTOG score at the beginning of treatment to all patients. Results: Our cohort consist of 75 patients with pelvic tumors of which 53 or 70.7% were female and 22 or 29.3% of male. The average age of the patients involved in the research was 57.5 years (SD ± 11.2 years) range 33-77 years. The average age of the female patients involved in the research was 56.1 years (DS ±11.1 years), range 33 – 77 years. The average age of the male patients involved in the research was 60.8 years (SD ±11.1years), range 37 – 74 years. Females are with 3 various types of carcinomas (cervical and endometrial) and males with only 1 (rectal). The 75 patients involved in the research 30 or 40.0% were rectal carcinomas, 28 or 37.3% were cervical carcinomas and 17 or 22.7% were endometrial carcinomas. Conclusions: No significant differences in treatment related site effects between radiotherapy and hemoradiation groups were found. In the follow up after 3 months from 75 patients involved in the research, 11 patients (14.7 %) had G1 GU toxicity that did not need any kind of treatment. 5 patients (6.7%) had G2 GU toxicity. Whereas in the follow up after 6 months 15 patients (20%) had G1 GU toxicity, 7 patients (9.3%) G2 GU toxicity and 4 patients (5.3%) had G3 GU toxicity. Compering grade of toxicity between follow up 3 and 6 months no significant differences have been appeared according RT treatment.

Introduction

The American Cancer Society estimate for 2016 in the USA tumors arising in the pelvic including uterus, cervix, rectum account for 168,260 new cases will be diagnosed[1].

Concurrent hemoradiation has improved survival of patients with cervical carcinoma and rectal carcinoma.

The development of radioactivity by Henri Becquerel in 1896 and the discovery of radium by Marie and Pierre Curie in 1898 led to a new period in medical technology[2]. Pelvic radiotherapy (RT) now plays an important role in the management of these cancers. This treatment modality has been shown to have both early and late morbidity. The radiation-induced damage to tissue architecture develops in a linear threshold model. Damage to the basement membranes of blood vessels can lead to occlusion, thrombosis and neovascularization. The atrophy and contraction of tissue results from increased proliferation of fibroblasts[3]. All these changes have the potential to cause significant urinary tract injury. Bladder damage and loss of capacity can cause significant urinary symptoms. Neovascularization is an important factor for radiation cystitis and subsequent hemorrhagic cystitis.

Replacement of the corpus spongiosum with fibrosis and subsequent occlusion of the urethral lumen is an important factor for the increased incidence of urethral strictures after RT[2].

Acute and late urinary adverse effects (AEs) are usually graded using the Radiation Therapy Oncology Group (RTOG) system, which grades AEs on a scale of 0-4.

RTOG Acute Radiation Morbidity Scoring Criteria[4]

0. No change
1. Frequency of urination or nocturia twice, pretreatment habit/dysuria, urgency not requiring medication.
2. Frequency of urination or nocturia, that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic.
3. Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage.
4. Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration or necrosis.

Materials and methods

This is a retrospective study for the patients that have been finished treatment of RT or CCRT. Follow up have been done after 3 and 6 months. This study has been done in Institute of Oncology in Prishtina, Kosovo.

Including criteria

1. Pelvic carcinomas, cervical endometrial and rectal treated based on criteria for adjuvant treatment according NCCN Guidelines version 2. 2015.

Excluding criteria:

1. Patients with PGUM (Pre Treatment Genito Urinary Morbidity).
2. Patients that in the beginning of treatment have had G score from RTOG more than 0

Our cohort consist of 75 patients with pelvic tumors of which 53 or 70.7% were female and 22 or 29.3% of male.

The average age of the patients involved in the research was 57.5 years (SD ± 11.2 years) range 33-77 years. The average age of the female patients involved in the research was 56.1 years (SD ±11.1 years), range 33 – 77 years.

The average age of the male patients involved in the research was 60.8 years (SD ±11.1years), range 37 – 74 years.

Gynecological cancer and rectal cancer were treated with adjuvant radiotherapy or concurrent radio chemotherapy depends by stage and site of cancer.

The radiation therapy technique and doses were strictly defined and identical for all regimens.

Patients have been treated by whole pelvic RT with different site of pelvic carcinomas, following the International Commission on Radiation Units and Measurements (ICRU) No.50 recommendations[5].

The clinical target volume (CTV) have been define as pelvic lymph nodes and primary tumor region and have been contoured on individual axial CT slices. The lymph node regions have been determine by encompassing the blood vessels with a 2 cm margin and based upon primary tumor site. The planning target volume (PTV) have been create expanding the CTV by 1 cm. The dose have been prescribe, to encompass at least 95% of the PTV, ranged from total dose of 45 Gy or 50 Gy, administrated in 1.8 -2 Gy per fraction delivered in 25 to 30 daily fraction. Treatment planning have been generate using the Xio software for 3D RT. Dose volume restrictions used for pelvic OARs have been described.

In the 3D CRT, whole pelvic irradiation was delivered by anterior-posterior and posterior-anterior parallel ports or a four field box technique utilizing x-ray energies of 15 MV. Plans have been based on pelvic isocentric conformal fields with energy of 15-MV and patients have been treated with a Simens linear accelerator, equipped with 80-leaf multileaf collimator. The pelvic field extended from the upper margin of L5 to the midportion of the obturator foramen or the lowest level of disease with a 3 cm margin and laterally 1.5 to 2 cm beyond the lateral margins of the bony pelvic wall (at least 7 cm from the midline). For lateral fields, the anterior border was the pubic symphysis and the posterior border was the space between S2 and S3. The fields have been modified to include areas of known tumor.

Modification as necessary to include areas of known tumor where allowed according RTOG.

Measurements for renal function before treatment were: urea, creatinine, GFR (Cockroft-Gault), urological echo and urine sediment.

CreatClear = Sex * ((140 - Age) / (SerumCreat)) * (Weight / 72)

Equation parameters such as Sex have two or more discrete male 1, female 0.85 values that may be used in the calculation[6].

After 3DCRT, patients were followed up between 3 and 6 months with. Image studies were done when specific complaints occurred.

Urinary Toxicity – acute urinary toxicity was considered three months of the end of 3DCRT, late urinary toxicity was considered after six months of the end of 3DCRT, and was graded according questioner on Table-1. Information about patient complaint was obtained by physician interview.

Questionner

Adverse Event:	Date of Treatment:	Course Number:
Date of onset:		Grade at onset:
Date of first change in grade:		Grade:
Date of next change in grade:		Grade:
Did adverse event resolve?		Yes_____ No _____
If so, date of resolution of adverse event:		
Date of last observation (if prior to recovery):		
Reason(s) observations stopped (if prior to recovery):		
Was patient retreated?		Yes_____ No _____
If yes, was treatment delayed for recovery?		Yes _____ No _____
Date of next treatment?		
Doe reduced for next treatment?		Yes _____ No _____

Follow up was done at 3 and 6 months with: urea, creatinine, GFR (Cockroft-Gault), urological echo and urine sediment, cystoscopy where needed.

Data processing was done with statistical package SPSS.

The obtained data are presented with tables and graphs. From the statistical parameters are calculated index structure, the arithmetic mean, and standard deviation, minimum and maximum values. Testing of qualitative data was done with X2 – test, quantitative data that did not have a normal distribution with the Kruskal -Wallis test and Mann - Whitney test. Testing of quantitative data that had normal distribution with One Way ANOVA and T - test .Verification of tests was made with 99.7 % confidence level ($P < 0:01$) and the reliability of 95% ($P<0.05$).

Results

Table 1. Patients involved in research by group and gender

Age (years)		Sex				Total	
		F		M			
		N	%	N	%	N	%
30-39		5	9.4	2	9.1	7	9.3
40-49		9	17.0	1	4.5	10	13.3
50-59		17	32.1	5	22.7	22	29.3
60-69		15	28.3	10	45.5	25	33.3
70+		7	13.2	4	18.2	11	14.7
In total	N	53	100.0	22	100.0	75	100.0
	%	70.7	-	29.3	-	100.0	-

Table 2. Acute toxicity of GU Tract according to the RTOG scoring system at 3 and 6 months

Gender	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
F	53	41	35	10	11	2	5	0	2	0	0
M	22	18	14	1	4	3	2	0	2	0	0

From 75 patients involved in the research, at 3 months follow up 11 patients had G1 toxicity that did not need any kind of treatment. They appear minor symptoms. 10 from them are female and 1 male. With G2 toxicity are 5 patients that needs simple outpatient management.

Whereas follow up on 6 months 15 patients had G1 toxicity, 7 patients had G2 toxicity and 4 G3 toxicity from which 3 of them have need hospitalization daily catheterization and 1 of them requiring nephroureterectomy.

Table 3. Acute toxicity of GU Tract according to group Age

Group Age	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
30-39	7	6	4	0	1	1	2	0	0	0	0
40-49	10	8	8	2	2	0	0	0	0	0	0
50-59	22	16	14	5	6	1	1	0	1	0	0
60-69	25	21	16	2	4	2	2	0	3	0	0
over 70	11	8	7	2	2	1	2	0	0	0	0

Table 4. Acute toxicity of GU Tract according site of treatment – diagnoses

Diagnoses	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
Endometrial cancer	17	13	11	3	2	1	3	0	1	0	0
Rectal Cancer	30	26	20	1	5	3	3	0	2	0	0
Cervical Cancer	28	20	18	7	8	1	1	0	1	0	0

Table 5. Acute toxicity of GU Tract according to treatment

Treatment	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
CCRT	50	39	35	8	9	3	3	0	3	0	0
RT	25	20	14	3	6	2	4	0	1	0	0

Table 6. Acute toxicity of GU Tract according to dose of treatment

Doses	No	G 0		G 1		G 2		G 3		G 4	
Follow up		3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths	3 mths	6 mths
Over 50 Gy	35	25	7	8	3	2	2	0	1	0	0
Under 50 Gy	40	34	7	3	3	3	2	0	0	0	0

Discussion

Grade 1 and 2 AEs are commonly managed with observation or medical therapy and have minimal impact on quality of life. Grade 3 and 4 AEs are considered severe. These are often managed with a procedure and have a significant impact on quality of life.

In this retrospective study, we examined the incidence of acute and late radiation-induced side effects among patients curatively treated for cervical cancer, rectal and endometrial cancer that were followed for a 6 month period of time. The results revealed that grade 2 radiation-induced side effects occurred in a relatively large proportion of patients of which the majority suffered from urinary tract toxicities.

We expect to see urinary AEs following RT for rectal cancer due to the close proximity of the rectum to the bladder, as well as its blood and nerve supply. One trial reported urinary AEs such as frequency, cystitis, incontinence, urinary retention, and ureteral stricture[7].

Conclusion

Urinary AEs can manifest long after RT, and there is a paucity of studies describing rates of these long-term AEs. It is important that the possible complications of RT are recognized by providers and properly managed.

Grade 1 and 2 are relatively frequent side effects in curatively treated patients, but are not enhanced by the addition of chemotherapy. Their negative impact on health-related quality of life stresses the importance of new radiation techniques, that can reduce side effects.

Compering grade of toxicity between follow up 3 and 6 months no significant differences have been appeared according RT treatment.

Grade 3 AEs mostly have been appeared according to locally advanced cancer and progression after treatment.

Conflict interest statement.

There is no conflict interest of author and coauthor.

The work for publication is sent only to your Journal.

Abbreviations

GFR – Glomerular Filtration Rate
AEs – Adverse Effects
OAR - Organ At Risk
RT – Radio Therapy
GU – Genito Urinary
3DCRT – 3D Conformal Radio Therapy

TD – Tumor Dose
FU – Follow Up
PGUM - Pre Treatment Genito Urinary Morbidity
SD – Standard Deviation
CCRT - Concurrent chemo-radiotherapy
Gy – Grey
CTV - Clinical Target Volume
PTV - Planning Target Volume
RTOG – Radiation therapy oncology group
NCCN – National comprehensive cancer network
ICRU - International Commission on Radiation Units and Measurements
ANOVA – Analysis of Variance statistical test
SPPS – Software Package For Statistical Analysis

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