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Research Article

# Outcomes, Toxicities and Dosimetric Comparison of Different Hypofractionated Intensity Modulated Radiotherapy Techniques for Treatment of Localized Prostate Cancer

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## ABSTRACT

**Background:** conventional fractionation IMRT is the standard treatment for localized prostate cancer patients. The objectives of this study were to evaluate safety and efficacy of Hypofractionated radiotherapy with dosimetric comparison between 5, 7 and 9 IMRT fields.

**Methods:** Low or intermediate risk patients included. Three sets of Inverse planning IMRT were carried out (5, 7 and 9 Fields) for each patient with total dose of 70 Gy/28 fractions.

**Results:** 20 patients were recruited. Regarding PTV coverage, there were no statistically significant differences regarding D2%, D5%, D50%, D95%, D98%, Dmax, Dmin, Dmean, conformity index, homogeneity index, between 5, 7 or 9 Fields. (p=0.25, 0.38, 0.969, 0.057, 0.294, 0.057, 0.517, 0.969, 0.313 and 0.969, respectively). Statistically significant difference regarding longer treatment time (p=0.039) and more monitor units (p=0.015) between 5 and 9 fields with no significant difference between 7 and 9 fields. The mean doses to V25%, V35% and V50% of the rectum were significantly higher for the 5 fields compared to 7 and 9 fields (p=0.001, 0.001, 0.006). The 2 year biochemical control rate was 95% and the DFS was 100%. Acute gastero intestinal toxicities G1 55%, G2 40% and G3 5% while late toxicities G1 25% and G2 15%. Acute genitourinary toxicities G 1 60%, G2 35% and G3 5% and for late toxicities G1 30% and G2 10%. No late G3 nor G4 toxicities were observed.

**Conclusion:** Hypofractionated radiotherapy is safe and effective regarding the biochemical control and toxicity profile, more convenient and less costly.

**Keywords:** Hypofractionated radiotherapy; Localized prostate cancer; Dosimertric study;Toxicities

## INTRODUCTION

Prostate cancer is the second most common cancer in men after lung cancer and the fifth leading cause of cancer related deaths worldwide, accounting for 1,276,106 new cases and causing 358,989 deaths. Most of the patients are presented with localized disease [1].

Management strategy of localized disease depends on risk stratification system which is based on Prostate Specific Antigen (PSA) level, Gleason score, clinical stage TNM (tumor extension, seminal vesicle invasion, extra capsular extension, pelvic LN involvement and distant spread), number of positive biopsies, age and expected survival. For low and intermediate risk patients surgery and definitive radiotherapy have similar outcomes regarding local control, biochemical relapse, disease free survival and cancer specific survival [2].

External beam radiotherapy with conventional fractionation using IMRT technique is the standard treatment as it allows dose escalation up to 76-80 Gy over 38-40 fractions with more sparing of normal tissues than the conventional three dimension conformal radiotherapy. However, this long course duration is inconvenient for patients, more costly and increases the load over treatment machines [3-7].

The rationale for conventional fractionation (1.8-2 Gy) for irradiation of solid tumors is related to the $\alpha/\beta$ ratio which is a measure of intrinsic radiosensitivity of a cell in response to fraction size. Early responding tissues and most tumors typically have high $\alpha/\beta$ ratio (8-10) being less affected by the fraction size while late responding normal tissues have low $\alpha/\beta$ ratio (3-4) allowing for great repair capacity with conventional small fraction size, thus improving the therapeutic ratio [8,9].

In contrary to most other tumors, prostate cancer cells has a lower

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α/β ratio (≤ 2) than the surrounding late-responding normal tissue namely the rectum, so the larger the fraction size, the more tumor cell killing with the same normal tissue complications with the result of significant improvement of the therapeutic ratio [10-12].

Several studies had evaluated different moderate hypofractionated IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) compared to conventional fractionation. Toxicity was similar between hypofractionated and conventional regimens in some but not all of the trials. In addition, efficacy results varied among the trials, with some showing non-inferiority or similar efficacy and others showing that hypofractionation may be less effective than conventional fractionation schemes [13-16].

The primary objective of this study was to evaluate the safety and efficacy of Hypofractionated radiotherapy in the treatment of localized prostate cancer. The secondary objective is dosimetric comparison between using 5 fields, 7 fields and 9 fields Intensity modulated radiotherapy regarding target volume coverage and normal tissue sparing.

## MATERIALS AND METHODS

### Patients

This study was carried out in Ayadi Almostakbal Oncology Center during the period from April 2019 to January 2021. Inclusion criteria: any age, histologically confirmed prostatic adenocarcinoma. Low or intermediate risk Localized prostate cancer according to NCCN risk classification. Low-risk patients included cT1c–T2a, N0, M0, Gleason score 6 or less, and prostate-specific antigen (PSA) concentration <10 ng/mL. Intermediate-risk patients had at least one of the following criteria: T2b-c, Gleason score 7, and PSA 10–20 ng/mL.

Exclusion criteria: T3,4 lesions, extra capsular extension, seminal vesicle invasion, positive lymph node metastasis, Gleason score ≥ 8, risk of pelvic lymph node involvement>15% by Roch formula, PSA>20 ng/dl, metastatic disease, inflammatory bowel disease, previous radiotherapy to the pelvis. Unfavourable intermediate risk patients received zoladex for 6 months starting 2 months before radiotherapy.

All patients had pre-treatment staging including a complete history, physical examination, digital rectal examination, Tran's rectal ultrasound of the prostate, biopsy, Prostate-Specific Antigen (PSA) level and MRI pelvis.

### Methods

Patients were immobilized using body mattress extend from mid back to mid-thigh in the supine positions with hands above the head. Patients were instructed for a low residue diet and to empty the rectum using an enema the night prior to simulation. The anterior posterior diameter of the rectum should be less than 4 cm during simulation. Also, a comfortably full bladder (patients empty urinary bladder then drink 500 ml water and abstain urination for one hour before simulation). Patients were scanned in the treatment position from the L5-S1 level to the mid femur level on a Computerized Tomography (CT) simulator 3 mm slice thickness. CT simulation films and the pelvic MRI images were fused according to the bony landmarks.

### Delineation of target volume and organs at risk

CTV: prostate+proximal 1 cm of the proximal seminal vesicle.

PTV=CTV+0.8 cm except posteriorly 0.5 cm.

An additional 0.7-cm margin was added around the planning target volume (PTV) to account for penumbra.

The rectum defined by the outer rectal wall from the rectosigmoid junction till the anorectal junction, urinary bladder defined by the outer bladder wall, right and left femoral heads, penile pulb and bowel bag were contoured as critical normal tissue structures using the focal system.

### Plan design

After contouring of the target volumes and organs at risk, the CT images were transferred from focal system to the treatment planning system XiO 4.64 (Computerized Medical Systems, St. Louis, MO, USA) using the superposition algorithm. Three sets of Inverse planning IMRT were carried out using step-and-shoot technique (5 fields, 7 fields and 9 Fields) for each patient. An equidistant field were generated using 6 MV-15 MV photons and dosimertrically compared regarding target volume coverage and organ at risk sparing. All three plans were done using 6 MV–15 MV photons.

IMRT-5: beams were arranged with equal angle separation of 72 degrees between each two beams: 00,720, 1440, 2160 and 2880.

IMRT-7: 51 degrees equal angle separation between each two beams: 00, 510, 1020, 1530, 2040, 2550 and 3060.

IMRT-9: equal angle separation of 40 degrees between each two beams: 00, 400, 800, 1200, 1600, 2000, 2400, 2800, and 3200.

Target volume dosimetric parameters which are considered for comparison between the three planning techniques will be: maximum dose (Dmax), minimum dose (Dmin), mean dose (Dmean), 95% dose (V95%), median dose, homogeneity index (HI), and conformity index (CI) for irradiated tumour volumes.

For both rectum and urinary bladder: V15%, V25%, V35% and V50% were calculated. For right and left femori: maximum (Dmax) and mean dose (Dmean). These dosimetric parameters of the target volume and organs at risk were compared for the 3 sets of IMRT planning.

### Total dose and fractionation

70 Gy/28 fractions, 2.5 Gy/fraction, 5 fractions/week. Daily treatment verification using cone beam CT was done for all patients.

### Dose constrains

Dose constrains for organs at risk are listed in Table 1.

**Table 1:** Dose constrains for organs at risk.

| Bladder constraints | | Rectal constraints | | Femoral head | | Penile pulb |
|---|---|---|---|---|---|---|
| Dose | <Vol% | Dose | <Vol% | Dose | <Vol % | |
| 79 Gy | 15% | 74 Gy | 15% | 50 Gy | 2% | Mean<50Gy |
| 74 Gy | 25% | 69 Gy | 25% | | | |
| 69 Gy | 35% | 64 Gy | 35% | | | |
| 64 Gy | 50% | 59 Gy | 50% | | | |

### Plan evaluation

Plans were considered acceptable if ≥ 95% of the PTVs. received ≥ 95% of the prescription dose.

DVHs for the prostate PTV, rectum, bladder and bowel bag were calculated for each patient for the 3 planning techniques.

The conformity index (CI) and homogeneity index (HI) were defined to describe the quality of plans as follows:

CI=Vt ref/Vt X Vtref/Vref

Where Vt represents target volume, Vt, ref represents the target volume wrapped by reference isodose curve face (95%), and Vref represents all the volume wrapped by reference isodose curve (95%). A higher CI value, ranging from 0-1, represents better conformity.

HI=D2-D98/Dp

Where D2=dose to 2% of the target volume indicating the "maximum dose", D98=dose to 98% of the target volume, indicating the "minimum dose" and Dp=prescribed dose.

Lower HI is indicative of a more homogeneous dose distribution across the PTV.

The total number of MUs per fraction and the treatment time were used to evaluate the efficiency of treatment delivery.

After analysis of the differences between the dosimetric results in the three techniques based on dose-volume histograms (DVHs), the best technique of them will be recommended for the treatment of patients.

### Follow up

Patients were assessed clinically every other week during radiotherapy and monthly thereafter for 3 months and then every 3 months during follow up.

PSA was measured at base line and every 3 months during the first 2 years. Acute toxicity was defined as an event that developed during radiotherapy or within the first 3 months after the end of treatment. Late toxicity was defined as an event that manifested 3 months after the end of treatment. Acute and late events were graded according to Common Terminology Criteria for Adverse Events version 4.0 [17].

### Statistical analysis

Data were analyzed using SPSS statistical package version 22. Numerical data were summarized as median, mean and range. The Kruskal Wallis H test was used to determine statistical differences between volumes and doses in 5 field IMRT *vs.* 7 field IMRT *vs.* 9 field plans. The Mann Whitney test was used to determine statistical differences between volumes and doses in 5 field IMRT and 7 field IMRT or between 7 field IMRT and 9 field IMRT or 7 field IMRT and 9 field IMRT. P-value < 0.05 is considered significant.

## RESULTS

Between April 2019 and January 2021, 20 patients were recruited in this trial.

### Patient characteristics

The median age was 68 year and mean PSA was 13.2 ng/dl. Patients and tumor characteristics are summarized in Table 2.

**Table 2:** Patients and tumour characteristics.

| Data | Number (n=20) |
|---|---|
| **Age** | |
| <60y | 2(10%) |
| 60-70y | 10(50%) |
| >70y | 8(40%) |
| **Tumor stage** | |
| T1b-c | 3(15%) |
| T2a-b | 10(50%) |
| T2bc | 7(35%) |
| **Gleason score** | |
| ≤ 6 | 5(25%) |
| 7 | 15(75%) |
| PSA level | |
| <10 ng/ml | 5(25%) |
| 10-20 ng/ml | 15(75%) |
| **NCCN risk stratification** | |
| Low | 5(25%) |
| Favourable Intermediate | 6(30%) |
| Unfavourable intermediate | 9(45%) |
| LHRH agonist (zoladex) | 9(45%) |
| Yes | 11(55%) |
| No | |

### Dosimetric comparisons between three planning techniques for target volume coverage

Table 3 illustrates (mean), median and (range) of dosimetric parameters for target volume coverage in three planning techniques. There were no statistically significant differences regarding D2%,D5%,D50%,D95%, D98%, Dmax, Dmin, Dmean, conformity index, homogeneity index, monitor unit and treatment time were found between 5 Fields, 7 fields and 9 Fields. (p=0.25, 0.38, 0.969, 0.057, 0.294, 0.057, 0.517, 0.969 0.313, 0.969, 0.071 and 0.084 respectively).

**Table 3:** (Mean) median (range) of dosimetric parameters of target volume coverage in 5, 7 and 9 fields IMRT plans.

| Dosimetricparameters PTV | 5 Field IMRT (n=20) | 7 Field IMRT (n=20) | 9 Field IMRT (n=20) | P-Value |
|---|---|---|---|---|
| D2%(GY) | (71.29)70.87(70.30-72.43) | (71.14)70.72(70.29-72.11) | (71.12)70.66(70.22-72.13) | 0.252 |
| D5%(GY) | (71.13)70.74(70.14-72.21) | (71.01)70.60(70.19-71.93) | (70.99)70.54(70.11-71.91) | 0.386 |
| D50%(GY) | (70.23)70.09(69.07-71.12) | (70.32)70.12(69.51-71.22) | (70.27)70.08(69.29-71.24) | 0.969 |
| D95%(GY) | (68.17)68.04(66.54-69.53) | (68.81)68.43(68.12-69.69) | (68.82)68.53(68.20-69.60) | 0.057 |
| D98%(GY) | (67.75)67.91(66.03-69.06) | (67.91)67.95(66.10-69.31) | (67.95)68.04(66.09-69.25) | 0.294 |
| Dmax(GY) | (73.28)73.32(71.31-75.36) | (72.29)72.53(70.64-74.21) | (72.39)73.09(70.65-74.05) | 0.057 |
| Dmin(GY) | (50.79)59.55(27.34-67.45) | (52.35)64.91(28.17-68.29) | (52.75)65.05(29.76-68.16) | 0.517 |
| Dmean(GY) | (70.02)70.05(68.89-70.98) | (70.13)70.07(69.43-70.87) | (70.09)70.02(69.27-70.83) | 0.969 |
| CI | (0.99)0.99(0.99-1) | (0.99)0.99(0.99-1) | (0.99)0.99(0.98-1) | 0.882 |
| HI | (0.05)0.05(0.02-0.06) | (0.05)0.04(0.02-0.08) | (0.05)0.04(0.02-0.08) | 0.313 |
| MU | (1374.38)1361.2(1102.6-1800.4) | (1500.54)1382.7(1071.2-2044.4) | (1626.66)1561.5(1185.2-2190) | 0.071 |
| Treatment time | (11.99)12.04(9.5-12.3) | (13.16)13.26(10.7-15.74) | (14.34)14.32(11.83-17.01) | 0.084 |

Dosimetric comparison between 5 and 9 fields showed statistically significant difference regarding longer treatment time (p=0.039) and more monitor units (p=0.015) for the nine fields compared to the five fields, otherwise no statistically significant differences (Table 4).

**Table 4:** Dosimetric comparison between 5 *vs.* 7 fields (P1), 7 *vs.* 9 fields (P2) and 5 *vs.* 9 fields (P3).

| P-value | P1 | P2 | P3 |
|---|---|---|---|
| D2% | 0.132 | 0.574 | 0.189 |
| D5% | 0.349 | 0.349 | 0.259 |
| D50% | 0.851 | 0.851 | 0.851 |
| D95% | 0.057 | 0.574 | 0.059 |
| D98% | 0.189 | 0.574 | 0.189 |
| Dmax | 0.056 | 0.349 | 0.058 |
| Dmin | 0.349 | 0.574 | 0.349 |
| Dmean | 0.851 | 0.851 | 0.851 |
| HI | 0.189 | 0.851 | 0.189 |
| CI | 0.851 | 0.574 | 0.851 |
| MU | 0.574 | 0.189 | 0.015 |
| Treatment time | 0.574 | 0.092 | 0.039 |

**Note:**
P: p value for Kruskal Wallis test for comparing between 5field IMRT, 7field IMRT and 9field IMRT.
P1: p value for Mann Whitney test for comparing between 5Field IMRT and 7field IMRT.
P2: p value for Mann Whitney test for comparing between 7field IMRT and 9field IMRT.
P3: p value for Mann Whitney test for comparing between 5field IMRT and 9field.
*: Statistically significant at p≤0.05.

## Dosimetric comparisons between three planning techniques for Organs at Risk (OARs)

The mean doses to V25%, V35% and V50% of the rectum were significantly higher for the 5 fields compared to 7 and 9 fields (p=0.001, 0.001, 0.006). Regarding the urinary bladder, right and left femoral heads no statistically significant differences between the 3 planes (Tables 5 and 6).

Based on the above comparative dosimetric results between 5, 7 and 9 fields, all patients were treated with 7 fields IMRT as it significantly spare the rectum when compared to 5 fields. Dosimetric comparison between 7 and 9 fields showed no statistically significant difference regarding target volume coverage or risk organ sparing with less monitor units and treatment time for the 7 fields.

## Efficacy

The median follow-up duration was 24 months (range: 20-36 months). Biochemical failure is defined as nadir PSA+2 ng/ml (ASTRO and Phoenix definition). The mean PSA at base line was 13.2 ng/dl, mean nadir level was 1.02 ng/dl. The 2 year biochemical control rate was 95% and the DFS was 100%.

## Early and late toxicities

Regarding acute gasterointestinal toxicities (rectal pain, diarrhoea, tenesmus), the occurrence of acute G1 55%, G2 40% and G3 5% while late toxicities (diarrhea, rectal pain) G1 25% and G2 15%, no late G3 nor G4 toxicities were observed. For genitourinary toxicities (dysuria and frequency), acute G1 60%, G2 35% and G3 5% and for late toxicities G1 30% and G2 10%, no late G3 nor G4 toxicities were observed. No rectal bleeding, no urine retention, no incontinence and no haematuria were detected (Tables 5-7).

**Table 5:** Dosimetric comparisons between three planning techniques for organs at risk.

| Organ at risk | Dosimetric parameters | 5 Field (n=20) | 7 Field (n=20) | 9 Field (n=20) | P |
|---|---|---|---|---|---|
| Rectum | V15% | (64.39)64.70(61.35-67.49 ) | (62.75)62.06(57.71-68.66) | (64.91)64.82(57.90-71.74) | 0.214 |
| | V25% | (58.20)58.57(55.7-60.14) | (54.30)53.03(52.08-57.4) | (54.23)52.45(50.71-58.96) | 0.001 |
| | V35% | (50.34)49.99(48.09-55.48) | (46.16)45.54(43.38-51.86) | (45.98)44.80(43.44-52.36) | 0.001 |
| | V50% | (35.70)34.05(31.16-37.76) | (32.45)32.24(30.85-33.91) | (31.91)32.09(30.06-33.86) | 0.006 |
| Bladder | V15% | (64.57)66.48(54.77-70.39) | (66.53)68.54(54.50-77.74) | (64.31)67.40(53.98-70.74) | 0.517 |
| | V25% | (56.13)56.12(46.14-68.2) | (55.90)56.77(43.42-68.99) | (55.63)56.86(44.09-68.94) | 0.969 |
| | V35% | (48.58)44.86(39.14-62.4) | (48.20)46.94(35.72-63.2) | (45.74)41.24(35.03-62.8) | 0.428 |
| | V50% | (34.79)30.9(19.92-50.11) | (35.71)31.80(21.51-51.76) | (35.76)32.02(22.49-50.6) | 0.665 |
| Head of right | Dmax Gy | (44.82)43.32(41.31-45.36) | (42.29)42.53(40.64-44.21) | (42.39)43.09(40.65-44.05) | 0.47 |
| femur | Dmean | (12.61)11.83(11.32-14.25) | (10.54)10.58(9.80-11.68) | (10.88)13.29(9.01-13.54) | 0.51 |
| Head of left | Dmax Gy | (34.13)37.47(17.96-47.52) | (29.06)31.96(17.07-36.22) | (28.07)30.57(17.51-36.36) | 0.057 |
| femur | Dmean | (14.37)10.99(9.71-12.81) | (12.98)12.55(12.30-13.96) | (12.23)11.82(10.89-14.06) | 0.59 |

**Table 6:** Dosimetric comparison between 5 vs. 7 fields (P1), 7 vs. p 9 fields (P2) and 5 vs. 9 fields (P3).

| Organ at risk | P-value of Kruskal Wallis | P1 | P2 | P3 |
|---|---|---|---|---|
| Rectum | V15% | 0.092 | 0.189 | 0.214 |
| | V25% | 0.001 | 0.452 | 0.005 |
| | V35% | 0.001 | 0.851 | 0.001 |
| | V50% | 0.015 | 0.189 | 0.005 |
| Bladder | V15% | 0.574 | 0.189 | 0.851 |
| | V25% | 0.851 | 0.851 | 0.851 |
| | V35% | 0.851 | 0.349 | 0.189 |
| | V50% | 0.574 | 0.851 | 0.349 |
| Right head of femur | Dmax | 0.092 | 0.851 | 0.189 |
| | Dmean | 0.46 | 0.63 | 0.349 |
| Left head of femur | Dmax | 0.39 | 0.851 | 0.39 |
| | Dmean | 0.51 | 0.092 | 0.092 |

**Note:**
P: p value for Kruskal Wallis test for comparing between 5field IMRT, 7field IMRT and 9field IMRT.
P1: p value for Mann Whitney test for comparing between 5Field IMRT and 7field IMRT.
P2: p value for Mann Whitney test for comparing between 7field IMRT and 9field IMRT.
P3: p value for Mann Whitney test for comparing between 5field IMRT and 9field.
*: Statistically significant at $p \leq 0.05$.

**Table 7:** Early and late GI and GU toxicities.

| Toxicity | Gastrointestinal (GI) | | Genitourinary (GU) | |
|---|---|---|---|---|
| | Acute | Late | Acute | Late |
| G0 (None) | 0(0%) | 12(60) | 0(0) | 12(60%) |
| G1 | 11(55%) | 5(25%) | 12(60%) | 6(30%) |
| G2 | 8(40%) | 3(15%) | 7(35%) | 2(10%) |
| G3 | 1(5%) | 0(0) | 1(5%) | 0(0) |
| G4 | 0(0) | 0(0) | 0(0) | 0(0) |

## DISCUSSION

Radiotherapy access is of global concern especially in the developing countries. IMRT is the standard of care for early and locally advanced cases as it significantly spare organ at risk especially the rectum which allow for dose escalation which improve local control, biochemical control and disease free survival significantly [18]. Usually between 5 to 9 static or dynamic fields are used and in general dose homogeneity and conformity improve as the number of treatment fields increases, however the benefit with field numbers beyond 7 to 9 diminishes [19,20].

Mahdavi et al. compared the dosimetric coverage of the Planned Target Volume (PTV) and the dose given to the major Organs at Risk (OARs) using the 5 and 7-field IMRT approach. Except for the monitor units, no statistically significant difference regarding PTV coverage nor organ at risk sparing between 5 and 7 fields. In our study 7 fields was chosen as it is significantly spare the rectum compared to 5 fields with significantly less monitor units and treatment time when compared with 9 fields [21]. The difference may be due to the beam angels used 1800, 2700, 900, 450 and 3200 in the present study compared to 00,720, 1440, 2160 and 2880 in our study.

Hypofractionation regimens provide the opportunity to increase treatment capacity by reducing the overall patients' treatment time. Several randomized controlled trials compared hypofractionation and conventional fractionation for treatment of localized prostate cancer; the primary endpoints were toxicity of grade 2 or more and the biochemical control [22].

Dearnaley et al. conducted a multicenter randomized controlled trial at 11 UK centers (CHHiP study) (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer). 3216 Patients were randomized in a 1:1:1 ratio to receive conventional fractionation (74 Gy/37 fr) or one of 2 hypofractionation regimens: (60 Gy/20 fr) or (57 Gy/19 fr) using IMRT which was mandatory, image guided radiotherapy (IGRT) was optional. 15% of patients were low risk, 73% intermediate risk and 12% high risk [23].

There were statistically significant higher acute GI toxicities ≥ G2 (25% vs. 38% vs. 38%) (p=<0.0001) and non-significant ≥ G2 GU toxicities (46% vs. 49 vs. 46%) (p=0.9) for the hypofractionation regimen. After 5 years median follow up non-significant late GI toxicities G ≥ 2 (14% *vs.* 12% *vs.* 11%) and also non-significant ≥ G2 GU toxicities (9% vs. 12% vs. 7%) (p=0.48). No G4 toxicity was observed [24].

Regarding the PROFIT study, 608 patients were included; all were intermediate risk randomized to conventional fractionation 78 Gy/38 fr or hypofractiontion 60 Gy/20 fractions using either 3D-CRT or IMRT with IGRT which was mandatory. ADT was not permitted. Acute ≥ G2 gastrointestinal (GI) 10% versus 6% (p=0.003), similar acute ≥ G2 genitourinary (GU) 27% in both regimens. Late ≥ G2 GI 11% versus 7% (p=0.006), ≥ G2 GU 19% versus 20% which is not statistically significant. The 5-year BCFS was 85% in both arms (HR 0.96, 90% CI 0.77–1.2) [25].

The RTOG 0415 conducted a randomized study including 1115 patients; all were low risk comparing a dose of 73.8 Gy in 1.8 Gy fractions to moderate hypofractionation to a dose of 70 Gy in 28 fractions 31. Target volume was the prostate only; both 3D-CRT and

IMRT were allowed with IGRT which was mandatory. Acute ≥ G2 GI toxicities 10% vs. 11%, ≥ G2 GU toxicities 27% vs. 27% with no statistically significant difference. Significantly worse late ≥ G2 GI toxicity 14% vs. 22% (p=0.002) and late ≥ G2 GU toxicities 23% vs. 3% (p=0.05). The 5-year DFS 85.3% in the 73.8 Gy arm and 86.3% in the 70 Gy arm (HR 0.85, 95% CI 0.64-1.14); with no statistically significant difference [26].

The Dutch HYPRO study also randomized 820 patients (intermediate risk 26% and high risk 74%) between a conventional (78 Gy/39 fr) and hypofractionated dose regimen (64.6 Gy/19 fr, 3.4 Gy/fr, 3 fractions/week) and there was a ~95% utilization of IMRT and IGRT in both arms 32. Significantly higher acute ≥ G2 GI toxicities 31% vs. 42%, GU toxicities 58% vs. 61%. Regarding late toxicities, after 5 year median follow up ≥ G2 GI toxicities 18% vs. 22% and GU toxicities 39% vs. 41%. The 5-year RFS was 80.5% in the 64.6 Gy arm and 77.1% in the 78 Gy arm (p=0.36); no significant difference between arms [27].

In the present study, acute GI toxicities (diarrhoea, tenesmus) G1 55%, G2 40% and G3 5%. Acute GU toxicities G 1 60%, G2 35% and G3 5% while late toxicities GI, G1 25% and G2 15%. Late GU toxicities (dysuria and frequency), G1 30% and G2 10%. No late G3 nor G4 toxicities were observed.

The difference between the results of the above mentioned trials and our study could be explained by the small number of patients included in our study (only 20 patients) compared to hundreds or thousands in other studies, shorter follow up time (only 2 years) as the late adverse events which are estimated at the end of follow up decreases as time from treatment elapsed, higher dose of radiotherapy (compared to CHHiP trial), patient inclusion risk stratification criteria (low, intermediate or high), CHHiP study included patients low (15%), 73% intermediate (73%) and high (12%) risk, while RTOG study included only patients with low risk criteria (100%). For the HYPRO trial 26% intermediate and 74% were high risk [28].

Also, the use of 3DCRT, IMRT and IGRT which differ between different trials. The target volume definition (prostate only, prostate and proximal 1 cm of the seminal vesicle or prostate and whole seminal vesicle), the prostatic size, the PTV margin and different radiotherapy doses either conventional or hypfractionation and different contouring protocol for the rectum and the urinary bladder (filling of the rectum and bladder and the drawing technique) [29,30].

Overall, meta-analysis of ten randomized clinical trials including more than 8400 patients suggested that higher acute GI toxicity for hypo and similar acute GU toxicity in both groups. Comparable late GI and GU toxicity between the hypo and conventional fractionation regimens, although RTOG 0415 and HYPRO reported a higher incidence of late toxicity with hypofractionation. Similarly, there were no differences in overall survival (HR 0.94, 95% CI 0.83–1.07) or prostate cancer-specific survival (HR 1.00, 95% CI 0.72–1.39) between hypofractionation and conventional fractionation [31].

## CONCLUSION

Although the small number of patients and the short follow up period, hypofractionated radiotherapy appears to be safe and effective regarding the biochemical control and toxicity profile for treating localized low and intermediate risk prostate cancer patients. It is more convenient, less costly with decreased burden on the health care system. Recruitment of more patients, longer follow up duration and direct comparison with conventional fractionation and with other hypo fractionated regimens are recommended.

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## AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: sherif Elzawawy, Taha Hewala and Doaa Elzayat. Treatment planning and dosimetric data collection: sherif Elzawawy, Doaa Elzayat, Ramadan Hammam; analysis and interpretation of results: sherif Elzawawy, Taha Hewala, Doaa Elzayat ; manuscript preparation and revision: sherif Elzawawy, Taha Hewala and Ramadan Hammam. All authors reviewed the results and approved the final version of the manuscript.

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## DATA AVAILABILITY

The datasets from the current study are not publicly available prior to reporting of mature outcomes from the parent clinical trial. Requests for data and materials should be sent to the corresponding author.

## DECLARATIONS OF INTEREST

None

## ETHICAL APPROVAL

The study was reviewed and approved by the Ethics committee, faculty of Medicine, Alexandria University in accordance with the Helsinki Declaration.

## CONSENT TO PARTICIPATE

All patients have consented to participate in the study.

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