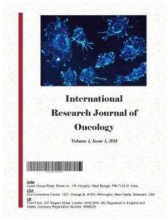

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Hypofractionated Radiotherapy for Localized Prostate Cancer: Clinical Outcome (Mansoura University)

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Authors' contributions

This work was carried out in collaboration between both authors. Author AHA designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Author MFA wrote the protocol, managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Purpose: In this study, we describe the efficacy and safety of hypo fractionated radiotherapy in treating patients with localized prostate cancer.
Patients and Methods: A total of 70 patients diagnosed with localized (T1-T2) prostatic adenocarcinoma. Low and intermediate risk groups were prospectively recruited between November 2012 and November 2016. Patients were treated with hypo-fractionated RT of 60 Gy in 20 fractions over 4 weeks. Androgen deprivation therapy was permitted for intermediate risk patients. The primary outcome was biochemical relapse free survival which defined as the nadir PSA post-radiotherapy plus 2 ng/ml according to PHOENIX criteria. Overall survival and treatment toxicity were secondary end points.
Results: With medium follow-up of 30 months; the three year biochemical relapse-free survival was 93.6%. Acute GU toxicity was detected as follows: 13(18.6%) patients experienced G1 toxicities

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while 11(15.7%) patients developed G2 toxicities. Acute G1 toxicity was detected with, 11.4% of patients reporting G1 toxicity and 10% experiencing G 2 toxicity. During the follow-up, three patients died; two from systemic disease progression; one patient expired due to cardiac cause. The 5 years overall survival was 90%.

Conclusion: Our data show that a Hypo-RT using 3D-CRT produces an excellent biochemical control and a low incidence of late GI and GU toxicity. Also in absence of IGRT or IMRT, we should use rigid restrictions and adequate margins to get reasonable rate of late toxicity.

Keywords: Prostate cancer; hypofractionation; radiotherapy; prospective study.

1. INTRODUCTION

Prostate cancer (PCa) is the second most commonly diagnosed male cancer in the Western countries with most patients diagnosed with localized tumor at presentation [1,2].

Definitive radiotherapy is considered a main treatment arm for localized prostate cancer patients. The current standard definitive radiotherapy regimen consists of conventionally fractionated (1.8-2 Gy per fraction) intensity modulated radiation therapy (IMRT) for approximately 8-9 weeks (76-80 Gray [Gy]). Although this has been demonstrated to be efficacious, the long treatment time can result in increased healthcare costs and is inconvenient for some patients [3].

Hypo- fractionation (delivering larger doses per fraction up to a lower total dose with shortening of overall treatment time) has been tried in various types of cancers like breast and early-stage lung cancer. As well as in prostate cancer a lot of trials investigating hypofractionation have been performed [4].

The idea of hypofractionation in prostate cancer is the comparatively low a/ß for prostate cancer (1.5 Gy), that point to a greater sensitivity to large fraction size, allowing for dose-escalation. The a/ß for organs at risk in prostate radiotherapy is higher (rectum and bladder; a/ß 3–5 Gy) in contrast to prostate. This is the idea for enhancing the therapeutic ratio of hypofractionation, while delivering to the prostate an isoeffective dose [5].

Three multicenter, randomized, non-inferiority trials comparing moderate hypofractionation (2.5 Gy to 3.0 Gy per fraction) with conventional fractionation (1.8 Gy to 2.0 Gy per fraction) have reported similar effectiveness and toxicity for intact prostate cancer [6,7,8].

Compared to conventional fractionation, hypo-fractionation has reduced the number of treatment visits and treatment cost. This is of great value in a financially limited health care system. The challenge is to weigh the gains regarding cost and convenience with maximum response [9].

We therefore aimed at describing our initial experience in treating localized prostate cancer patients with a hypofractionated regimen in terms of efficacy and safety.

2. PATIENTS AND METHODS

2.1 Patient's Eligibility

Between November 2012 and November 2016, 70 patients diagnosed with localized (T1-T2) prostatic adenocarcinoma, low and intermediate risk groups were prospectively enrolled. All patients have signed a written consent. All patients had pathologically proven diagnosis by transrectal ultrasound (TRUS) biopsies and scored according to the Gleason Score. The trial protocol was approved by Mansoura faculty of medicine Institutional Research Board (IRB),

2.2 Pre-treatment Evaluation

Before entering the study, all patients underwent full history taking, accurate examination, digital rectal examination (DRE), abdominopelvic magnetic resonance imaging (MRI), chest computed tomography (CT) scan with contrast, bone scan, blood tests and PSA level.

Low risk group includes patients with all the following; clinical T1–T2a prostate cancer, Gleason Score = 6 and PSA value < 10 ng/mL while intermediate risk group includes patients with any clinical T2b–T2c prostate cancer, Gleason Score = 7 or PSA value ranging from 10 -20 ng/mL before treatment], according to the

National Comprehensive Cancer Network (NCCN) guidelines [10].

2.3 Treatment

Before simulation, patients were taught to evacuate the rectum and to attain a comfortably full bladder. CT simulation is performed with 3 mm slice thickness, immobilization within thermoplastic body mask to ensure fixation and reproducibility with the arms on chests. We scan the patient from the abdomen till the mid-thigh to allow contouring of all the organs at risk. All patients were fixed in the supine position. The CTV included the prostate gland and the proximal one cm of the seminal vesicles in intermediate risk group while, we excluded seminal vesicles in low risk patients. We extend the CTV by 1 cm in all directions except posteriorly (only 6 mm) to decrease dose to the rectum. The prescribed dose is 60 Gy/4 weeks/ 20 fractions.

Organs at risk were rectum up to the sigmoid flexure, bladder, femoral heads and penile bulb. Contouring of the rectum starts from slice when the rectum becomes a posterior rounded structure and ends at the level of ischial tuberosities. Bladder contouring starts from the bladder dome till the lowest slice of bladder base. Proximal femurs contouring start from the uppermost cut of femoral head down to ischial tuberosities including the trochanters. Penile bulb including the part of bulbous spongiosum of the penis immediately below the genitourinary diaphragm. Treatment was delivered by 3D conformal radiotherapy on linear accelerator (Elekta) using energies of 6 MV and 15 MV X-ray photon beams according to each individual case.

We visualized all field arrangements by displaying beam eye views (BEVs). Beam apertures were created using MLC beam shapes. Collimation was asymmetric and wedges were used when necessary.

We used a Six fields (coplanar beams) technique with gantry angles of (40^o, 90^o, 115^o, 245^o, 270^o and 320^o) or (55^o, 90^o, 125^o, 235^o, 270^o and 305^o) giving the same dose distribution). Dose distribution was calculated with homogeneity corrections. Dose prescription was normalized at the isocentre to 100% and isodose surface of 95% covered PTV volume of 95%. The maximum dose within the PTV is below 107%.

Patients submitted to androgen deprivation therapy consisted of LHRH-analogue plus anti-androgen (bicalutamide 50 mg PO once daily) to a total duration of 6 months for intermediate risk while hormonal therapy was not used for low risk patients.

2.3.1 Toxicity and follow-up

All patients were clinically assessed weekly during the delivery of radiation therapy and acute gastrointestinal and genitourinary adverse effects were recorded and graded using RTOG/ EORTC acute radiation scoring criteria [11]. After radiation, patients were followed every 3 month for the first 2 years and every 6 month afterwards. During follow-up, patients underwent full examination and PSA assessment. Late toxicities were also monitored. All toxicities occurring ninety days after ending radiotherapy were considered to be late toxicities.

2.3.2 End points

Biochemical relapse free survival which was defined as the nadir PSA post-radiotherapy plus 2 ng/ml according to PHOENIX criteria was the primary end point [12]. Overall survival and treatment toxicity were secondary end points.

2.4 Statistical Analysis

The data analysis was carried out on December 2017.Overall survival (OS) and biochemical relapse-free survival were estimated using the Kaplan–Meier method. Statistical analyses were done by SPSS statistical software package version 14.0. A p-value of <0.05 was statistically significant.

3. RESULTS

3.1 Patients' Characteristics

From November 2012 to November 2016, 70 patients were recruited and completed the treatment protocol. Patient's data are listed in Table 1. Median age at diagnosis was 68 years (range, 57-83 years) with 30% (21/70) low risk and 70% (49/70) intermediate risk patients. All patients were treated with 3D conformal technique.

3.2 Biochemical Control

After 30 months of median follow-up (9– 57 months); three year biochemical relapse-free survival was 93.6% (Fig. 1). Four patients developed disturbed biochemical tests: three patients developed bone metastasis, while one

patient developed locoregional lymph nodes with liver metastasis. All these patients started total androgen deprivation therapy soon after relapse; one case became hormone refractory and initiated chemotherapy. Metastatic patients with painful bone metastasis received palliative radiotherapy.

Table 1. Baseline data of the 70 patients

Baseline characteristics	No(70)	%
Age(years): median	68 (57-83)	
<65	20	28.6
≥65	50	71.4
PSA at the diagnosis (ng/mL)		
< 10	27	38.6
10 -20	43	61.4
Gleason Score		
≤ 6	24	34.3
7(3+4)	40	57.1
7(4+3)	6	8.6
Clinical Stage		
T1a/T1b/T1c/T1x	19	27.1
T2a/T2b/T2c/T2x	51	72.9
risk group		
Low	21	30
Intermediate	49	70

3.3 Acute Toxicities

It include toxicities that occur during RT and within 90 days after ending of RT. Acute grade 1 gastrointestinal toxicity had developed in 11.4% of patients while 10% of patients experienced acute grade 2 GI toxicity. Acute genitourinary toxicity was detected as follows: 13 (18.6%) patients experienced G1 toxicity while 11 (15.7%) patients developed G2 toxicity. Acute toxicity is summarized in Table 2.

3.4 Late toxicities

Eleven patients (15, 7%) developed Grade1 toxicities and 5 patients (7.1%) developed Grade 2 toxicities (3 cases late GU and 2 cases late GI). The GI and GU toxicities prevalence are shown in Table 3.

Table 2. Acute toxicities according to RTOG scale

Acute Toxicity	G1	G2	G3	G4
Gastrointestinal (GI)				
Bowel frequency	3	4	0	0
Proctitis	4	3	0	0
Rectal bleeding	1	0	0	0
Genitourinary (GU)				
Dysuria	5	8	0	0
Urinary frequency	3	2	0	0
Hematuria	2	0	0	0
Incontinence	3	1	0	0

Table 3. Late toxicities according to RTOG scale

Late Toxicity	G1	G2	G3	G4
Gastrointestinal (GI)				
Bowel frequency	3	2	0	0
Proctitis	1	0	0	0
Rectal bleeding	0	0	0	0
Genitourinary (GU)				
Dysuria	4	2		
Urinary frequency	2	1	0	0

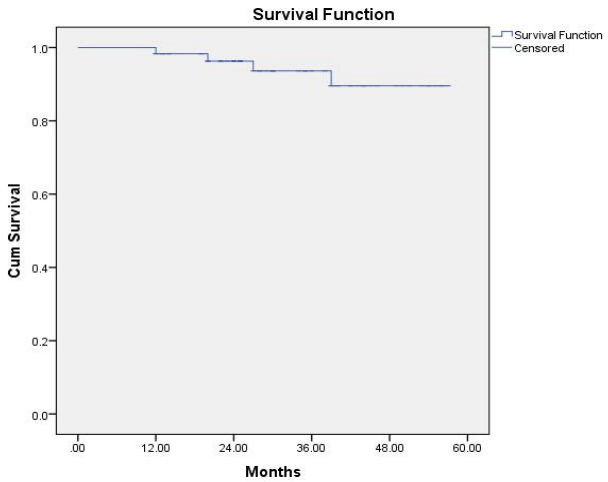

Fig. 1. Kaplan-Meier estimate of biochemical relapse-free survival in all patients

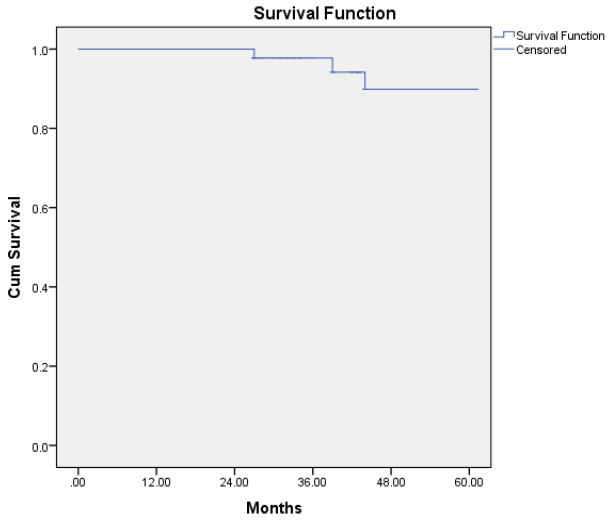

Fig. 2. Kaplan-Meier estimate of overall survival in all patients

3.5 Overall Survival

During the follow-up, three patients died; 2 from systemic disease progression; one patient expired due to cardiac cause. The 5 years overall survival was 90% as described in Fig. 2.

4. DISCUSSION

Recently, the use of moderate hypofractionation in prostate cancer is increasing. The benefit of moderate hypofractionated radiotherapy was evident as the prostate has a lower a/ß ratio in comparison to the nearby organs [13].

Shortening treatment duration, saving medical resources, and helping the patient's convenience, are benefits can be gleaned from moderate H-RT [14].

The outcomes have been inconsistent; however, these studies have shown the tolerability and efficacy of moderate hypofractionated radiotherapy in contrast to conventional radiotherapy in localized prostate cancer [15]. Therefore, we use this study to further assess our initial experience in treating localized prostate cancer patients with a hypofractionated regimen in term of efficacy and safety.

In this study, we presented the clinical outcomes of 70 prostate cancer patients (low/intermediate risk)treated with hypofractionation schedule of 60 Gy in 20 fractions which is biologically equivalent to 77.14 Gy in 43 fractions of 1.8 Gy, according to the linear quadratic formula when assuming an a/b ratio of 1.5 for the prostate cancer.

In our study there was no G 3 or 4 GI or GU toxicity. The incidence of G 2 acute GI toxicity was 10% and GU toxicity was 15.5%. The reported rates of GI and GU toxicities of grade 2 or more in previously published studies show a wide range of incidence. A comparison of reported rates of acute toxicity from studies which have used the same moderate hypofractionation schedule of 60 Gy/20 Fr/4 weeks have reported grade 2 GI toxicities of 10% to 25% and grade 2 GU toxicities of 7% to 35%. [16,17,18] This shows that toxicity rates in our patients are in keeping with those in published literature.

In several phase II studies, HyRT in treatment of prostate cancer patients showed improved biochemical control rates based on risk stratification and tolerability, with 3% to 25% ≥ Grade 2 GU and GI late toxicity [18-23]. In the current study, 2.9% patients had ≥Grade 2 late GI toxicity and 4.3% patients expressed ≥Grade 2 late GU toxicity. Our results are similar to those in the literature.

In present study the 3-year biochemical relapse free survival was 93.6% after a median follow up of 30 months, grade 2 late G1 toxicity was 2.9% and grade 2 late GU toxicity were detected in 4.2%, which is consistent with Valeriani et al who treated 105 intermediate risk prostate cancer patients with hypofractionated protocol with or without image guided radiotherapy (IGRT) and

reported 93.7% 3-year biochemical relapse free survival after a median follow-up of 31 months [24].

Our results also are in agreement with two recently randomized studies that compared moderately hypofractionated radiotherapy with conventional fractionation in localized prostate cancer.

Dearnaley et al (CHHiP trial)[16] in their study , compared 60 Gy in 20 fractions over 4 weeks (as ours) and 57 Gy in 19 fractions, with 74 Gy in 38 fractions in intermediate-risk patients, all patients received 6 months hormonal therapy before and during radiotherapy. The first schedule of Dearnaley and his colleagues, as in our study was comparable to standard, but the other two regimens were not.

Catton et al (PROFIT trial) [25] reported that 78 Gy in 39 fractions was comparable to 60 Gy in 20 fractions in intermediate risk prostate cancer.

On the contrary, the HYPRO trial compared standard fractionation with 39 fractions of 2 Gy in 8 weeks to hypofractionation with 19 fractions of 3.4 Gy in 6.5 weeks (three fractions per week) and reported increased GU and GI late toxicity in the hypofractionated arm. [26] This study was planned to have a biologically higher dose in the experimental treatment arm, which is mostly responsible for these results.

However, we realize that radiotherapy technique used in the present study is overpassed in some developed countries. The 3D-CRT could be the extreme utility to treat prostate cancer in low-income countries. We think that these results will improve with modern technique such as IMRT and IGRT.

There are some limitations in our study. One is the relatively old technique but unfortunately is the only available in our locality and other factor is the relatively small numbers of cases being in a single institution that also enforced us to do single arm trial. Our study is the first reported trial on using hypofractionated radiation therapy in treating localized prostate cancer in our institution.

5. CONCLUSION

Our data show that a Hypo-RT using 3D-CRT produces an excellent biochemical control and a low incidence of late GI and GU toxicity. Also in absence of IGRT or IMRT, we should use rigid restrictions and adequate margins to get reasonable rate of late toxicity.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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