Outcomes, Toxicities, and Dosimetric Comparison of Different Hypo-fractionated 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 the safety and efficacy of hypo-fractionated radiotherapy with a 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 a 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, or 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). The 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 of V25%, V35%, and V50% of the rectum were significantly higher for the 5-fields compared to the 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 gastrointestinal 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: Hypo-fractionated radiotherapy is safe and effective regarding the biochemical control and toxicity profile, more convenient, and less costly.

Keywords: hypo-fractionated radiotherapy, localized prostate cancer, IMRT.

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Background:

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 presented with localized disease [1].

Management strategy of the localized disease depends on a risk stratification system which is based on prostate-specific antigen (PSA) level, Gleason score, clinical stage TNM (tumor extension, seminal vesicle invasion, extracapsular extension, pelvic LN involvement, and distant spread), several 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 the 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 on treatment machines [3-7].

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

Contrary to most other tumors, prostate cancer cells have a lower 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 hypo-fractionated IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) compared to conventional fractionation. Toxicity was similar between hypo-fractionated 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 Hypo-fractionated radiotherapy in the treatment of localized prostate cancer. The secondary objective is a dosimetric comparison between using 5-fields, 7-fields, and 9-fields of Intensity-modulated radiotherapy regarding target volume coverage and normal tissue sparing.

Methods and Material:

Patients:

This study was carried out at 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, extracapsular 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. Unfavorable 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, transrectal ultrasound of the prostate, biopsy, prostate-specific antigen (PSA) level, and MRI pelvis.

Methods

Patients were immobilized using a body mattress extend from mid back to mid-thigh in the supine positions with hands above the head. Patients were instructed to have a low-residue diet and to empty the rectum using an enema the night before the 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 the 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 bulb, 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 the 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 the step-and-shoot technique (5-fields, 7-fields, and 9-Fields) for each patient. Equidistant fields were generated using 6MV- 15 MV photons and dosimetrically compared regarding target volume coverage and organ at risk sparing. All three plans were done using 6MV – 15MV photons.

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

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

IMRT-9: equal angle separation of 40 degrees between every 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 tumor 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 constraints:
Dose constraints for organs at risk are listed in (table 1).

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 was 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 / V t   X   Vt ref / V ref

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, monthly thereafter for 3 months, and then every 3 months during follow-up.

PSA was measured at baseline 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.

Table 1: Dose constraints for organs at risk

Bladder Constraints		Rectal Constraints		Femoral head		Penile bulb
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%			

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

Patient characteristics:
The median age was 68 years, and the mean PSA was 13.2 ng/dl. Patients and tumor characteristics are summarized in (table 2).

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).

Dosimetric comparisons between three planning techniques for organs at risk (OARs):

The mean doses of 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, and right and left femoral heads no statistically significant differences between the 3 planes (table 5) (table 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 spares 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 fewer 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 baseline 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 gastrointestinal toxicities (rectal pain, diarrhea, 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 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. No rectal bleeding, no urine retention, no incontinence, and no haematuria were detected (table 7).

Table 2: Patients and tumor 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)	
Yes	9 (45%)
No	11 (55%)

Dosimetric comparisons between three planning techniques for Target volume coverage:

Table (3) illustrates (the 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 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).

Dosimetric comparison between the 5 and 9-fields showed a statistically significant difference regarding

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

Dosimetric Parameters 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

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

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 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 femur	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
	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 femur	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
	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	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 the femur	Dmax	0.092	0.851	0.189
	Dmean	0.46	0.63	0.349
Left head of the femur	Dmax	0.39	0.851	0.39
	Dmean	0.51	0.092	0.092

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 developing countries. IMRT is the standard of care for early and locally advanced cases as it significantly spares organ at risk, especially the rectum which allow for dose escalation which improves 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 were chosen as they significantly spare the rectum compared to 5-fields with significantly fewer monitor units and treatment time when compared with 9-fields [21]. The difference may be due to the beam angles 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 the 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 Hypo-fractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer). 3216 Patients were randomized in a 1:1:1 ratio to receive conventional fractionation (74Gy/37fr) or one of 2 hypofractionation regimens: (60Gy/20 fr) or (57Gy/19 fr) using IMRT which was mandatory, image-guided radiotherapy (IGRT) was optional. 15% of patients were low risk, 73% were intermediate risk, and 12% were 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 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, and all were intermediate-risk randomized to conventional fractionation 78 Gy/ 38 fractions or hypo-fractionation 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 of whom 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). The 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 73.8Gy arm and 86.3% in the 70Gy 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 (78Gy/39 fr) and hypo-fractionated dose regimen (64.6Gy/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 a 5-year median follow-up, ≥ G2 GI toxicities were 18% vs 22% and GU toxicities 39% vs 41%. The 5-year RFS was 80.5% in the 64.6Gy arm and 77.1% in the 78Gy arm (p=0.36); no significant difference between arms [27].

In the present study, acute GI toxicities (diarrhea, 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% were intermediate and 74% were high-risk [28].

Also, the use of 3DCRT, IMRT, and IGRT differs 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 hypo-fractionation and different contouring protocol for the rectum and the urinary bladder (filling of the rectum and bladder and the drawing technique) [29-30].

Overall, a meta-analysis of ten randomized clinical trials including more than 8400 patients suggested 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, hypo-fractionated 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 and less costly with the 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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