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Hypofractionated Simultaneous Integrated Boost (SIB) versus Conventional Fractionation in Localized Prostate Cancer: A Randomized Pilot Study

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Abstract

Purpose: Radical prostatectomy or radiotherapy has comparable results in the treatment of localized prostate cancer. High dose external irradiation entails a prolonged 7–8 weeks of treatment with significant inconvenience to elderly patients. Hypofractionated regimen in prostate cancer depends on the distinctive radiobiological properties of prostate cancer cells; their relative low alpha beta ratio compared to that for late-reacting rectal tissue allows for significant dose escalation per fraction without expected increase in late normal tissue reaction.

Patients and Materials

Between July 2012 and December 2013, twenty patients were blindly randomized into two groups. The planning target volume in the study group received 65Gy to 67.5Gy/25 fractions over 5 weeks. The patients in the control arm received 74Gy to 78Gy in 2Gy/fraction. Cost–benefit was evaluated for both regimens.

Results

Both groups were comparable regarding risk factors, with no significant statistical differences. Four

patients in the study group developed grade 2 urinary toxicity and one patient had grade 3 during treatment. At six months no patient had urinary symptoms. In the control arm 4 patients have grade 2 toxicity during treatment which disappeared at six months. The two groups showed no statistical difference in the mean quality of life. Serum PSA reached a nadir value of 0.02 and 0.04 in the study and control groups respectively at 3 month post-treatment. The cost of treatment for the study group was 25000 L.E. per patient compared to 40000 L.E. in the control group. The hypofractionated group consumed 31138 MU compared to 45611 MU for the control group with a p-value of 0.015.

Conclusion

Hypofractionated IMRT with concomitant boost for localized cancer prostate is a feasible option with lesser cost and comparable toxicities. Longer follow-up is required to assess the late effects before recommending it as a standard of care.

Keywords

IMRT, prostate cancer, hypofractionation, local tumour control

Introduction

Radical prostatectomy used to be the standard treatment for localized prostate cancer, with radiation limited to locally advanced disease and the elderly, however, the expanding evidence of the competitive results for radiotherapy versus surgery as reported in literature has encouraged the use

of radical radiotherapy treatment ⁽¹⁾. Megavoltage external beam radiotherapy was introduced in the

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late 1960s for the treatment of prostate cancer. With the development and integration of modern imaging modalities, treatment planning systems and modern treatment techniques, more accurate target definition was achieved, allowing for more normal tissue sparing and dose escalation, thus ultimately improving outcome ⁽²⁾. Compared with the conventional three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT) offers many potential benefits. It can improve dose conformity around the target volume, thereby increasing the therapeutic ratio which can permit tumor dose escalation, resulting in improved local control and reduced risk of treatment related complications ⁽³⁾. Another advantage of IMRT is its ability to generate dose distributions of specific levels of non-uniformity in target volumes. Accordingly, different dose levels can be prescribed to different targets or different regions of the target. An immediate application of this characteristic of IMRT is to plan and treat the boost dose together with the large field prescription dose. Simultaneous treatment of multiple targets with different prescribed doses is called the simultaneous integrated boost (SIB) technique. This permits delivery of graded dose levels to tumor-bearing tissues and tissues at risk of subclinical tumor spread, and spares normal tissues to the greatest extent possible. The SIB-IMRT strategy not only produces superior dose distributions but also is an easier, more efficient, and perhaps less error-prone way of planning and delivering IMRT because it involves the use of the same plan for the entire course of treatment ⁽⁴⁾. The aim of this study is to assess the feasibility of applying hypofractionated simultaneous integrated boost in intensity modulated radiation therapy for the treatment of localized prostate cancer and comparing it to conventionally fractionated IMRT, with regards to its effect on treatment toxicity, as well as impact on treatment delivery, patient convenience and quality of life and its overall cost benefit.

Patients and Methods

The current study is a prospective randomized pilot feasibility trial designed to assess hypofractionated simultaneous integrated boost for the treatment of localized prostate cancer and comparing it to conventionally fractionated IMRT with a sequential boost, with regards to treatment related toxicity,

impact on treatment delivery, as well as patient convenience and quality of life and its overall cost benefit.

The study was conducted at the Clinical Oncology and Radiation Department (NEMROCK), Faculty of Medicine, Cairo University between July 2012 and December 2013, after approval of the institutional scientific and ethical committees.

Patient Characteristics

Twenty males with localized prostate cancer were recruited for our study, the Inclusion criteria were: age between 40–80 years, performance Status (WHO) 0–2, pathologically proven prostatic adenocarcinoma, Gleason's score 2–10, baseline serum prostatic antigen >4 ng/dl, TNM Stage T1a–T3a, N0, M0, patient written informed consent and adherence to treatment, patient weight \geq 140kg, adequate hematological, renal and hepatic profiles. The exclusion criteria were as follows: extra-prostatic soft tissue extension invading adjacent structures (T3b/T4), lymph node metastasis (LN+ve), bony metastasis (M1), previous pelvic surgery or radiation, concomitant neoplastic disease or previous anti-neoplastic non-hormonal therapy, urinary bladder stones, performance Status (WHO) 3–4, patient refusing treatment (Patients' Characteristics are shown in (Table 1).

Treatment

Hormonal therapy

The patient starts 2–6 months of neoadjuvant combined hormonal treatment (LHRH agonist and an antiandrogen), followed with concomitant hormonal treatment during the radiation course for intermediate and high risk groups then adjuvant hormonal for 2–3 years in the high risk group (Roach, et al., 2000).

Radiotherapy

Simulation was done with an empty rectum and a half-full bladder in the supine position with the arms in the supine position. CT cuts were taken at 2.5mm intervals starting at the level of the 4th lumbar vertebrae at 5cm below the ischial tuberosity. Pelvic MRI was done in same setup and preparation condition for accurate CT-MRI fusion was done ⁽⁵⁾, and images were transferred to the Eclipse treatment

| Parameter | | Experimental | | Control | | P-value |
|------------------------------|------------------|--------------------|----|--------------------|----|---------|
| | | Number | % | Number | % | |
| Age | Mean (\pm SD) | 70.2 (\pm 3.99) | – | 64 (\pm 5.0) | – | 0.009 |
| | Median (Range) | 69.5 (65–77) | – | 65 (53–70) | – | |
| PS | 0 | 4 | 40 | 4 | 40 | 1.0 |
| | 1 | 6 | 60 | 6 | 60 | |
| Gleason | 6 | 6 | 60 | 3 | 30 | 0.591 |
| | 7 | 3 | 30 | 6 | 60 | |
| | 8 | 0 | 0 | 1 | 10 | |
| | 9 | 1 | 10 | 0 | 0 | |
| T-Stage | 1c | 1 | 10 | 0 | 0 | 1.0 |
| | 2a | 3 | 30 | 1 | 10 | |
| | 2b | 3 | 30 | 4 | 40 | |
| | 2c | 3 | 30 | 5 | 50 | |
| Risk Group | Low | 2 | 20 | 0 | 0 | – |
| | Intermediate | 4 | 40 | 2 | 20 | |
| | High | 4 | 40 | 8 | 80 | |
| SV Risk | Mean (\pm SD) | 25.4(\pm 22.0) | – | 47(\pm 24.7) | – | 0.066 |
| | Median (range) | 17 (6–73) | – | 41 (8–86) | – | |
| | >15% | 5 | 50 | 9 | 90 | |
| LN Risk | Mean (\pm SD) | 34.5 (\pm 29.6) | – | 59.5 (\pm 34.2) | – | 0.116 |
| | Median (range) | 25(8–100) | – | 53 (12–130) | – | |
| | >15% | 6 | 60 | 9 | 90 | |
| HRT* Duration (months) | Average | 6.1 (\pm 10.1) | – | 3.9 (\pm 1.22) | – | 0.525 |
| | Median | 3 (0–36) | – | 3 (0–6) | – | |

*HRT: Hormonal Therapy, SV: seminal vesicle, LN: lymph nodes, PS: performance status

Table 1 : Patients' Characteristics

| PTV–T | Parameter | Experimental | Control | Target | p–value |
|-------------------|------------------|---------------------|----------------------|------------|---------|
| D95 | Mean (\pm SD) | 95.4 (\pm 0.84) | 95.2 (\pm 0.63) | 95 | 0.556 |
| | Median (Range) | 96 (94–96) | 95 (94–96) | | |
| Dmax | Mean (\pm SD) | 105.4 (\pm 3.16) | 104.9 (\pm 2.47) | \leq 107 | 0.699 |
| | Median (Range) | 105.5 (100–110) | 105 (102–110) | | |
| Dmin | Mean (\pm SD) | 92.4 (\pm 1.58) | 92.6 (\pm 0.97) | \geq 90 | 0.736 |
| | Median (Range) | 92 (90–94) | 92 (90–94) | | |
| Mean Dose | Mean (\pm SD) | 100.3 (\pm 1.49) | 101 (\pm 1.49) | – | 0.308 |
| | Median (Range) | 101 (98–102) | 101 (99–104) | | |
| Homogeneity Index | Mean (\pm SD) | 0.132 (\pm 0.04) | 0.117 (\pm 0.02) | 0=ideal | 0.278 |
| | Median (Range) | 0.13 (0.07–0.19) | 0.11 (0.10–0.16) | | |
| Conformity Index | Mean (\pm SD) | 1.027 (\pm 0.02) | 1.019 (\pm 0.007) | 1=ideal | 0.211 |
| | Median (Range) | 1.025 (1.0–1.05) | 1.02 (1.01–1.03) | | |

Table 2 : Plan parameters

planning system (version 8.6). Fusion of the MRI and CT images were accomplished using spatial software by the TPS depending on bony/soft tissue anatomy. Clinical target volume included the prostate, seminal vesicle, and pelvic lymph nodes. MRI T–2 weighted images were used for guiding prostatic delineation from base to apex ⁽⁶⁾. In cases where MRI imaging was not feasible the apex was identified as the hourglass or slit shape that results from the in–bowing of the levatorani, about 1cm above the penile bulb ⁽⁷⁾. PTV included the CTV with 10mm margin in all directions, except posteriorly 5mm ⁽⁸⁾. Pelvic lymph node and risk structures delineation followed the RTOG atlas guidelines (www.RTOG.org). Median dose in the hypofractionation arm was 65Gy to 67.5Gy in 25 fractions (2.6–2.7Gy per fraction / 5 times per week / over 5 weeks) and in the control arm 74Gy to 78Gy in 37 fractions (2Gy per fraction / 5 times per week / over 7.5 weeks). Pelvic lymph node received only 45–50Gy with 1.8–2Gy per fraction in both arms. Planning was performed using Eclipse

(Varian Medical Systems, California, USA) treatment planning system (version 8.6) with a pencil beam dose calculation algorithm and a 2.5mm grid size. Nine fields IMRT plan with gantry angles 180°, 220°, 260°, 300°, 340°, 20°, 60°, 100° and 140° was used. Two separate plans were done for the sequential boost group.

Statistical Methods

All data were tabulated and statistically studied by descriptive analysis in relation to different prognostic factors. Comparison between the two groups was done using Equivalent 2–tailed Student t–test. Differences will be considered significant if the p–value is <0.05 . All statistical calculations, data management and analysis were performed using the SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) software version 17.

Results

Patients were evenly distributed between the two arms of the study in terms of performance status, Gleason's score, T-stage, baseline PSA, seminal vesicle and lymph node metastatic risk and hormonal treatment duration. However, there was a statistically significant higher mean age group in the experimental arm 70.2 years compared to 64 years in the the control arm ($p=0.009$).

Dosimetric outcome

All plan parameters for PTV coverage, minimum, maximum, conformity and homogeneity indices were almost identical for both groups (Table 2).

Treatment related toxicity

Baseline obstructive or irritative urinary symptoms were found in 4 patients of each arm. During radiation 4 patients developed grade 2 toxicity in both arms, with one patient having grade 3 toxicity in the experimental arm. Symptoms subsided completely by the first month of follow-up. There was no statistical significance in the occurrence of urinary toxicities between the two arms either during treatment ($p=0.689$) or at 3 months follow-up ($p=0.660$) (Table 3).

No GI toxicity observed during treatment or on follow-up in the experimental arm with only one

patient developing grade 2 diarrhea in the control arm. Erectile dysfunction was attributed to the use of neoadjuvant hormonal treatment.

Quality of Life

Quality of life assessment was done using patient-based RTOG questionnaire. The quality of life questionnaires QLQ c-30 for patient general health and QLQ c-25 for prostate cancer assessment were both used. The combined scores of both questionnaires were expressed as a percentage for comparative analysis. The 2 groups showed no statistically significant difference in mean quality of life score, with an observed pattern of decrease score reaching its lowest at the end of treatment followed by an improvement of QOL achieving pre-treatment levels by 6 months follow-up (Figure 1).

PSA Nadir

There was no statistical significant difference in PSA between the 2 study groups with a decrease in value from baseline assessment to 6 months follow-up, (Figure 2).

Cost estimate comparison

With regards to linear machine usage, hypofractionation consumes a statistically lower mean value of total monitor units at 31138 MU compared to 45691 MU with conventionally fractionated

| GUT Toxicity | | Experimental | Control | p-value |
|------------------|--------------|-----------------|-----------------|---------|
| Baseline | | Present=4 (40%) | Present=4 (40%) | 1.0 |
| During Treatment | Onset (week) | W3: 2pt. (43%) | W2: 1pt. (20%) | 0.689 |
| | | W4:3pt. (57%) | W4:2pt. (40%) | |
| | | | W5:2pt. (40%) | |
| Grade | | G2=4 (40%) | G1=1 (10%) | |
| | | G3=1 (10%) | G2=4 (40%) | |
| 3m Follow-Up | | G1=3 (30%) | G1=4 (40%) | 0.660 |
| 6m Follow-Up | | 0 | 0 | |

Table 3 : Genito-urinary toxicity profile for the two study groups

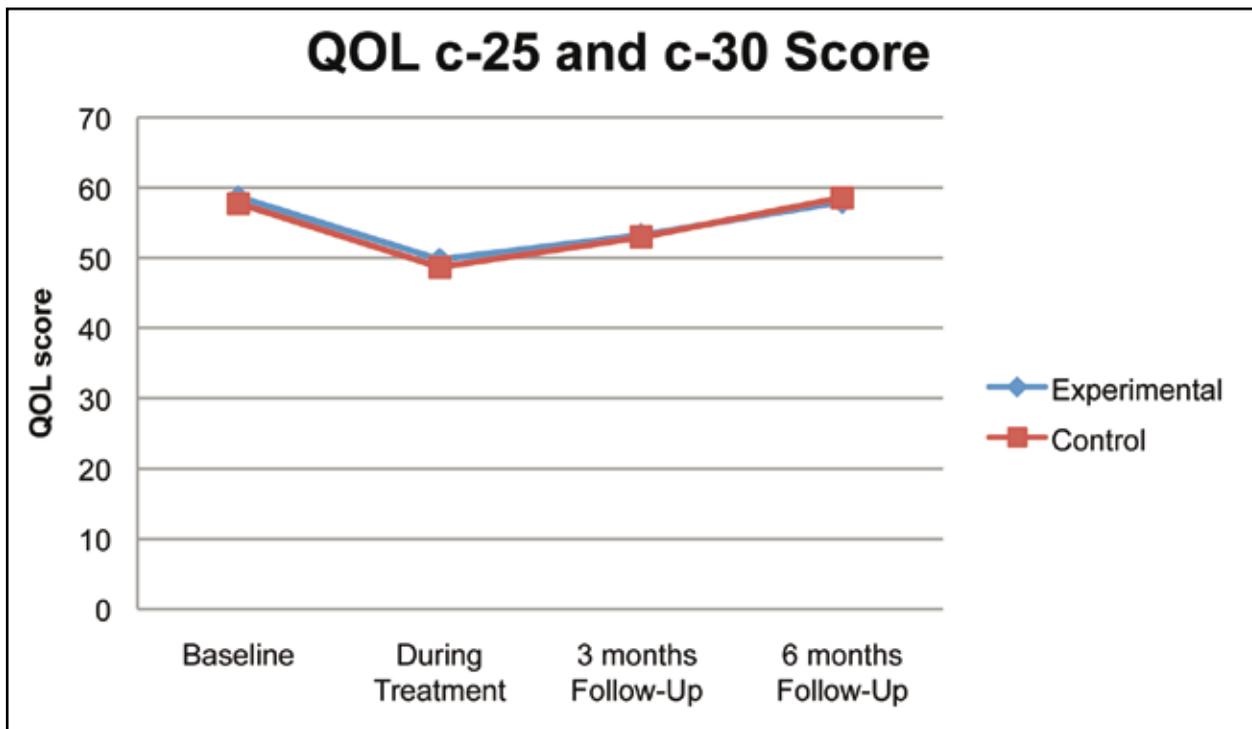


Figure 1 : Mean Quality of life score for the 2 study groups

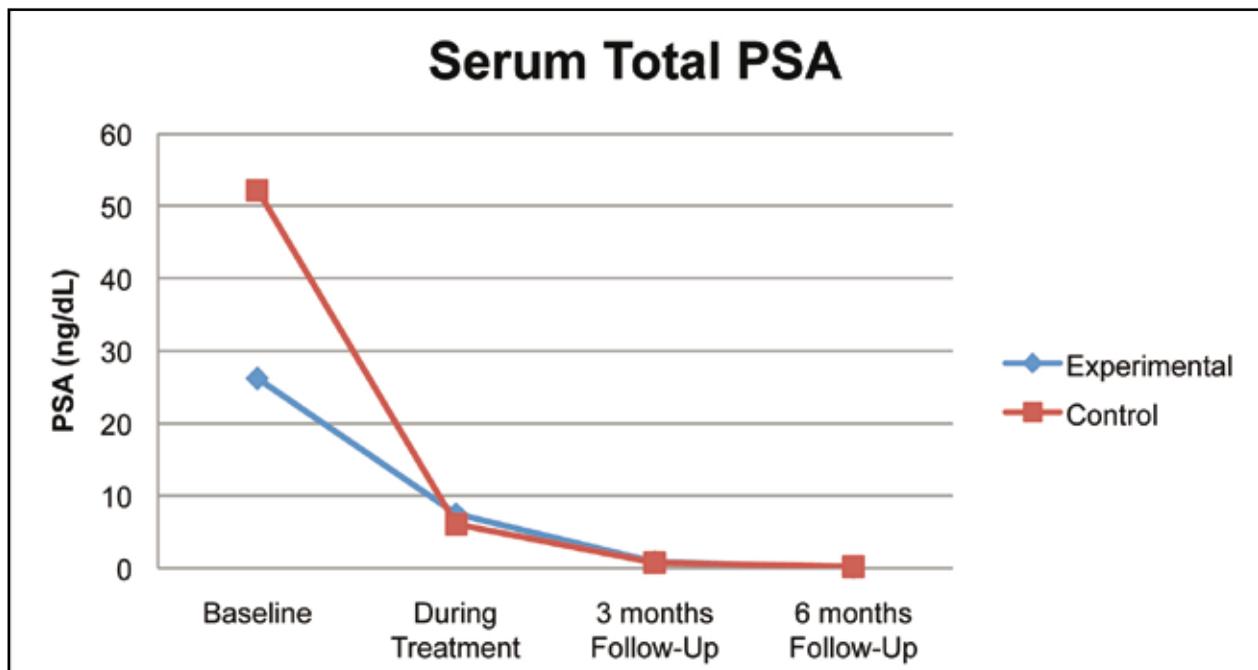


Figure 2 : Mean PSA for the 2 study groups

treatment ($p=0.015$) (Table 4). As for the financial cost of treatment for the patient, hypofractionation is much more cost-effective, since the price of IMRT treatment is 5000LE per week in the private sector. Accordingly, a hypofractionated course of 5 weeks would cost 25000LE compared to 40000LE for an 8 week course with conventional fractionation.

Discussion

This work is an interim analysis of a prospective randomized clinical trial aimed at assessing the possibility of shortening the period of radiation treatment for localized prostate cancer by evaluating the acute toxicity, quality of life and cost/benefit of hypofractionation compared to conventional

| Total Monitor Units | Experimental | Control | p-value |
|---------------------|----------------------|----------------------|---------|
| Mean (\pm SD) | 31138 (\pm 10057) | 45691 (\pm 13788) | 0.015 |
| Median (Range) | 31128 (18700–52170) | 49627 (22100–62159) | |

Table 4 : Total Monitor Units expenditure in the 2 study groups

fractionation. Many prostate cancer patients prefer radical prostatectomy over radiotherapy simply because of the long treatment duration of external beam radiotherapy. Hypofractionation schedule may be more convenient for our patients specially the older ones, as well as to reduce the load in our busy department.

In addition, biological models suggested that prostate cancer tumor cells may have lower α/β ratio than the surrounding normal tissues, thus increasing dose per fraction can improve the therapeutic ratio⁽⁹⁾. Extensive evidence from animal studies suggests

that for late rectal sequelae, α/β ratio is 4Gy i.e., it is higher than most other late sequelae. This higher value for late rectal damage is supported by clinical results that suggest that much late rectal injury is actually consequential of early effects, and thus a high α/β ratio for late rectal damage is not unreasonable⁽¹⁰⁾. If the α/β ratio for prostate cancer is less than that for the surrounding late–responding normal tissue then an increase in dose per fraction would increase tumor control more than the increase in late complication, and so hypofractionation at the appropriate dose, would yield an improved

| Organ | Control Arm Constraint | Control Arm Objective | Experimental Arm Constraint | Experimental Arm Objective |
|---------------|------------------------|-----------------------|-----------------------------|----------------------------|
| Rectum | V75 | $\leq 15\%$ | V68 | $\leq 15\%$ |
| | V70 | $\leq 20\%$ | V64 | $\leq 20\%$ |
| | V65 | $\leq 25\%$ | V59 | $\leq 25\%$ |
| | V60 | $\leq 35\%$ | V55 | $\leq 35\%$ |
| | V50 | $\leq 50\%$ | V45 | $\leq 50\%$ |
| Bladder | V75 | $\leq 25\%$ | V64 | $\leq 25\%$ |
| | V70 | $\leq 35\%$ | V60 | $\leq 35\%$ |
| | V65 | $\leq 50\%$ | V55 | $\leq 50\%$ |
| Penile Bulb | D90 | $\leq 50\text{Gy}$ | D90 | $\leq 44\text{Gy}$ |
| | D60 | $\leq 70\text{Gy}$ | D60 | $\leq 61\text{Gy}$ |
| | Mean Dose | $\leq 50\text{Gy}$ | Mean Dose | $\leq 44\text{Gy}$ |
| Femoral Heads | Dmax | $\leq 50\text{Gy}$ | Dmax | $\leq 44\text{Gy}$ |
| Bowel Bag | V45 | $\leq 195\text{cc}$ | V40 | $\leq 195\text{cc}$ |

Table 5 : Organs at risk dose –volume constraints

therapeutic ratio ⁽¹¹⁾. However, if the α/β ratio for prostate cancer is indeed similar or greater than that of the surrounding late-responding normal tissue, hypofractionation would produce an increase in tumor control less than that of late sequelae, and therefore yield a therapeutic ratio which is worse or comparable to conventional fractionation. This is in addition to patient convenience and financial advantages, with the potential for biologically based individualized treatments expected from using hypofractionated treatment ⁽¹²⁾.

The dose selection for conventional fractionation i.e. 78Gy/34 fractions at 2Gy per fraction over 8 weeks, in the control arm was chosen based on the results of several dose escalation trials that proved improved b-DFS with doses ≥ 76 Gy in the intermediate and high risk group ⁽¹³⁻¹⁵⁾.

The doses selected in the experimental arm were derived using Withers' isoeffect formula for achieving biological equivalence with conventional fractionation ⁽¹⁶⁾. The reported α/β ratio of prostate cancer varied between 1-4Gy, according to various authors ⁽¹⁷⁾. In the present work, an intermediate value of 3Gy was used despite the fact that a number of other studies used an α/β ratio of 1.5Gy. A more conservative value was used in this study to account for the heterogeneous nature of prostate cancer. Thus, the prescribed dose in both arms would be biologically equivalent and so any differences in outcome would be attributed to the treatment method.

The doses-volume constraints for the organs at risk in the control arm are based upon the QUANTEC model for normal tissue tolerance ⁽¹⁸⁾. The doses-volume constraints for the organs at risk in the experimental arm were derived using Withers' isoeffect formula for achieving biological equivalence with conventional fractionation (Table 5). The α/β ratios used according to biological models were as follows: rectum 4Gy (higher than that of the prostate so as to assume benefit of hypofractionation), bladder, penile bulb, femoral heads and bowel bag 3Gy (10). The acute genito-urinary and rectal toxicity for various hypofractionation regimens with GU toxicity \geq grade 2 ranging between 5-47% and GI toxicity \geq grade 2 ranging between 8-36%, (Tables 3). These results are comparable to the current study with GU toxicity \geq grade 2 at 50% and GI toxicity \geq grade 2 at 0% in the hypofractionation arm. These acute toxicities in the experimental arm were comparable to those in the control arm with GU toxicity \geq grade 2 at 40% and GI toxicity \geq grade 2 at 10%, with no statistical significance between them ($p=0.689$) (Table 6), although, there was one patient who developed grade 3 GU toxicity which was resolved by medical treatment. It is worth mentioning that GU toxicity appeared one week earlier in the hypofractionation arm.

In the current study it was observed that patients with pre-existing genito-urinary symptoms before treatment experienced more GU toxicity, 4 out of 5

| Study | Patient N# | Dose/Fraction N#/Dose per Fraction | Acute Toxicity (%) | | | | |
|-------------------------|------------|------------------------------------|--------------------|----|-----|--------|----|
| | | | Urinary | | | Rectal | |
| | | | 1 | 2 | 3 | 1 | 2 |
| Norkus, et al., 2009 | 47 | 57Gy/19F/3Gy | - | 47 | - | - | - |
| Soete, et al., 2006 | 36 | 56Gy/16F/3.5Gy | - | 44 | - | - | 36 |
| Ritter, et al., 2009 | 100 | 64.7Gy/22F/2.9Gy | - | 30 | - | - | 9 |
| Menkarios, et al., 2011 | 80 | 45Gy/9F/5Gy | 29 | 31 | 5 | 30 | 14 |
| Salinas, et al., 2012 | 36 | 70Gy/28F/2.5Gy | 58 | 25 | 5.5 | 44 | 8 |

Table 6 : Acute toxicity rates for various hypofractionation trials

patients who developed toxicity \geq grade 2 have pre-treatment urinary symptoms, a finding also verified by Pollack, et al. ⁽¹⁹⁾. This confirms the importance of treating any urinary symptoms before starting external beam radiotherapy.

The majority of patients in both groups have erectile dysfunction before starting treatment, probably due to neoadjuvant ADT. Therefore, it was not possible to evaluate the effect of radiation on erectile function during the short observation time. In cases where they received radiation therapy alone, the literature demonstrated that erectile dysfunction can be observed in 40–60% of patients after 6 years follow-up ⁽²⁰⁾.

The patients' Quality of Life with radiation treatment was comparable to that observed in literature. Salinas, et al used a similar QOL assessment method using the QOL c-30, c-25 and IPSS score. C-30 reflected mild transient worsening and returns to baseline at 3 months except for physical functioning. C-25 demonstrated a decline of sexual activity and transient worsening of urinary and bowel symptoms with treatment, which improved by 3 months and remained mild, most probably due to continued ADT. Katz, et al. demonstrated that Mean Expanded Prostate Cancer Index Composite (EPIC) score for urinary and bowel QOL declined at 1 month post-treatment and returned to baseline by 2 years. Mean EPIC sexual QOL declined by 23% at 1 month ⁽²¹⁾. Jereczek-Fossa, et al. showed a significant deterioration in erectile function on the International Index of Erectile Function-5 with time only in patients without androgen deprivation. No change with time was observed in urinary symptom-related quality of life on the QLQ c-25 or International Prostate Symptom Score. Slight deterioration in QLQ c-25 bowel symptom related quality of life was observed. Overall QLQ c-30 Global Health Status improved with time ⁽²²⁾. Similar observations were recorded in the present work with no difference between the two arms. This study has a few limitations which may have hindered result interpretations and conclusions drawn. First of all, the small sample size attributed to the low flow rate of localized prostate cancer cases to our institution and the high cost of the procedure decreased the statistical power of the study. Secondly, the unavailability of more advanced image-guidance technology such as cone-beam

CT or fiducial markers impeded more accurate treatment delivery and result interpretation, such as systemic and random error of treatment isocenter movement. Lastly, the impact of hypofractionation on biochemical disease-free and overall survival together with late treatment toxicity could not be assessed due to the short follow-up period.

Conclusions

1. Hypofractionation with simultaneous integrated boost yielded similar nadir in PSA value in both arms, denoting the efficacy of this hypofractionation regimen.
2. Hypofractionated radiotherapy for prostate cancer is feasible and improves patient's quality of life with the same treatment-related toxicity.

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