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Simultaneous Integrated Boost-Intensity Modulated Radiotherapy (SIB-IMRT) for the Whole Pelvis did not Lead to Significantly Higher Toxicity Rates than Prostate-Only IMRT in Prostate Cancer Patients

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Abstract

Purpose: To explore the controversy of including pelvic nodes in radical radiotherapy for prostate cancer with the adopted of precise advanced techniques of Intensity Modulated Radiotherapy (IMRT) and verified through image-guidance.

Patients and Methods: Twenty prostate cancer patients were treated using SIB-IMRT whole pelvis irradiation for high-risk (10) patients. They received a median dose of 77.7 Gy to prostate and 54-58 Gy to nodes over a median of 37 fractions. Intermediate-risk (10) patients received a similar prostate dose over the same overall treatment time.

Results: The dose coverage to the prostate was identical in both groups with a mean PITV of 1.2 ± 0.1 and a confirmation index of 0.73 ± 0.07. Although the volume of the bladder and rectum that received 50,60,65,70 Gy (V50,V60,V65,V70) in the whole pelvis group were larger than the corresponding volume in prostate group yet, none of the difference was statistically significant. The mean dose received by femoral head was higher in the whole pelvis than in prostate group. However their D5 (volume received ≥5 Gy) were almost identical. No significant acute toxicity difference was experienced by the patients in the 2 groups. The 4-year cumulative bladder late toxicity-free rate was 100% in prostate group while it was 67 ± 27% in the whole pelvis group (p=0.116). On the other hand, no late rectal toxicities were reported in the 2 groups.

The biochemical failure-free and overall survival rates were 85.7 ± 13.2% and 100% in prostate group and 75.0 ± 21.7% & 80.0 ± 12.6% in the whole pelvis group with no statistical significance.

Conclusion: Although the acute and late radiation toxicities were slightly higher with whole pelvis than prostate irradiation yet, it was not of statistical significance.

Keywords: Prostate cancer; High-risk; Intermediate-risk; Simultaneous integrated boost-intensity modulated radiotherapy; SIB-IMRT; Acute toxicity; Late toxicity

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Introduction

Higher radiation dose with or without hormonal manipulation was established as one of the standard treatment for prostate cancer. Combined hormonal therapy and radiotherapy is considered the standard treatment for high-risk prostate cancer [1,2]. Dose escalation proved to improve the biochemical relapse-free, distant metastasis-free and prostate cancer-free survival rates especially in intermediate and high-risk patients [3-5]. Consequently, radiation toxicity with such dose escalation was raised as an important issue in conventional and 3DCRT techniques. However, the use of Intensity Modulated Radiotherapy (IMRT) verified by image guidance (IGRT) lead to improvement of the therapeutic ratio. The radiation dose distribution for the surrounding organs at-risk including the urinary bladder, rectum and bowel using IMRT were decreased by 30-55% when compared to 3 dimentional conformal (3DCRT) and 50-70% compared to 2D planning [6]. Toxicity was reported to be minimal.

Pelvic nodes treatment in prostate cancer has been controversial for many years. The elective pelvic node treatment should-theoretically improve the disease-free survival in a subset of patients

harboring occult pelvic node metastases without systemic spread. The benefit of the whole pelvis vs. prostate only irradiation was shown in some studies but not in others [7-9]. This still raise the inquiry of the effect of extending the treatment field to include the whole pelvis on the acute and more importantly the late toxicities of such extension. Furthermore, the adoption of simultaneous integrated boost (SIB) with the delivery of different doses within the target by IMRT allows to simultaneously treating prostate with conventional dose fractions and pelvic nodes with lower dose fractions that are better tolerated by large volumes [10]. The aim of this study was to investigate the effect of the treatment volume in both acute and late toxicities through treating intermediate-risk patients with prostate only and comparing this to whole pelvis as a treatment volume for high-risk prostate cancer patients.

Patients and Methods

This is a retrospective study included 20 patients with locally advanced prostate cancer (10 intermediate- and 10 high-risk) patients. All patients presented to the radiation oncology department, Children's Cancer Hospital, Egypt (CCHE) between November 2009 and October 2014 and fulfilling the following eligibility criteria were included:

1. Histological confirmation of prostate adenocarcinoma and belonging to the category intermediate- or high-risk.
2. ECOG performance scale equals 0-2.
3. Adequate liver and renal functions.
4. No evidence of distant metastasis, previous malignancy or pelvic irradiation.
5. Signed written informed consent.

All patients were subjected to through history taken and clinical examination, laboratory investigations including CBC, liver and kidney functions and PSA, radiological and imaging investigations including chest x-ray, abdominopelvic computed tomography, pelvic magnetic resonance and isotopic bone scan. The eligible patients were already categorized into either intermediate-risk (10 patients) or high-risk (10 patients) according to Roach criteria [1] (T3a-c, PSA=10-20 and/or Gleason score=7).

All patients were instructed to evacuate their large bowel the night before simulation, drink a liter of water one hour prior to CT simulation. Pelvic thermoplastic immobilization mask was prepared for each patient and intravenous contrast (ultravist) was injected. The CT images were taken every 3mm in supine position using pelvic resolution window. Upon sending these images to the treatment planning system (Xio CMS), all organs at risk including the bladder, rectum, penile bulb, femoral heads and intestinal bowel (small and large) were delineated. The CTV volume including prostate and seminal vesicles with or without pelvic lymph nodes depending upon patient's risk status. Pelvic MRI were fused in most of the patients for better precise prostate delineation. Contouring of the prostate usually began with mid-gland where the prostate borders are more easily identifiable. Caudally, the prostate apex is identified at the convergence of the levator ani muscle. The lateral borders are the medial border of the levator ani, while the anterior boundary is the anterior fibromuscular stroma, posteriorly the rectum is opposed at the mid-gland. Superiorly the seminal vesicles (SV) but not the associated vasculature were incorporated to the contour. Caudally, the delineation was completed just above the genitourinary diaphragm (GUD).

Lymphatic target delineation started at the lower common iliac nodes below L5-S1 interspace and extended to include the external iliac, internal iliac at the top of femoral head. The inferior nodes were contoured at the superior aspect of pelvic symphysis. KonRad Siemens planning system was used for inverse planning technique and transferred through the Oncology Information System (OIS) Lantis for execution via the linear accelerator treatment machine. The adopted set up verification protocol (using MV cone beam CT weekly and electronic portal image device, EPID, applied daily) was applied for all patients. The prescribed dose to the prostate-seminal vesicles ranged between 7600 to 7807 cGy in 37-38 fractions (200-211 cGy per fraction). The lymphatic dose was given through simultaneous integrated boost (SIB) technique supplying a dose ranged between 5400 and 5800 cGy with a median dose of 5600 cGy in 37 fractions (151 cGy per fraction).

All patients were clinically seen weekly reporting on the acute bladder, rectal and intestinal toxicity, High risk patients received hormonal therapy for 18-24 months, while the intermediate risk patients received it for 4-6 months. All patients were followed up regularly bimonthly in the first year and every 3 months thereafter, with PSA determination in each session.

Statistical methods

Numerical data were expressed as mean and standard deviation or median and range as appropriate. Quantitative data were expressed as frequency and percentage. Survival analysis was performed using Kaplan-Meier product limit method. A p-value of ≤0.05 was considered significant. All analysis was performed using IBM.SPSS advanced statistics version 20 (SPSS inc. Chicago, IL).

Results

Twenty patients were eligible for this study. Their age ranged from 45 to 86 years with a mean of 70.0 ± 9.6 years and a median of 71 years. Out of these 20 patients 11 (55%) initially presented with dysuria, 4 (20%) with urinary retention, 4 (20%) with interrupted micturition and 3 patients (15%) having high PSA discovered during regular medical checkup. Thirteen patients were staged as T2c, two as T3a, 4 as T3b and one as T4a. Nodal involvement detected on pelvic CT/MRI in 2 (10%) patients. PSA at diagnosis ranged from 4 to 371 ng/dl with a median of 15 ng/dl. The mean Gleason score was 6.9 ± 0.75 and a median of 7. All patients, but one who underwent bilateral sub-capsular orchiectomy prior to radiation, were treated with hormonal manipulation for 4-6 months in intermediate-risk and 18-24 months in high-risk cases. The whole group was treated with IMRT; for the prostate-seminal vesicle in the intermediate-risk and simultaneous integrated boost IMRT (SIB-IMRT) pelvic irradiation in the high-risk including both the prostate-seminal vesicles and pelvic lymph nodes.

The Planning Target Volume (PTV) for intermediate-risk patients ranged from 55.6 cc to 375.2 cc with a mean of 175.0 ± 71.1 cc while the PTV of the whole pelvis (high-risk patients) ranged from 239.9 to 1068 with a mean of 704 ± 275.2 cc. The coverage of the prostatic PTV had a mean D95 (the dose covering 95% of the PTV volume) was determined to be 7368 ± 166 cGy and a median D95 dose of 7375 cGy which represents 94.9 ±1.6 of the prescribed dose. The PITV (prescription in-dose volume over the target volume) ranged between 1.1 and 1.5 with a mean of 1.2 ± 0.1. The confirmation number (PTV

Table 1: Comparison between different dose levels received by organs-at-risk in prostate irradiation and whole pelvis irradiation.

	V50	V60	V65	V70
Bladder				
Prostate	30.6 ± 9.4	21.8 ± 9.3	18.0 ± 8.2	14.2 ± 7.6
Whole pelvis	44.0 ± 18.1	30.5 ± 17.1	25.4 ± 15.1	20.1 ± 12.1
p	0.161	0.233	0.274	0.272
Rectum				
Prostate	25.9 ± 10.9	15.6 ± 7.4	11.2 ± 6.5	7.3 ± 5.7
Whole pelvis	25.9 ± 11.0	16.5 ± 10.1	12.5 ± 8.3	8.9 ± 7.3
P	0.920	0.721	0.611	0.632

volume divided by treated volume) ranged from 0.64 to 0.88 with a mean of 0.73 ± 0.07.

The volume of the organ at risk (% from the total delineated volume) that received the doses of 50,60,65,70 Gy were determined (V50,V60,V65 and V70) (Table 1). Although the volume that received the above mentioned doses in the whole pelvis group were larger than the corresponding volumes in the prostate-seminal vesicle group yet, none of these differences reach to the level of significance neither in bladder nor the rectum. The mean dose received by the right and left femur in the whole pelvis group were 15.1 ± 3.2 and 15.4 ± 3.5 Gy compared to 10.6 ± 5.5 and 10.8 ± 5.8 Gy in the prostate group respectively. These differences proved to be statistically significant (p=0.016 and 0.029). Both femuri dose was 15.3 ± 3.3 Gy in whole pelvis compared to 10.7 ± 5.6 Gy in prostate only group (p= 0.021). However, the femoral head D5 (the volume received 5 Gy or above) were 23.5 ± 9.7 and 23.0 ± 8.7 cc for the whole pelvis and prostate groups respectively. The difference was statistically insignificant. Moreover, Furthermore, the bowel bag received a higher mean dose in the whole pelvis group compared to that in the prostate group. However, this difference did not rank to the level of significance (p=0.4).

It is worth mentioning that the overall treatment time ranged from 48 to 60 days with a median of 53 days with no difference between the 2 groups.

The volume parameter V70 was chosen to correlate with the clinical urinary bladder (dysuria and frequency) & rectal late toxicities as the bigger the volume receiving the high dose the higher the expectation of toxicity. However, no statistical significant difference in the 2 groups for bladder or rectal acute toxicities were detected (Table 2).

The cumulative bladder toxicity-free rate at 4 years was 100% in prostate only (intermediate-risk) compared to 67 ± 27% in the whole pelvis (high-risk) group. This difference was not statistically significant (p=0.116). On the other hand, the rectal late toxicity-free rate was 100% in both groups as none of the patients in the 2 groups reported late rectal toxicities.

The 4-year biochemical failure-free and overall survival rates was 75.0 ± 21.7 % for the whole pelvis (high-risk) group compared to 85.7 ± 13.2 % for prostate only (intermediate-risk) group (p=0.580). The 4-year overall survival was 80.0 ± 12.6 % for the whole pelvis group compared to 100% for prostate only group with a p-value of 0.561 (statistically insignificant).

Discussion

IMRT is highly conformal treatment allowing for sparing more normal tissue and reducing side-effects. In a recent meta-analysis including 9556 patients, Yu et al. [11] showed that IMRT was significantly associated with decreased grade 2-4 acute GI toxicity (RR=0.59) and late GI toxicity (RR=0.54), late rectal toxicity (RR=0.48) better than conformal radiotherapy. In the other hand, in this meta-analysis IMRT achieved the same grade 2-4 acute rectal toxicity, late GU toxicity as conformal technique. Image-guided radiotherapy (IGRT) had been adopted for real-time localization of the prostate to match the daily shifts in the position of the target, leading to greater accuracy and smaller treatment margins [5]. Moreover, the SIB technique, used instead of the sequential approach, resulted in many advantages. The first is the shortening of the overall treatment time (OTT) assuming that the reduction of treatment duration minimizes the risk of tumor clonogens regrowth in the last phase of treatment [12]. The second is increasing fraction size of the boost allowing for more tumor cell kill. Therefore, both the total prescribed dose and biologic dose be increased [13]. On the other hand, the SIB-IMRT can also be used in conventional fractionation (2 Gy/fr) to the boost volume while a smaller fraction dose was delivered to the bigger volume, simultaneously with the same number of fractions, to the elective volume (1.6–1.8 Gy/fr) [14] leading to lower normal tissues side effects expectations. Optimal fractionation regimen should consider not only the probability of tumor control, but also the risk of toxicity to normal tissues.In the present study, a mean of 37 fractions was given in 7.4 weeks, for a total dose of 77.70 Gy to the boost volume (fraction size of 2.1 Gy) may participate in lowering the toxicity to the surrounding normal tissues. However, this entailed increasing the elective volume prescribed dose to 56 Gy (fraction size of 1.51 Gy), this radiotherapy regimen was successfully tested by [13] and led to good results. Moreover, several investigators suggested that IMRT has an ability to create much superior dose distributions when it is designed and delivered using the simultaneous integrated boost (SIB-IMRT) fractionation scheme, the dose distributions with SIB-IMRT are more conformal, and the schedule is more convenient for patients, with reduction in the length of the RT course and in the overall treatment cost. More conformity in SIB-IMRT and better coverage of boost volume sparing more normal tissues, which can improve the therapeutic outcome. SIB-IMRT was tested and approved in many studies in prostate cancer treatment. It can decrease the dose to rectal wall and reduce normal tissue complications with capability to escalate the dose to the prostate to more than 76 Gy with equivalent GU and GI toxicity [15,16].

In the present study, SIB-IMRT was used to deliver an inhomogeneous dose distribution to treat the pelvic nodes in high-risk patients, while escalating the dose to the prostate area through the same overall treatment time. Using this technique, the patients received pelvic total doses that are equivalent or slightly higher than the standard 45–50 Gy doses when delivered in 2 Gy fractions, and simultaneous boost doses to the prostate area higher than that given in the RTOG 9413 trial [17,18]. The prescribed dose to the prostate ranged between 7600 cGy and 7808 cGy, with a median dose to the prostate of 7770 cGy. The lymphatics prescribed dose ranged from 5400 cGY to 5800 cGy with a median of 5600 cGy received in median of 37 fractions (7770 cGy to the prostate in 210 cGy/ fraction simultaneous with 5600 cGy to the lymphatics in 151 cGy/ fraction) using the same radiobiological bases applied in the other studies, with an α/β ratio of 1.5, as suggested by [19]. SIB-IMRT technique results in more practical, more efficient with less uncertainty related to the IMRT planning and delivering as the same plan is used for the entire

course of RT away from the major difficulty of achieving a high level of dose conformation with the combing IMRT-boost to the original large volume [15].

Elective pelvic nodes treatment for prostate cancer has been controversial for many years. This elective treatment should theoretically improve the disease-free survival in a subset of patients harboring occult pelvic node metastases without systemic spread. The benefit of the whole pelvis (WPRT) vs. prostate only irradiation (PRT) was shown in some studies but not all [7,18,20]. Two large, randomized, Phase III clinical trials, RTOG 94-13, [17], and GETUG-01 [20] and its subset analysis [18] showed benefit in progression-free survival in favor of WPRT over PRT when neoadjuvant hormone therapy was used.

With the fact that at least 30% to 50% of localized (intermediate or high risk) prostate cancer patients who has no clinically involved pelvic lymph nodes (i.e. cN0), treated initially with a curative intent will manifest biochemical failure, suggesting a combination of persistent local, periprostatic, regional (pelvic lymph nodes) or distant disease, despite higher doses of radiation that adds to the controversy of including pelvic nodes in the radiation volume. [21,22].

Similarly Arcangeli et al. [23] treated twenty-four (24) out of fifty-five (55) patients using SIB-IMRT to pelvis and prostate with a dose ranged from 74–76 Gy (7 pts), to 76–78 Gy (6 pts), and to 79–80 Gy (11 pts) in 2 Gy fractions, and whole pelvis was treated in the same number of fractions to a total dose ranging from 51 to 59 Gy. The electively irradiated nodes received lower doses per fraction to a total dose adjusted to be equivalent to about 45–50 Gy when given in 2 Gy fractions. They found no correlation between acute GU and rectal toxicities and the dosimetric variables: V70,V50, the absolute volume of the organ and the D90 of PTV prostate and PTV pelvis that was similarly affirmed in our group of patients.

It is recommended in normal tissue planning to limit rectum, bladder doses receiving ≥70 Gy (V70) and ≥50 Gy (V50) to be not more than 30% and 50% of the rectum, respectively, and not more than 50% and 70% of the bladder volume, respectively [23]. In the present study, dosimetric results for rectum, bladder doses receiving ≥70 Gy (V70) and ≥50 Gy (V50) were not exceeding 10% and 26% for the rectum, respectively, and no more than 20% and 44% for the bladder respectively, denoting better tissue sparing in the present series. A comparable results to our study were presented by the Memorial Sloan-Kettering Cancer Center on a similarly limited number of patients (N=13) [6].

PTV coverage in the present study intermediate and high-risk patients were adequate as PITV in the whole 20 patients ranged from 1.1 through 1.5 (mean: 1.23 ± 0.11) and the confirmation number ranged from 0.64 through 0.88 (mean; 0.725 ± 0.067) indicating a high degree of dose homogeneity and precision of the accepted treatment plans. All patients received hormonal management for 4-24 months, with one having bilateral orchiectomy. This led to an acceptable OS of 100% and 80.0% and biochemical relapse-free survival of 85.7% and 75.0% for intermediate- and high-risk patients respectively. These rates though comparable to results of large series yet long term follow up is needed for more solid data in such prostate cancer cases known to experience long term results.

The rectal acute toxicity (proctitis), could not illustrate differences of statistical significance in comparing patients received whole pelvic radiotherapy and those who received radiation to the prostate and seminal vesicle only. V70 parameter was used for clinical correlation of proctitis grade to the applied volume of radiation. No more than grade 2 (acute or late) rectal toxicity were experienced in our patients. Only one patient in prostate only treated patients and no patient from the whole pelvis group developed grade 2 rectal toxicity).

Table 2: Comparison between acute bladder toxicity inpatients received prostate irradiation using IMRT and those received whole pelvis irradiation using SIB-IMRT.

	Prostate	Whole pelvis	P
Dysuria G 0	4	3	0.267
Dysuria G 1	5	5	
Dysuria G2	1	2	
Frequency G 0	6	7	0.241
Frequency G 1	3	3	
Frequency G 2	1	0	

Similar results were reported by Arcangeli et al. [23] who confirmed no G3 toxicities in their patients who underwent radiotherapy to the prostate only. Similarly In the present study, no more than G2 rectal or bladder acute or late toxicities were reported neither in patients received prostate only nor whole pelvis irradiation. Patients with acute G2 urinary and rectal toxicity were 15% and 5%, respectively, which compare well with the average of 35% (range 28–56%) and 30% (range 14–52%) G2 or more (≥) rectal and bladder toxicity of other series summarized by Pollack et al. [24].

Ashman et al. [6] reported in a limited number of patients (N=13) the toxicity of pelvic IMRT to a dose of 45 Gy followed by a prostate boost to 81 Gy. Only 1out of the 13 patient (8%) developed grade 2 acute rectal toxicity and none experienced diarrhea which compared well to our result. Forty percent of our patients developed ≥grade 2 acute dysuria Furthermore, the late toxicity ≥grade 2 experienced by the present study patients was absent in gastrointestinal system and minimal in genitourinary system (4%).

However, Chung et al. [25] claimed that the magnitude of the irradiated volume affects much the extent of both acute and late toxicities. They analyzed the dosimetry related to acute toxicities of 25 high-risk patients who received pelvic radiotherapy and received either IMRT (with weekly portal images) or image-guided (IG) IMRT using intra-prostatic fiducial markers. Planning target volume margins differed significantly between the two groups (0.5 to 1.0 cm for IMRT vs. 0.2 to 0.3 cm for IG-IMRT). As expected, bladder and rectal doses were significantly less with IG-IMRT, which translated to significantly less grade 2 rectal (80% vs. 13%; P=.004) and bladder (60% vs. 13%; P =.014) toxicities. No more than grade 2 toxicity was observed. These low toxicity are comparable to what has been documented in the present study 5% (1/20) developed grade 2 acute rectal toxicity-and none of our patients experienced Grade 2 or more late GI toxicity. Forty percent of our patients developed ≥grade 2 acute dysuria and only 1 (4%) experienced a late grade 2 GU toxicity.)

Guckenberger et al. [26] analyzed the toxicity after Image guided SIB-IMRT to pelvic lymphatics and prostate (with inclusion of the seminal vesicle) in 25 fractions then followed by eight fractions escalation dose to prostate only on 25 patients (who received SIB escalation with a dose per fraction of 2.31 Gy to the prostate and seminal vesicle while the dose per fraction to the pelvic nodes was 1.84 Gy for the PTV- LN) out of 100 patients in the whole study. All patients had completed their treatment as planned. No acute GI and

GU toxicity was experienced by 6% while 46% of patients reporting grade ≥2 GI toxicity and 4% suffering from GU toxicity grade 3. This acute toxicity resolved rapidly after the end of radiotherapy with 12% of the patients still having grade ≥2 toxicity 6 weeks after treatment. They reported 57% of their patients free from any late GU toxicity at 24 months, 15% suffering from grade 1 toxicity, 7.6% grade 2 and 1.5% grade 3. This GU late toxicity remained constant 6-24 months after treatment. Late GI toxicity was rare with 4% of patients having ≥2 late GI toxicity.

In the present study, despite the fact that it has a relatively short follow up period (mean=41.2 months and median=38.8 months), the cumulative bladder late toxicity-free survival at 4 years was-100% in prostate only (Intermediate group received IG-IMRT) and 67 ± 27% in the high-risk patients received SIB-IGIMRT. This difference was not statistically significant (p=0.116).

Furthermore, late toxicity in an Italian study [23] revealed no patient experienced a late >G1 intestinal or urinary toxicity with a late G2 toxicity consisted only in rectal bleeding. The actuarial 2-year rate of freedom from G2 rectal bleeding was 92%, perfectly compared to our results.

Nevertheless, the rectal late toxicity-free rate was100% in both groups as none of the patients experienced late rectal toxicity, this was similar or even less than what had been found in the RTOG 9413 study Roach et al. [1], though of the higher radiation dose received in the present study. In RTOG 9413, the patients received 50.4 Gy whole pelvic irradiation with an additional boost to the prostate up to 70.2 Gy. The 2-year rates of late grade 3 or higher GU and GI toxicity were 2% and 1.7%, respectively.

Zapatero et al. [27] in a phase 3 randomized controlled study (DART01/05 GICOR), showed no significant difference in biochemical disease-free survival between patients who were or were not given whole pelvic radiotherapy. The significant difference in both total 5-year biochemical disease-free survival was related to the duration of androgen deprivation (90% among patients receiving long-term androgen deprivation and 80% among those receiving short-term treatment (p=0.01) and 5-year overall survival (95% in long-term androgen deprivation vs. 86% among those receiving short-term treatment (p=0.009).

Within the limitation of limited patient number and relatively short follow up, it may be concluded that the adoption of dose escalation IMRT coupled with image guidance lead to good treatment end results especially with low acute and late toxicities. The issue of including prophylactic pelvic lymph nodes in the irradiated volume though did not lead to significantly higher acute or late toxicities yet, it is still controversial.

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