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Comparative study between treatments related acute toxicity in patients receiving 3DCRT/IMRT as a definitive radiotherapy for localized prostatic carcinoma with assessment of quality of life in those patients

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SUMMARY

Background: Prostate cancer is a leading cause of mortality and morbidity globally. In Egypt, prostate cancer comes in the sixth rank. External Beam Radiation Therapy (EBRT) is well-established line of treatment in prostate cancer. EBRT can be delivered by many modalities including 3DCRTand IMRT. IMRT offered less gastrointestinal and genitourinary side effects and hence better health related quality of life for many patients in several studies.

Aim: Comparison between acute gastrointestinal, genitourinary, haematological toxicities, fatigue related to radiotherapy and health related quality of life in patients receiving 3D conformal radiotherapy and IMRT for localized /locally advanced prostatic cancer.

Patients and methods: This prospective study was carried out at clinical oncology departments Tanta university hospitals and Alexandria university hospitals through the period from May 2018 to May 2019 and included 30 intermediate and high risk prostate cancer patients received 2 modalities of radiotherapy divided into 2 arms. Fifteen patients received 3D conformal radiotherapy concurrent with ADT (Arm A) and 15 patients received IMRT concurrent with ADT (Arm B).

Results: IMRT resulted in significantly lower incidence of rectal pain and microscopic haematuria and dysuria and lower incidence of grade ≥ 2 diarrhoea, proctitis, rectal pain and cystitis during radiotherapy compared to 3DCRT but with little impact in overall quality of life which was better in IMRT group but without statistical significance except 6 months after radiotherapy. Conclusion: IMRT may offer lower gastrointestinal and genitourinary radiation toxicity but with no or little difference in overall health related quality of life.

Key words: prostate cancer, 3DCRT, IMRT, radiation toxicity, quality of life

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INTRODUCTION

Prostate cancer remains the most common cancer and the third leading cause of cancer mortality in men [1]. Newly diagnosed men with localized prostate cancer have several treatment options that include watchful waiting, radical prostatectomy, radiotherapy (external beam or brachytherapy), hormonal ablation and a combination of these modalities [2]. External Beam Radiation Therapy (EBRT) is a principle treatment for prostate cancer (both localized and locally advanced). Dose-escalation to the prostate was proved to enhance biochemical PFS; however, this can be on expense of more Gastrointestinal (GI) and Genitourinary (GU) adverse effects [3]

Radiotherapy related toxicities include gastrointestinal, GU toxicity, sexual dysfunction, hematological toxicity and fatigue. These treatment-related toxicities may be acute (typically within 3 months) or chronic and greatly affect quality of life.

Attempts to enhance the therapeutic range, particularly a reduction in treatment-related adverse effects, have made progress in modern RT techniques such as Intensity Modulated Radiation Therapy (IMRT) [4]. Moreover, IMRT has been shown to improve the local control and DFS in localized prostate cancer patients [5].

The main characteristic of IMRT in comparison with 3-dimensional conformal radiation therapy (3D-CRT) is the potential to escalate the dose of radiation to the prostate [6], while minimizing the radiation dose to neighbouring healthy tissues, including the rectum and bladder, therefore reducing treatment related toxicities [7].

Image Guided Intensity Modulated Radiotherapy (IG-IMRT) has created a higher accuracy of the dose delivery and consequently decreased radiation toxicity [8].

AIM

Comparison between acute gastrointestinal, genitourinary, haematological toxicities, fatigue related to radiotherapy and health related quality of life in patients receiving 3D conformal radiotherapy and IMRT for localized/locally advanced prostatic cancer.

PATIENTS AND METHODS

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The following data was collected; careful history and Clinical examination with assessment of ECOG performance status, initial clinical TNM staging according to AJCC eighth edition 2017, categorization of patients according to prognostic risk grouping from the National Comprehensive Cancer Network (www.nccn.org) risk classification depending on T stage, Gleason score and pre-treatment serum PSA.

Inclusion criteria

Patients with non-metastatic prostatic adenocarcinoma, unfavourable intermediate, high risk and very high-risk criteria with ECOG performance status ≤ 2.

Exclusion criteria

Patients with metastatic prostate cancer, history of radical prostatectomy, pathology other than adenocarcinoma eg. (neuroendocrinal tumor, sarcoma or lymphoma), ECOG performance status >2.

METHODS

Careful history and Clinical examination with assessment of ECOG performance status, initial clinical TNM staging according to AJCC eighth edition 2017, categorization of patients according to prognostic risk grouping from the National Comprehensive Cancer Network (www.nccn.org) risk classification depending on T stage, Gleason score and pre-treatment serum PSA were done.

Radiotherapy

A planning Computed Tomography (CT) simulation with (2-3 mm) slice thickness was done for all patients in a supine position with arms folded on the chest and out of field.

All patients were advised to empty bladder and drink 600 ml water (small bottle of water) 30 minutes and an enema to empty the rectum before CT simulation. Immobilization techniques were used during CT simulation and all treatment fractions. Fusion between planning CT and MRI was done (if available).

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Organs At Risk (OARs) including femoral heads, rectum, bladder, penile bulb and bowel were contoured following the recommendations of the Radiation Therapy Oncology Group (RTOG) [9].

Dose to PTV nodal was 45 Gy and dose prescribed to PTV primary ranged from 70 to 78 Gy. All patients received conventional protocol. Treatment plan was given in two phases.

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Quality Assurance (QA) including QA for IMRT treatment planning, IMRT delivery system QA and patient specific QA to make sure that the delivered dose distributions agree with the planned ones. X-ray digital portal images using bone landmarks were done daily before RT session for all cases.

Androgen Deprivation Therapy (ADT)

All patients received Androgen Deprivation Therapy (ADT) using (Luteinizing Hormone Releasing Hormone) LHRH analogue with anti-androgen (in the first week) as neoadjuvant, concurrent and adjuvant. Intermediate risk group patients received short term ADT (4-6 months) while high risk group patients will continue long term ADT for 2-3 years.

Patient assessment

Toxicity data were collected from all patients during the last week of radiotherapy, 3 months and 6 months after finishing radiotherapy according to the Common Terminology Criteria for Adverse Events (CTCAE version 5.0). Assessment of quality of life done for all patients as base line, during the last week of radiotherapy, 3 months and 6 months after finishing radiotherapy by using EORTC QLQ-C30 for general health related quality of life (HRQOL) and QLQ-PR25 for prostate specific Health Related Quality of Life (HRQOL). The higher the score was, the worse the quality of life.

Statistical analysis

The used tests were Chi-square test for categorical variables, to compare between different groups and Student t-test for normally distributed quantitative variables, to compare between two studied groups by IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp).

End points

The end points of this study were evaluation of acute toxicity and assessment of quality of life for our patients. Acute toxicity was defined any reaction related to radiation that occurred up to 6 months after radiation course.

RESULTS

The clinic pathological features of patients in both groups were gathered in (Table 1).

Tab. 1. Comparison between the clinicopathological features of patients in both groups

	3DCRT (n=15)		IMRT (n=15)		p
	No.	%	No.	%	
Age (years) Mean ± SD	67.87 ± 5.42		68.13 ± 7.64		0.913
Smoking					
No	12	80	9	60	0.427
Yes	3	20	6	40	
Comorbidity					
No Comorbidity	5	33.3	8	53.3	
DM	7	46.7	2	13.3	
HTN	1	6.7	0	0	0.145
DM+HTN	2	13.3	2	13.3	
HTN+IHD	0	0	2	13.3	
Chronic osteoarthritis	0	0	1	6.7	
Family history					
No	15	100	14	93.3	1
Yes	0	0	1	6.7	
Previous pelvic surgery					
No	14	93.3	11	73.3	0.33
Yes	1	6.7	4	26.7	
T stage					0.659
T1c	1	6.7	2	13.3	
T2b	6	40	5	33.3	
T2c	6	40	7	46.7	
T3a	0	0	1	6.7	
T4	2	13.3	0	0	
Mean ± SD Initial PSA	26.69 ± 18.58		28.79 ± 22.71		0.784
Gleason score					
≤ 6	0	0	5	33.3	0.365
7	13	86.6	9	60	
10-Aug	2	13.3	1	6.7	
Risk group					
Intermediate	7	46.7	6	40	0.404
High risk	6	40	9	60	
Very high risk	2	13.3	0	0	
Total dose Gy Mean ± SD		73.31 ± 2.60	76.13 ± 1.60		0.002*

Tab. 2. Gastrointestinal toxicity in studied groups during the period of study

Grade of Gastrointestinal Toxicity	3DCRT (n=15)						IMRT (n=15)						p
	0		1		2-3		0		1		2-3		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
During													
Abdominal pain	3	20.0	12	80.0	0	0.0	8	53.3	7	46.7	0	0.0	0.058
Diarrhea	3	20.0	7	46.7	5	33.3	6	40.0	8	53.3	1	6.7	0.200
Proctitis	5	33.3	4	26.7	6	40.0	10	66.7	2	13.3	3	20.0	0.296
Rectal hemorrhage	15	100.0	0	0.0	0	0.0	15	100.0	0	0.0	0	0.0	–
Rectal pain	5	33.3	4	26.7	6	40.0	11	73.3	4	26.7	0	0.0	0.016
3 months after													
Abdominal pain	13	86.7	2	13.3	0	0.0	12	80.0	3	20.0	0	0.0	1.000
Diarrhea	13	86.7	2	13.3	0	0.0	11	73.3	4	26.7	0	0.0	0.651
Proctitis	8	53.3	7	46.7	0	0.0	11	73.3	4	26.7	0	0.0	0.256
Rectal hemorrhage	15	100.0	0	0.0	0	0.0	15	100.0	0	0.0	0	0.0	–
Rectal pain	10	66.7	5	33.3	0	0.0	13	86.7	2	13.3	0	0.0	0.390
6 months after													
Abdominal pain	15	100.0	0	0.0	0	0.0	15	100.0	0	0.0	0	0.0	–
Diarrhea	15	100.0	0	0.0	0	0.0	15	100.0	0	0.0	0	0.0	–
Proctitis	11	73.3	4	26.7	0	0.0	15	100.0	0	0.0	0	0.0	0.100
Rectal hemorrhage	15	100.0	0	0.0	0	0.0	15	100.0	0	0.0	0	0.0	–
Rectal pain	12	80.0	3	20.0	0	0.0	14	93.3	1	6.7	0	0.0	0.598

Toxicity assessment

Gastrointestinal toxicity: During radiotherapy, 80% 0f patients in group A had G1 abdominal pain vs 46.7% in group B (p=0.058). Diarrhoea was reported in 80% of group A (33% G2-3) versus 60% of group B (6.7% G2-3). Number of patients with proctitis (G1or G2-3) in group A was double the number in IMRT group. Rectal pain (G2-3) was experienced in 40% of patients in group A versus 0% in group B (p=0.016). Three months after radiotherapy, only grade 1 GI toxicity was reported in both groups with no significant difference. Six months after radiotherapy, GIT toxicity was limited to G1 proctitis and rectal pain (26.7% and 20% in group A vs 0% and 6.7% in group B) (Table 2).

Genitourinary toxicity: During radiotherapy, the most common GU toxicities were cystitis, dysuria and hematuria in both groups. Grade 2-3 cystitis was 33.3% of patients in group A versus 20% in group B (p=0.435) (Table 3).

Tab. 3. Genitourinary toxicity in studied groups during the period of study

Only Grade 1 dysuria was reported in both groups (100% in group A versus 86.7% in group B) (p=0.483). Hematuria was grade 1 in both groups (53.3% in group A versus 13.3% in group B) with significant difference (p=0.020). Three months after radiotherapy, cystitis and dysuria remained the most common GU toxicity in both groups. Dysuria was 100% and 46.7% in group A, B respectively (p=0.002). Six months after radiotherapy, one third of patients had residual grade 1 cystitis or dysuria in both groups with no significant difference.

Fatigue: During radiotherapy, 46.7% of patients in group A had G2-3 fatigue versus 26.7% in group B (p=0.394). Three months after radiotherapy, G2-3 fatigue was similar in both groups. Six months after radiotherapy G2-3 fatigue was 46.7% in group A versus 13.3% in group B (p=0.195) (Figure 1).

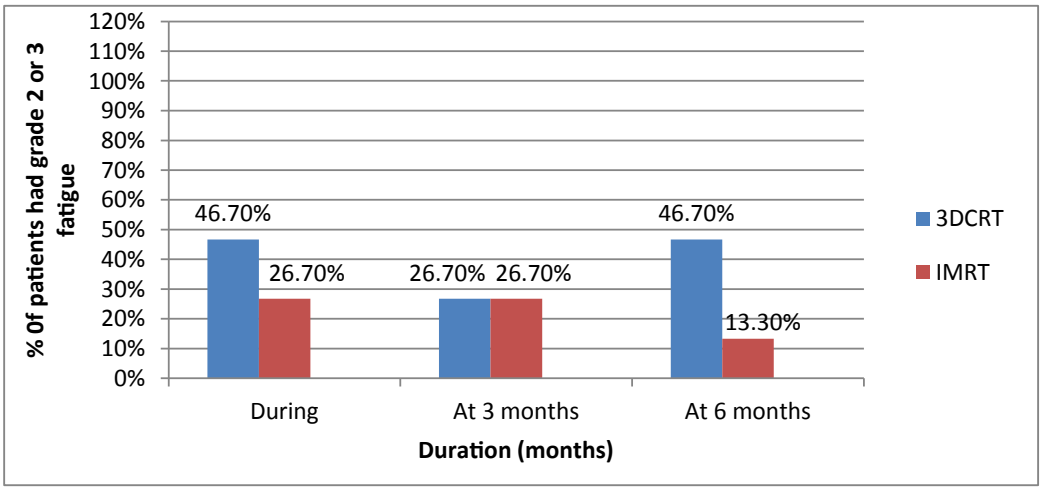

Fig. 1. Fatigue in both studied groups during the period of study

Tab. 3. Genitourinary toxicity in studied groups during the period of study

Grade of Genitourinary Toxicity	3DCRT (n=15)						IMRT (n=15)						p
	0		1		2-3		0		1		2-3		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
During													
Cystitis	0	0.0	10	66.7	5	33.3	2	13.3	10	66.7	3	20.0	0.435
Dysuria	0	0.0	15	100.0	0	0.0	2	13.3	13	86.7	0	0.0	0.483
Hematuria	7	46.7	8	53.3	0	0.0	13	86.7	2	13.3	0	0.0	0.020
Bladder spasm	7	46.7	4	26.7	4	26.7	11	73.3	4	26.7	0	0.0	0.126
Urine incontinence	8	53.3	7	46.7	0	0.0	10	66.7	4	26.7	1	6.7	0.457
3 months after													
Cystitis	10	66.7	5	33.3	0	0.0	8	53.3	5	33.3	2	13.3	0.605
Dysuria	0	0.0	15	100.0	0	0.0	8	53.3	7	46.7	0	0.0	0.002
Hematuria	15	100.0	0	0.0	0	0.0	14	93.3	1	6.7	0	0.0	1.000
Bladder spasm	15	100.0	0	0.0	0	0.0	14	93.3	1	6.7	0	0.0	1.000
Urine incontinence	13	86.7	2	13.3	0	0.0	10	66.7	4	26.7	1	6.7	0.399
6 months after													
Cystitis	15	100.0	0	0.0	0	0.0	12	80.0	3	20.0	0	0.0	0.230
Dysuria	12	80.0	3	20.0	0	0.0	12	80.0	3	20.0	0	0.0	1.000
Hematuria	15	100.0	0	0.0	0	0.0	15	100.0	0	0.0	0	0.0	–
Bladder spasm	15	100.0	0	0.0	0	0.0	15	100.0	0	0.0	0	0.0	–
Urine incontinence	15	100.0	0	0.0	0	0.0	13	86.7	2	13.3	0	0.0	0.483

Tab. 4. Quality of life in both studied groups during the period of study

	3DCRT (n=15)	IMRT (n=15)	p
Physical subscale			
QOL0	7.73 ± 1.44	8.27 ± 3.03	0.545
QOL3	7.73 ± 1.22	7.80 ± 3.28	0.942
QOL6	7.40 ± 1.06	7.33 ± 2.85	0.933
Emotional			
QOL0	5.67 ± 0.98	5.40 ± 1.40	0.551
QOL3	4.47 ± 0.52	5.80 ± 2.21	0.037
QOL6	4.67 ± 0.72	5.47 ± 1.64	0.100
Cognitive			
QOL0	2.93 ± 0.70	2.93 ± 0.88	1.000
QOL3	3.27 ± 0.70	2.93 ± 0.88	0.263
QOL6	3.53 ± 0.52	3.07 ± 1.10	0.153
Social and financial			
QOL0	5.67 ± 1.23	4.27 ± 1.33	0.006
QOL3	5.13 ± 1.13	4.0 ± 1.0	0.007
QOL6	5.33 ± 0.82	3.47 ± 0.83	<0.001
Role function			
QOL0	3.87 ± 0.99	3.53 ± 1.85	0.544
QOL3	3.40 ± 0.51	3.0 ± 1.20	0.248
QOL6	3.53 ± 0.52	2.47 ± 0.92	0.001
Global			
QOL0	6.87 ± 0.99	6.0 ± 2.10	0.165
QOL3	5.67 ± 0.49	5.53 ± 1.73	0.777
QOL6	5.40 ± 1.64	4.93 ± 1.10	0.368
Symptoms scale			
QOL0	18.40 ± 2.67	17.0 ± 3.51	0.229
QOL3	15.27 ± 1.33	15.53 ± 3.16	0.767
QOL6	15.47 ± 1.30	14.20 ± 2.98	0.143
Urinary symptoms			
QOL0	17.73 ± 3.56	17.93 ± 4.89	0.899
QOL3	11.87 ± 1.92	14.0 ± 3.53	0.052
QOL6	11.07 ± 1.22	11.27 ± 3.26	0.827
Bowel symptoms			
QOL0	5.53 ± 1.25	5.27 ± 1.62	0.618
QOL3	4.73 ± 0.70	4.53 ± 0.52	0.382
QOL6	4.33 ± 0.49	4.53 ± 0.52	0.285
Hormonal symptoms			
QOL0	8.87 ± 1.60	8.0 ± 1.36	0.121
QOL3	10.13 ± 1.36	9.13 ± 1.30	0.049
QOL6	10.33 ± 1.68	9.47 ± 1.19	0.113
Sexual activity			
QOL0	6.07 ± 1.10	5.80 ± 1.26	0.543
QOL3	6.0 ± 1.07	5.27 ± 1.67	0.165
QOL6	6.27 ± 1.22	5.47 ± 1.68	0.148
Sexual function			
QOL0	11.08 ± 1.51	9.67 ± 1.50	0.031
QOL3	11.85 ± 1.34	10.0 ± 1.54	0.004
QOL6	12.83 ± 1.11	10.0 ± 1.83	0.001
Overall Quality of life			
QOL0	98.20 ± 13.82	92.13 ± 12.77	0.222
QOL3	87.93 ± 6.10	85.53 ± 10.43	0.448
QOL6	87.60 ± 4.84	78.33 ± 8.86	0.001

Hematological toxicity: There were no hematological events in both groups through all time points.

Quality of life assessment: Through the period of study, there was a significant difference between both groups as regard to emotional, social, role function, hormonal symptoms and sexual function which were better in IMRT group (Table 4). After 6 months the overall QoL was better in IMRT group (p=0.001).

DISCUSSION

One of the principle definitive treatment for prostate cancer is external beam Radiation Therapy (RT). IMRT is a progress of 3D-CRT that can safely escalate the dose to non-uniform target volume by changing the intensity of the beam with potential lower radiation toxicity compared to 3DCRT [10]. In our study, cases who received definitive radiotherapy using

IMRT had less sever GI toxicity but there were similar sever GU toxicity compared to 3DCRT matched with Sujenthiran et al. and Michalski et al. [10, 11]. Our results regarding incidence of rectal pain and microscopic hematuria were higher in 3DCRT group in line with RTOG 0126 prostate cancer trail, in which the use of IMRT in high dose (79.2 Gy) for men with localized prostate cancer was associated with significantly lower incidence of acute GI and GU toxicity

Viani et al. concluded that IMRT decreased the delivery of considerable dose to bladder and rectum and this was reflected on toxicity with lower incidence of grade 2-3 GI and GU toxicity and better quality of life in IMRT [12].

Bruner et al. in RTOG 0126 prostate cancer trail, investigated and compared patient reported outcomes in similar high dose 3DCRT and IMRT and demonstrated no significant differences between IMRT and 3DCRT in bowel and urinary domains of QoL at any time point up to 24 months matched to our results [13]. Our study was a limited study done in 2 hospitals with small number of patients included in both groups so larger number of patients is required for better assessment of QoL. Also, the total radiation dose received was not constant among study population. Moreover, Self-administrated QoL questionnaires were not feasible due to lack of Arabic translated form.

CONCLUSION

IMRT was associated with significant lower incidence of gastrointestinal and genitourinary toxicity especially Grade 2-3. After treatment finishing QoL was better in IMRT group. IMRT for patients selected for definitive radiotherapy for prostate cancer especially in whom low dose limits for organs at risk couldn't be achieved with 3DCRT plans. More studies in larger set of patients my possibly help in better evaluating health related quality of life in prostate cancer patients receiving definitive radiotherapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Prostate cancer remains the most common cancer and the third leading cause of cancer mortality in men [1]. Newly diagnosed men with localized prostate cancer have several treatment options that include watchful waiting, radical prostatectomy, radiotherapy (external beam or brachytherapy), hormonal ablation and a combination of these modalities [2]. External Beam Radiation Therapy (EBRT) is a principle treatment for prostate cancer (both localized and locally advanced). Dose-escalation to the prostate was proved to enhance biochemical PFS; however, this can be on expense of more Gastrointestinal (GI) and Genitourinary (GU) adverse effects [3]

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The clinic pathological features of patients in both groups were gathered in (Table 1).

Toxicity assessment

Gastrointestinal toxicity: During radiotherapy, 80% 0f patients in group A had G1 abdominal pain vs 46.7% in group B (p=0.058). Diarrhoea was reported in 80% of group A (33% G2-3) versus 60% of group B (6.7% G2-3). Number of patients with proctitis (G1or G2-3) in group A was double the number in IMRT group. Rectal pain (G2-3) was experienced in 40% of patients in group A versus 0% in group B (p=0.016). Three months after radiotherapy, only grade 1 GI toxicity was reported in both groups with no significant difference. Six months after radiotherapy, GIT toxicity was limited to G1 proctitis and rectal pain (26.7% and 20% in group A vs 0% and 6.7% in group B) (Table 2).

Genitourinary toxicity: During radiotherapy, the most common GU toxicities were cystitis, dysuria and hematuria in both groups. Grade 2-3 cystitis was 33.3% of patients in group A versus 20% in group B (p=0.435) (Table 3).

Only Grade 1 dysuria was reported in both groups (100% in group A versus 86.7% in group B) (p=0.483). Hematuria was grade 1 in both groups (53.3% in group A versus 13.3% in group B) with significant difference (p=0.020). Three months after radiotherapy, cystitis and dysuria remained the most common GU toxicity in both groups. Dysuria was 100% and 46.7% in group A, B respectively (p=0.002). Six months after radiotherapy, one third of patients had residual grade 1 cystitis or dysuria in both groups with no significant difference.

Fatigue: During radiotherapy, 46.7% of patients in group A had G2-3 fatigue versus 26.7% in group B (p=0.394). Three months after radiotherapy, G2-3 fatigue was similar in both groups. Six months after radiotherapy G2-3 fatigue was 46.7% in group A versus 13.3% in group B (p=0.195) (Figure 1).

Quality of life assessment: Through the period of study, there was a significant difference between both groups as regard to emotional, social, role function, hormonal symptoms and sexual function which were better in IMRT group (Table 4). After 6 months the overall QoL was better in IMRT group (p=0.001).

DISCUSSION

One of the principle definitive treatment for prostate cancer is external beam Radiation Therapy (RT). IMRT is a progress of 3D-CRT that can safely escalate the dose to non-uniform target volume by changing the intensity of the beam with potential lower radiation toxicity compared to 3DCRT [10]. In our study, cases who received definitive radiotherapy using IMRT had less sever GI toxicity but there were similar sever GU toxicity compared to 3DCRT matched with Sujenthiran et al. and Michalski et al. [10, 11]. Our results regarding incidence of rectal pain and microscopic hematuria were higher in 3DCRT group in line with RTOG 0126 prostate cancer trail, in which the use of IMRT in high dose (79.2 Gy) for men with localized prostate cancer was associated with significantly lower incidence of acute GI and GU toxicity

Viani et al. concluded that IMRT decreased the delivery of considerable dose to bladder and rectum and this was reflected on toxicity with lower incidence of grade 2-3 GI and GU toxicity and better quality of life in IMRT [12].

Bruner et al. in RTOG 0126 prostate cancer trail, investigated and compared patient reported outcomes in similar high dose 3DCRT and IMRT and demonstrated no significant differences between IMRT and 3DCRT in bowel and urinary domains of QoL at any time point up to 24 months matched to our results [13]. Our study was a limited study done in 2 hospitals with small number of patients included in both groups so larger number of patients is required for better assessment of QoL. Also, the total radiation dose received was not constant among study population. Moreover, Self-administrated QoL questionnaires were not feasible due to lack of Arabic translated form.

CONCLUSION

IMRT was associated with significant lower incidence of gastrointestinal and genitourinary toxicity especially Grade 2-3. After treatment finishing QoL was better in IMRT group. IMRT for patients selected for definitive radiotherapy for prostate cancer especially in whom low dose limits for organs at risk couldn't be achieved with 3DCRT plans. More studies in larger set of patients my possibly help in better evaluating health related quality of life in prostate cancer patients receiving definitive radiotherapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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