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# Moderate Hypofractionated Irradiation and Androgen Deprivation Therapy in Clinically Pelvic Nodes Prostate Cancer, Treatment Outcome; Single Institution Experience

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## Abstract

***Objectives:*** To test the feasibility of hypofractionated irradiation using VMAT and IGRT in non-metastatic clinically pelvic nodes prostate cancer with evaluating toxicity and survival outcomes.

***Methods:*** Database was reviewed for all non-metastatic prostate cancer patients with initial clinical pelvic nodes between 2012 and 2017 which have received hypofractionated irradiation 50-60Gy in 20-25 fractions. All 48 patients had hormonal therapy for 24-36 months.

***Results:*** With a median follow up 42 months (10-80), median age was 68 years, 50% of patients had Gleason score 7, initial PSA was between 21-100ng/ml in 56% of patients, T2 stage was in 42% of patients, 73% of patients received neoadjuvant hormonal therapy for 7-12 months, median lymph node size was 1.3cm, median PSA before irradiation was 0.6ng/ml, 45 patients received 60Gy in 25 fractions. No acute or chronic grade 3 or 4 toxicity was recorded according to RTOG toxicity scale. Local failure was in 3 patients and distant metastasis in 3 patients. Predictors of relapse were low irradiation dose (50Gy had 100% relapse vs. 6.7% of 60Gy [P=0.001]) and initial PSA which had marginally significant effect (P=0.069). Initial PSA >100ng/ml and irradiation dose had significant effect on Disease Free Survival (P=0.001 & < 0.001 respectively). Local Recurrence Free Survival was 100%, 85% and 85% at 3, 5 and 6 years respectively. Distant Metastasis Free Survival was 93.3%, 89.6% and 89.6% at 3, 5 and 6 years respectively. DFS was 93.3%, 74.1% and 74.1% at 3, 5 and 6 years respectively. All patients were a live at last follow up visits.

***Conclusion:*** The moderate hypofractionated radiotherapy regimen is well tolerated in this cohort of clinically pelvic nodes prostate cancer patients. The patients who received higher dose of 60Gy in 25 fractions had better outcomes. We propose further dose escalation with modern radiotherapy techniques.

**Keywords:** ***High Irradiation, Prostate Cancer, Pelvic Nodes***

## Background

Prostate cancer is one of the most common cancers among men worldwide and represents 13.1% of cancer in the U.S [1], while it is less common in Arab countries and represents 4.7% to 6.4% of all cancers [2-3]. Advances in imaging modalities play a major role in detection of clinically node positive prostate cancer such as multiparametric MRI, PSMA and choline PET scans. Treatment of prostate cancer with pelvic lymph nodes remains a controversial issue [4]. Prostate cancer has a favorable prognosis with a 5-year relative survival of 97.5% [5]. Localized prostate cancer can be effectively treated by surgery or radiotherapy [6]. Radiotherapy has many advantages over surgery as there are no perioperative complications, feasible in a wide range of ages in addition to low urinary complications and erectile function preservation [7].

The disadvantages of radiotherapy include a long course of treatment, low urinary and rectal toxicity however the new hypofractionation schedules and modern irradiation techniques managed these issues [7-8]. To our knowledge; this is the first study presented in the Middle East Region treating clinically pelvic lymph nodes prostate cancer by using a combination of hormonal therapy and hypofractionated irradiation using VMAT and IGRT with evaluating toxicity and survival outcomes.

## Materials & Methods

### Cohort selection

Database was reviewed for all non-metastatic clinically pelvic lymph nodes prostate cancer patients who referred to radiation Oncology section - King Faisal Specialist Hospital and Research Center (KFSH & RC) - Riyadh, Saudi Arabia between June 2012 and December 2017. For retrospective review of the data with less than the minimal risk for the patients, no patient consent was required however Research Ethics Committee approved this project via Research Advisory Council number 2151032. All patients had biopsy proven prostate adenocarcinoma, serial PSA, initial staging by abdominal- pelvic MRI or CT scan and whole-body PET/CT (Choline or PSMA) scans.

### Treatment plan

All patients treated with a combination of ADT and high dose irradiation by VMAT/IGRT 50-60Gy in 20-25 fractions. The radiotherapy details (preparation, simulation, verification and arc technique) utilized was described previously [9].

### Planning Target Volume

PTV60 was delivered to prostate and seminal vesicle. PTV55 was delivered to clinically pelvic lymph nodes post hormonal therapy. PTV50 [9] was delivered to whole pelvic lymph nodes. There were


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three cases who received 50Gy in 20 fractions; PTV50 was delivered to prostate and seminal vesicle, PTV45 was delivered to whole pelvic lymph nodes. Organs at risk OAR contouring was followed the RTOG guidelines of normal tissues of pelvis.

**Follow up visits**

It was described before [9]; patients were evaluated for toxicity and survival outcomes. LRFS was calculated from end of radiation treatment to date of local recurrence or last visit seen free. DMFS was calculated from end of radiation treatment to date of distant metastasis or last visit seen free. DFS was calculated from end of radiation treatment to date of relapse or last visit seen free.

**Statistical analysis**

Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number (percentage). LRFS, DMFS and DFS time-to-event distributions were estimated using Kaplan-Meier plot method and compared using two-sided exact log-rank test. All tests were two sided. A p-value <0.05 was considered significant. All statistics were performed using SPSS 22.0 for windows (IBM Inc., Chicago, IL, USA) and Med Calc 13 for windows (Med Calc Software bvba, Ostend, Belgium).

## Results

**Cohort characteristics**

All patients' characteristics are at table 1. With a median follow up 42 months (10-80), median age was 68 years, 50% of cases had Gleason score 7, initial PSA was between 21-100ng/ml in 56% of cases, T2 stage in 42% of patients, the majority of patients (73%) received neoadjuvant hormonal therapy for 7-12 months, median lymph node size was 1.3cm, median PSA before irradiation was 0.6ng/ml, 6% of cases received 50Gy in 20 fractions (due to borderline performance status) while the rest received 60Gy in 25 fractions. All patients had hormonal therapy for 24-36 months.

**Toxicity outcome**

No acute or chronic grade 3 or 4 toxicity was recorded according to RTOG toxicity scale during irradiation (no treatment interruption during irradiation course) or follow up visits.

**Survival outcome and predictors of relapse**

Local failure was in 3 patients (6.25%), distant metastasis in 3 patients (6.25%) at paraaortic lymph nodes so relapse was in 6 patients (12.5%). Predictors of relapse (table 2) were low irradiation dose (50Gy patients had 100% relapse vs. 6.7% of 60Gy patients [P=0.001]) while initial PSA had marginally significant effect on relapse (P=0.069). Initial PSA (>100ng/ml) and irradiation dose (50Gy) had significant effect on DFS (P=0.001 & < 0.001 respectively) as shown at table 3. LRFS was 100%, 85% and 85% at 3, 5 and 6 years respectively as shown at figure 1. DMFS was 93.3%, 89.6% and 89.6% at 3, 5 and 6 years respectively as shown at figure 2. DFS was 93.3%, 74.1% and 74.1% at 3, 5 and 6 years respectively as shown at figure 3. Initial PSA between 21-100 ng/ml had poor DFS at 3, 5 and 6 years (81.1%, 35.1% and 35.1%) owing to the low irradiation dose given in this cohort which represent 50% of relapse while DFS for other groups was 100% at 3, 5 and 6 years as shown at figure 4. DFS was 33.3% at 3 years for patients received 50Gy while it was 100%, 82.7% and 82.7% at 3, 5 and 6 years for patients received 60Gy as shown at figure 5. All patients were a live at last follow up visits.

**Table 1:** Basic characteristics and outcome of 48 patients with prostate cancer

| Parameters | All patients (N=48) No. % | | Parameters | All patients (N=48) No. % | |
|---|---|---|---|---|---|
| Age (years) Mean ± SD | 70.72 ± 8.21 | | LN size pre-RT (cm) Mean ± SD | 1.42 ± 0.56 | |
| Median (Range) | 68 (60 – 85) | | Median (Range) | 1.30 (1 – 3.90) | |
| ≤65 years | 18 | 37.5% | ≤1 cm | 8 | 16.7% |
| >65 years | 30 | 62.5% | 1.1-2 cm | 34 | 70.8% |
| | | | > 2 cm 6 | 12.5% | |
| Gleason score | | | PSA pre-RT | | |
| Mean ± SD Median (Range) | 7.85 ± 0.96 7.50 (7 - 10) | | Mean ± SD Median (Range) | 1.32 ± 1.61 0.62 (0.10 - 6.80) | |
| 7 | 24 | 50% | <0.25 | 13 | 27.1% |
| 8 | 9 | 18.8% | 0.25 – 0.42 | 6 | 12.5% |
| 9 | 13 | 27.1% | >0.42 | 29 | 60.4% |
| 10 | 2 | 4.2% | RT dose | | |
| 7 | 24 | 50% | 50 Gy | 3 | 6.2% |
| 8-10 | 24 | 50% | 60 Gy | 45 | 93.8% |
| iPSA pre-NAH | | | PSA post-RT | | |
| Mean ± SD | 68.37 ± 72.10 | | Mean ± SD | 0.20 ± 0.26 | |
| Median (Range) | 35 (10 – 406) | | Median (Range) | 0.12 (0.01 – 1.40) | |
| ≤20 | 11 | 22.9% | Radiological Response | | |
| 21-100 | 27 | 56.2% | CR | 42 | 87.5% |
| >100 | 10 | 20.8% | PR | 6 | 12.5% |
| T | | | FU duration (months) | | |
| T2 | 20 | 41.7% | Mean ± SD | 40.66 ± | 19.22 |
| T3a | 19 | 39.6% | Median (Range) | 42 (10 | – 80) |
| T3b | 9 | 18.8% | | | |
| NAH duration (months) | | | Relapse | | |
| Mean ± SD | 10.75 ± | 4.25 | Absent | 42 | 87.5% |
| Median (Range) | 10 (6 – | 25) | Present | 6 | 12.5% |
| ≤6 months | 4 | 8.3% | Distant metastasis | | |
| 7-12 months | 35 | 72.9% | Absent | 45 | 93.8% |

| | | | | | |
|---|---|---|---|---|---|
| >12 months | 9 | 18.8% | Present | 3 | 6.2% |
| | | | Local failure<br>Absent | 45 | 93.8% |
| | | | Present 36.2% | | |

**Table 2:** Predictors for relapse.

| Relapse | | | | | | | |
|---|---|---|---|---|---|---|---|
| | All patients (N=48) | | Absent (N=42) | | Present (N=6) | | p-value |
| Parameters | No. | % | No. | % | No. | % | |
| Age group | | | | | | | |
| ≤65 years | 18 | 37.5% | 15 | 83.3% | 3 | 16.7% | 0.658[b] |
| >65 years | 30 | 62.5% | 27 | 90% | 3 | 10% | |
| Gleason score | | | | | | | |
| 7 | 24 | 50% | 21 | 87.5% | 3 | 12.5% | 0.940[a] |
| 8 | 9 | 18.8% | 8 | 88.9% | 1 | 11.1% | |
| 9 | 13 | 27.1% | 11 | 84.6% | 2 | 15.4% | |
| 10 | 2 | 4.2% | 2 | 100% | 0 | 0% | |
| 7 | 24 | 50% | 21 | 87.5% | 3 | 12.5% | 1.000[b] |
| 8-10 | 24 | 50% | 21 | 87.5% | 3 | 12.5% | |
| iPSA pre-NAH | | | | | | | |
| ≤20 | 11 | 22.9% | 11 | 100% | 0 | 0% | 0.069[a] |
| 21-100 | 27 | 56.2% | 21 | 77.8% | 6 | 22.2% | |
| >100 | 10 | 20.8% | 10 | 100% | 0 | 0% | |
| T | | | | | | | |
| T2 | 20 | 41.7% | 17 | 85% | 3 | 15% | 0.406[a] |
| T3a | 19 | 39.6% | 18 | 94.7% | 1 | 5.3% | |
| T3b | 9 | 18.8% | 7 | 77.8% | 2 | 22.2% | |
| NAH duration | | | | | | | |
| ≤6 months | 4 | 8.3% | 4 | 100% | 0 | 0% | 0.708[a] |
| 7-12 months | 35 | 72.9% | 30 | 85.7% | 5 | 14.3% | |
| >12 months | 9 | 18.8% | 8 | 88.9% | 1 | 11.1% | |
| LN size pre-RT | | | | | | | |
| ≤1 cm | 8 | 16.7% | 8 | 100% | 0 | 0% | 0.244[a] |
| 1.1-2 cm | 34 | 70.8% | 28 | 82.4% | 6 | 17.6% | |
| >2 cm | 6 | 12.5% | 6 | 100% | 0 | 0% | |
| PSA pre-RT | | | | | | | |
| <0.25 | 13 | 27.1% | 13 | 100% | 0 | 0% | 0.280[a] |
| 0.25 – 0.42 | 6 | 12.5% | 5 | 83.3% | 1 | 16.7% | |
| >0.42 | 29 | 60.4% | 24 | 82.8% | 5 | 17.2% | |
| RT dose | | | | | | | |
| 50 Gy | 3 | 6.2% | 0 | 0% | 3 | 100% | 0.001[b] |
| 60 Gy | 45 | 93.8% | 42 | 93.3% | 3 | 6.7% | |
| Response | | | | | | | |
| CR | 42 | 87.5% | 36 | 85.7% | 6 | 14.3% | 1.000[b] |
| PR | 6 | 12.5% | 6 | 100% | 0 | 0% | |

*a: Chi-square test; b: Fisher's exact test; p-value<0.05 is significant.*

**Table 3:** Disease Free Survival.

| | N | | | Disease Free Survival (DFS) | | | | p-value[a] |
|---|---|---|---|---|---|---|---|---|
| | | Mean | (months) | (95%CI) | 3-years | 5-years | 6-years | |
| All patients | 48 | 70.32 | months | (63.53 – 77.11) | 93.3% | 74.1% | 74.1% | -------- |
| Age group | | | | | | | | |
| ≤65 years | 18 | 67.93 | months | (58.11 – 77.76) | 92.3% | 71.2% | 71.2% | 0.835 |
| >65 years | 30 | 71.27 | months | (62.35 – 80.18) | 94.1% | 96.9% | 96.9% | |
| Gleason score | | | | | | | | |
| 7 | 24 | 71.91 | months | (63.97 – 79.86) | 100% | 75% | 75% | 0.674 |
| 8-10 | 24 | 56.53 | months | (50.92 – 62.14) | 86.7% | 80% | -------- | |
| iPSA pre-NAH | | | | | | | | |
| ≤20 | 11 | 62 | months | | 100% | 100% | -------- | 0.001 |
| 21-100 | 27 | 52.45 | months | (42.57 – 62.33) | 81.8% | 35.1% | 35.1% | |
| >100 | 10 | 80 | months | | 100% | 100% | 100% | |
| T | | | | | | | | |
| T2 | 20 | 70.93 | months | (63.90 – 77.96) | 100% | 76.6% | 76.6% | 0.377 |
| T3a | 19 | 75 | months | (65.70 – 84.29) | 90% | 90% | 90% | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| T3b | 9 | 50.53 | months | (38.67 – 62.39) | 80% | 53.3% | -------- | |
| NAH duration | | | | | | | | |
| ≤6 months | 4 | 69 | months | | 100% | 100% | -------- | 0.592 |
| 7-12 months | 35 | 67.83 | months | (58.80 – 76.85) | 90% | 67.8% | 67.8% | |
| >12 months | 9 | 59.57 | months | (55.16 – 63.97) | 100% | 85.7% | 85.7% | |
| LN size pre-RT | | | | | | | | |
| ≤1 cm | 8 | 69 | months | | 100% | 100% | -------- | 0.245 |
| 1.1-2 cm | 34 | 66.39 | months | (57.45 – 75.33) | 90.9% | 63.4% | 63.4% | |
| >2 cm | 6 | 62 | months | | 100% | 100% | -------- | |
| PSA pre-RT | | | | | | | | |
| <0.25 | 13 | 60 | months | | 100% | 100% | -------- | 0.286 |
| 0.25 – 0.42 | 6 | 42.75 | months | (35.53 – 49.96) | 75% | -------- | -------- | |
| >0.42 | 29 | 68.12 | months | (59.48 – 76.77) | 95% | 66.8% | 66.8% | |
| RT dose | | | | | | | | |
| 50 Gy | 3 | 34.66 | months | (28.97 – 40.36) | 33.3% | -------- | -------- | <0.001 |
| 60 Gy | 45 | 74.44 | months | (68.69 – 80.19) | 100% | 82.7% | 82.7% | |
| Response | | | | | | | | |
| CR | 42 | 67.35 | months | (58.90 – 75.80) | 91.7% | 66% | 66% | 0.147 |
| PR | 6 | 62 | months | | 100% | 100% | -------- | |

*95%CI: 95%Confidence Interval; a: Log-rank test; p-value<0.05 is significant.*

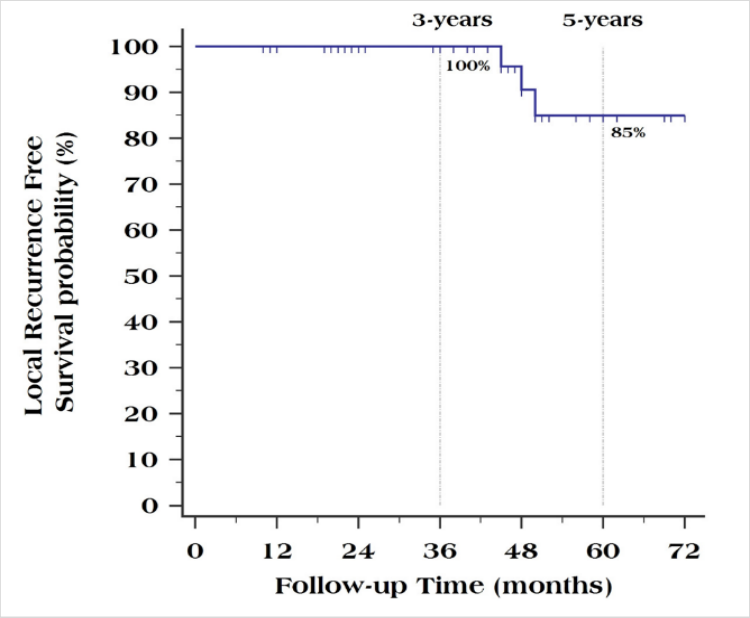


**Figure 1:** Kaplan Meier plot for LRFS among the studied patients.

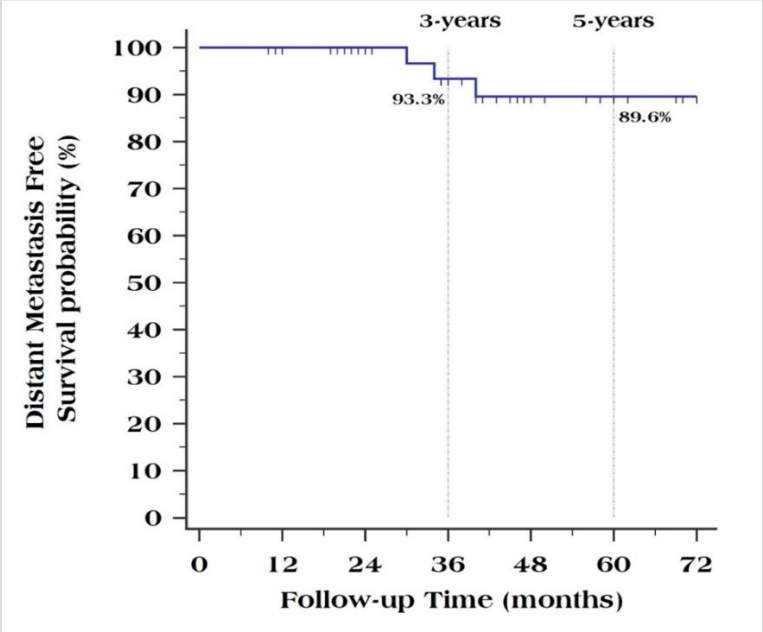


**Figure 2:** Kaplan Meier plot DMFS among the studied patients.

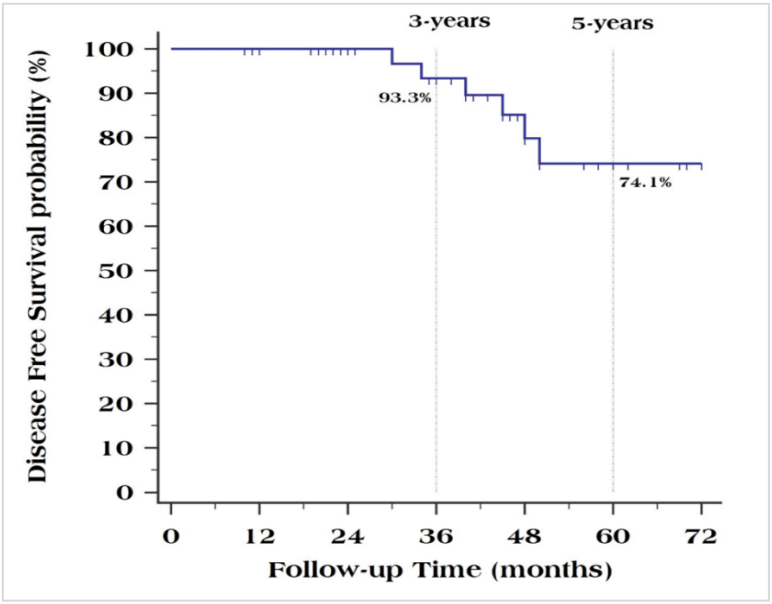


**Figure 3:** Kaplan Meier plot DFS among the studied patients.

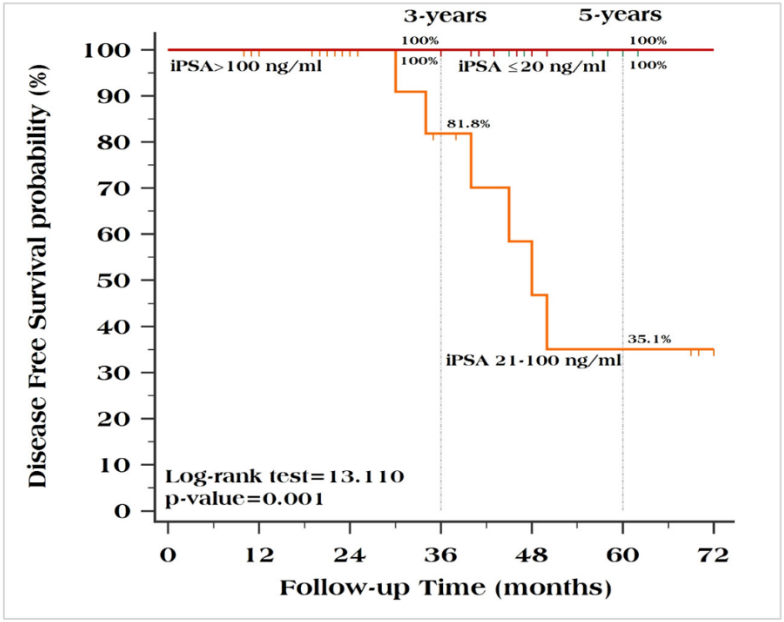


**Figure 4:** Kaplan Meier plot for DFS among the studied patients stratified by pre-NAH iPSA.

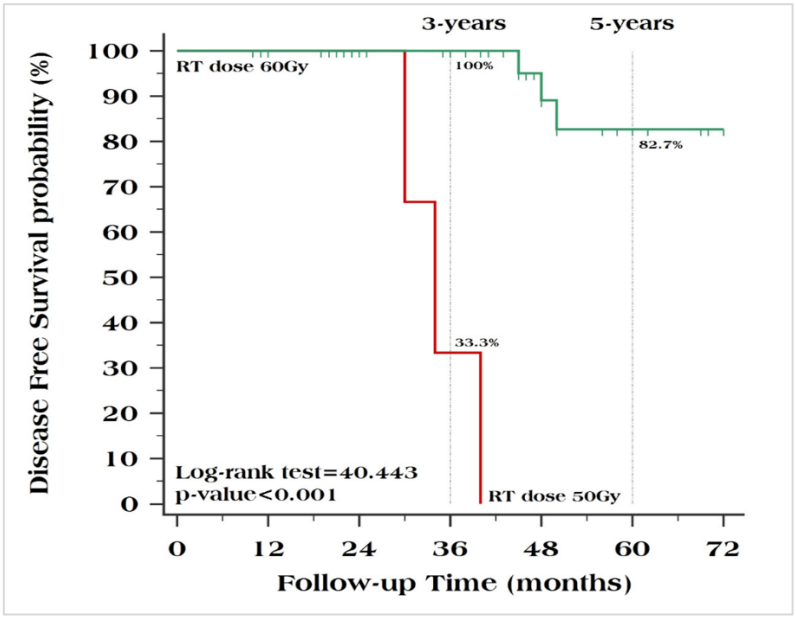


**Figure 5:** Kaplan Meier plot for DFS among the studied patients stratified by radiotherapy dose

## Discussion

The practice at our institution for clinically pelvic nodes non metastatic prostate cancer (T1-4N1M0) is a combination of ADT and concurrent radiation therapy. Local relapse was started at the end of fourth year (45, 48 & 52 months), while distant relapse (low radiation dose 50Gy in 20 fractions) was started at end of third year (30, 34 & 40 months). Resuming hormonal therapy alone have controlled the local failure while second line therapy or resuming hormonal therapy have controlled the distant relapse so no prostate cancer specific mortality was recorded during follow up period. No local failure at primary nodal disease so nodal irradiation was optimal however local failure was at the primary site so dose escalation should to be at primary not nodal areas.

In the 1990s, the RTOG 85-31 trial have reported a significant survival outcome in patients treated with combination of radiotherapy and ADT over patients receiving only radiotherapy and at the same time confirmed the need for ADT in patients with pathologically confirmed metastases in lymph nodes, who received adjuvant radiotherapy [10].

A similar result of combined modality have reported by Tward et al study in 2013 of 1100 patients [11], Rusthoven et al study in 2014 of 3787 patients [12], Lin et al study in 2015 of 3540 patients [13] and recently in the 2019, under PSA era and new imaging modalities recommendations of the Australian and New Zealand Radiation Oncology Genito-Urinary group to go for such combination [14].

In our cohort regarding to toxicity, all acute and late side effects were of grade ≤2, as noticed by Goldner et al [15], Krzysztofiak et al [16] and Urbano et al [17]. However Lilleby et al [18] reported grade 3 in 1% of GI and 11 % of GU toxicities, similar to Engels et al [19] who observed only acute GU toxicities of Grade 3 in 4% of patients, while Fonteyne et al [20] noted 3year actuarial risk of late grade 3 GI toxicity in 8% & late grade 3-4 GU toxicity in 6%. Mallick et al [21] and Onishi [22] et al showed similar results who observed no acute toxicity of grade 3 or 4 while late toxicity of grade 2 & 3 only. Mallick et al [21] observed late grade ≥ 2 GI and GU toxicities in 13% and 18% respectively. Onishi et al [22] reported grade ≥2 late GU and GI toxicities in 4.7% and 7.4% respectively. These variable results are owing to different radiation doses and techniques. In our series regarding to survival outcome, DFS at 3 years was 93.3% while it was lower in series by Fonteyne et al [20] which was 89%. In our series DFS at 5 years was 74.1%, comparable to Lilleby et al [18] which was 76.2% however lower DFS recorded by Goldner et al [15] and Crehange et al [23] (54% and 67% respectively), while higher in series by Onishi et al [22] which was 88.1%.DMFS was 93.3% and 89.6% at 3and 5 years better than Krzysztofiak et al [16] which was 76% at 3 and 5 years.

In our series local failure was in 3 (6.25%) and distant metastasis in 3 (6.25%) out of 48 patients at median follow up of 42 months, while Mallick et al [21] series had 4 (6.6%) out of 61patients with a median follow-up of 48 months contrary to Krzysztofiak et al [16] who had a median follow up 40 months with 5 (22.73%) failures out of 22 patients. Regarding to relapse predictors, In our series, Initial PSA (>100ng/ml) and irradiation dose (50Gy) had significant effect on DFS (P=0.001 & < 0.001 respectively), contrary to Crehange et al [23] who showed that both age and Gleason score were significant predictors for survival outcome, while Lilleby et al [18] noticed only high Gleason score had a strong independent prognostic impact on survival, however Krzysztofiak et al [16] found that only stage had effect on outcome.

In our series duration of neoadjuvant hormonal therapy did not have significant effect on outcome contrary to Hussain et al [24] who noticed that a PSA value ≤4 ng/mL after 7 months of hormonal therapy is associated with better outcome, while Lilleby et al [18] noticed that duration of ADT ≥28 months showed a significant independent association with improved outcome.In our series, lymph node involvement was not associated with survival endpoints as recoded by Krzysztofiak et al [16] and Lilleby et al [18].

## Conclusion

The moderate hypofractionated radiotherapy regimen is well tolerated in this cohort of clinically pelvic node prostate cancer patients. The patients who received higher dose of 60Gy in 25 fractions had better outcomes. We propose further dose escalation with modern radiotherapy techniques.

## Abbreviations

MRI: Magnetic Resonance Imaging
PSA: Prostate Specific Antigen
PSMA: Prostate Specific Membrane Antigen
PET: Positron Emission Tomography
VMAT: volumetric Modulated Arc Therapy
IGRT: Image Guided Radiotherapy
ADT: Androgen Deprivation Therapy
LRFS: Local Recurrence Free Survival
DMFS: Distant Metastasis Free Survival
DFS: Disease Free Survival
RTOG: Radiation Therapy Oncology Group
GI: Gastrointestinal
GU: Genitourinary

## Funding statement

None

## Competing interest

None

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