The impact of image guided external beam radiotherapy on outcome in treating intermediate risk cancer prostate

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Abstract:

Background: Intermediate-risk prostate cancer is a highly heterogeneous disease. Treatment options include various radiotherapy techniques with a short course of androgen deprivation therapy (ADT), or combination external beam radiotherapy (EBRT) with a brachytherapy (BT) boost with or without ADT.
The benefits of image guided radiotherapy (IGRT) have been shown in retrospective series and it has become the standard of care for delivery of external beam radiation treatment for prostate cancer.
Purpose of the study: To compare the biochemical and clinical tumor control in patients treated by means of high dose IGRT versus high dose non image guided (non IG EBRT) as well as the toxicity profile in both techniques.
Patients and Methods: This is a retrospective study that enrolled patients with localized cancer prostate of intermediate risk treated with EBRT either with or without image guidance between 1995 and 2012.
Results: A cohort of 388 consecutive patients was enrolled. IGRT achieved significantly longer biochemical failure free survival (p = 0.016) only patients with favorable criteria have gained this advantage (p=0.055). T1C, total Gleason score 6, percent of positive biopsy cores ≤ 50% gained significantly longer bFFS compared with other subgroups. Concerning distant failure, IGRT, percent of positive biopsy cores ≤ 50%, favorable criteria and T1C were significantly associated with longer DFFS. ADT with radiotherapy showed significantly lower DFFS rates. Only total Gleason score that significantly has affected the local failure free survival (LFFS).
Conclusions: Prostate cancer with unfavorable intermediate risk should ideally be treated with dose escalated IGRT with more longer treatment of ADT.

Introduction:

Prostate cancer is the fifth leading cause of death from cancer in men representing around 6.6% of total male cancer mortality [1]. Since the 1990s, most nations have had a reduction or stabilization in prostate cancer mortality [2]. Intermediate risk prostate cancer are those patients with prostate specific antigen (PSA) at 10 to 20 ng/ml, clinical stage T2b or T2c, or Gleason score [3].

Intermediate-risk prostate cancer includes a highly heterogeneous group of patients. Due to this heterogeneity and variable prognoses, it is challenging to have uniform treatment recommendations. Treatment options for these patients include active surveillance, partial gland ablation, radical prostatectomy, and various radiotherapy techniques with 4 to 6 months of androgen deprivation therapy (ADT), or combination external beam radiotherapy (EBRT) with a brachytherapy (BT) boost with or without ADT. Classification systems, such as the National Cancer Comprehensive Network guidelines, stratify this large cohort into subgroups with favorable or unfavorable disease, which may simplify treatment

recommendations but still leave substantial variability within strata [4,5].

Unfavorable intermediate-risk prostate cancer (UIR-PC) was defined as any intermediate-risk patient with a primary Gleason pattern of 4, percentage of positive biopsy cores (PPBC) ≥50%, or multiple intermediate-risk factors [6].

Relative to favorable intermediate-risk (FIR - PC) disease, men with UIR-PC disease have higher rates of biochemical recurrence, metastatic recurrence, and death from prostate cancer [5].

It is well accepted that dose escalation for prostate cancer is associated with improved biochemical and tumor control outcomes [7–10]. While dose escalation would lead to improved treatment outcomes, the hazard of increase in toxicity is a concern [11]. Technological advances have obviously enhanced the technology of radiation oncology by allowing more normal tissues to be spared with concomitant better target coverage [12].

As a result of advanced, highly conformal RT, is the risk of a “geographic miss”, which is a well documented phenomenon [13].

Many sources of geometric uncertainty exist including target delineation error, patient setup uncertainty and target position variation (due to interfraction and intrafraction movements during the course of treatment). Image-guided RT (IGRT) allows for the adjustment of patient daily set up and the positional correction of the radiation beams while the irradiation running. Failure to account for variations of the prostate position as a factor of the deformability and mobility of the surrounding normal gastrointestinal and genitourinary organs during irradiation can compromise the control rate and increase normal tissue toxicity [14]. The benefits of IGRT have been shown in retrospective patient series [15].

These series have demonstrated improvements in biochemical control and reduction in urinary and gastrointestinal toxicity with IGRT [16, 17, 18]. And it has become the standard of care for delivery of external beam radiation treatment for prostate cancer [15].

IGRT is often based on the implantation of fiducial gold markers in the prostate. With markers implanted in the prostate, the position of the prostate can be verified before each treatment fraction using portal imaging. This limits the interfractional variability in the position of the prostate and as a consequence the PTV margins can be reduced [17].

As regards the control of intrafractional movements of the prostate during irradiation, the Calypso System has developed as a target positioning device that continuously monitors the location of three implanted electromagnetic transponders at a rate of 10 Hz [19].

The aim of this study is to compare the biochemical and clinical tumor control in patients with intermediate risk prostate cancer treated by means of high dose IGRT versus high dose non image guidance (non IG EBRT) as well as the toxicity profile in both techniques.

Patients and Methods:

This retrospective study has enrolled patients with localized cancer prostate of intermediate risk treated in University of Michigan by means of EBRT between 1995 and 2012.

According to the National Comprehensive Cancer Network criteria, intermediate risk criteria include those patients with clinical stage T2b/T2c or total Gleason score = 7 or PSA 10 - 20 ng/mL.

Patients with advanced stages and/or patients treated with brachytherapy either alone or with EBRT were excluded from the study.

Before starting treatment, all patients had routinely undergone complete physical examination, digital rectal examination, complete blood count, kidney function tests and PSA.

Staging was done with CT chest, abdomen and, pelvis. Bone scan was done according to patients complaint and for patients with unfavorable criteria.

CT-based simulation was done in supine position with knee wedge immobilization device. About one hour before simulation, the patient was asked to drink water and not to empty his bladder. Target volume including the prostate and seminal vesicles was delineated.

The clinical target volume (CTV) is defined as the prostate and seminal vesicles. The planning target volume (PTV) is defined as the CTV with a margin to account for physical uncertainties including setup reproducibility and interfractional and intrafractional organ motion. A 1-cm margin is added to the CTV to form the PTV in all directions except posteriorly where the margin is reduced to 0.6 cm.

Weekly electronic portal imaging was done during the course of irradiation for corroborate set up.

When using image-guided approaches with daily target localization, margins are 6 mm circumferentially around the clinical target volume.

Normal tissues identified on each CT slice include the inner and outer walls of the rectum and bladder and, the femoral heads. Portions of the small bowel or sigmoid colon within 1 cm of the PTV are also contoured and taken into consideration during planning. In addition, the central 1-cm diameter portion of the prostate encompassing the prostatic urethra is defined for dosimetric consideration and evaluation during high-dose IMRT planning.

The median dose prescribed to the planning target volume (PTV) was 77.5 Gy in 7- 8 weeks in 1.8 - 2.0 Gy per fraction. Anterior and lateral permanent skin tattooing were routinely done to mark the isocenters of the irradiation fields. The patients were treated with a full bladder.

Weekly follow up with the physician during radiotherapy course was followed.

In patients treated with IGRT, our protocol based on using either gold seeds or Calypso 4 D localization system. In case of gold seeds implantation, three markers were inserted transrectaly into the prostate 1 – 2 wk before computed tomography (CT) under ultrasonic guidance, local anaethesia and antibiotic

coverage. The gold markers were inserted into the clinical target volume (CTV) of the prostate gland, one at the apex of the prostate and two others at the left and right of the base of the gland. Computed tomography of the small pelvis was then taken and the locations of the three fiducial markers were determined on 3D radiation treatment planning system. and projected onto digitally reconstructed radiographs, which were then used as reference images at the time of treatment. Each day before treatment, orthogonal kilovoltage radiographs of the patient were obtained Patient position was corrected if discrepancy in any direction exists.

For patients treated with IGRT using the Calypso system, 3 tiny Beacon electromagnetic transponders are implanted into the prostate through a simple outpatient procedure similar to trans rectal ultrasound-guided biopsy.

The System allows the three-dimensional position of the implanted transponders and target isocenter to be tracked providing continuous, real-time localization and monitoring of the prostate.

Androgen deprivation therapy was administered according to the discretion of the treating physician for 6 months. During the first 2 years following treatment, patients were followed with physical examination and serum PSA measured every 3 months. After that PSA was assessed every 6 months.

During follow up visits, biochemical failure free survival (bFFS), local failure free survival (LFFS) and, distant failure free survival (DFFS) were monitored as well as any genitourinary and intestinal toxicities.

PSA progression was defined as nadir PSA + 2 ng/mL based on the Phoenix consensus definition. Local recurrence is documented if confirmed pathologically and, distant metastasis were diagnosed based on imaging with or without biopsy (in uncertain cases).

Toxicities were scored using the Common Terminology Criteria for Adverse Events, version 4.0 [20].

Statistical analysis was done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA).

Subgroup analyses were performed by whether a patient had been treated with EBRT alone or with image guidance.

Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage.

Pearson's Chi-square test or Fisher's exact test was used to examine the relation between qualitative variables.

For quantitative data, comparison between two groups was done using either Student t-test for normally distributed data or Mann-Whitney test for not normally distributed data. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test.

Multivariate analysis was done using Cox-regression method for the significant factors affecting survival on univariate analysis. Hazard ratio (HR) with its 95% confidence interval (CI) was used for risk estimation. Rates of cumulative incidence of Grade 3 GU and GI toxicity were compared using the $\chi 2$ test. All tests were two-tailed. A p-value < 0.05 was considered significant.

Ethical Approval

The study has been presented to the Medical Research Ethics Committee Faculty of Medicine-Sohag University and has been approved.

Results:

Searching in department achieve for prostate cancer patients with intermediate risk treated between 1995 and 2012 with EBRT either alone or with image guidance revealed 388 consecutive patients. EBRT without image guidance was implemented in 214 / 388 patients (55%) and with image guidance in 173 / 388 patients (45%) either with gold seeds (105 / 173 patients) or with use of Calypso 4D localization system (68 / 173 patients). EBRT was given by means of 3 dimensional Conformal technique in 238 patients (61%) or with Intensity modulated radiotherapy technique (IMRT) in 150 patients (39%).

All patients had fulfilled the criteria of intermediate risk according to the National Comprehensive Cancer Network criteria mentioned above [20].

The patients in this study aged from 35 to 83 yr. with a median age at 69 yrs. The mean age of patients treated with IGRT (66.59 yr.) was significantly younger than that of patients treated without image guidance (68.99 yr.) as seen in table1.

The follow up period for the whole cohort ranged from 2 to 232 m with a median period at 86 m. Patients treated without image guidance had significantly longer period of follow up (mean at 94.39 m compared to those treated with image guidance (mean at 80 m) as seen in table1.

Patients with stage T1 disease composed 65% of the whole cohort and all were T1C while stage T2 disease composed 35% of the cohort as follows: T2A (13.7%), T2B (17.3%) and T2C (3.9 %). According to their T stage, patients were stratified into two groups: T1C/T2A and T2B/T2C. A significant difference in the distribution of both these groups was observed between the two arms of the study as seen in table 1.

In the 388 studied patients, serum PSA at diagnosis ranged from 1 to 20 ng/ml with a median at 7.75 ng/ml. A value < 10 ng/ml was observed in 259 patients (67%) while in 129 ones (33%), the value was ≥ 10 ng/ml. A significant difference was noticed in the mean value of PSA between both study groups as seen in table 1.

Biopsies taken from the tumors at the time of diagnosis were +ve for cancer in a percent ranged from 10 to 80% in all cores obtained. In 370 recorded cases, 269 patients (73%) had cancer in ≤ 50 % of cores obtained while 101 patients (27%) had +ve cancer in $>$ 50% of cores obtained.

Although there was a difference in distribution of the percent of cores +ve for cancer in both arms of the

study as seen in table 1, the difference was not significant.

For total Gleason score, Gleason score 7 was observed in 326/388 patients (84%), while Gleason score 6 was observed in 62/338 patients (16%). It is observed from table 1 that both arms were significantly different in distribution of total Gleason score especially in cases with total Gleason score 6. However, such a difference was not observed in the distribution of primary Gleason score between the two arms of the study either with primary Gleason score 3 or 4.

ADT was administered to 97 (25%) patients for a total of 6 m while 290 patients (75%) did not receive ADT. As seen in table 1, among those treated with ADT, the percentage is significantly higher in the arm treated by EBRT alone compared with the arm treated with image guidance.

Stratifying the patients into favorable (130 patients; 33.5%) and unfavorable risk groups (257 patients; 66.2%) was not significantly different in distribution between the two treatment groups as seen in table1.

Treatment outcome

In the whole cohort, biochemical failure (BF) was observed in 77/388 patients (19.8%). Biochemical failure free survival (bFFS) at 5 y was at 88% and at 10 y scored 73% as shown in figure 1.

In analyzing all cases together, IGRT patients had significantly longer 5 and 10 y bFFs than those treated with non IG EBRT as seen in figure 2 and table 2 with $p = 0.016$.

Such a finding was associated with a significant increase in hazard of BF in the non IG EBRT subgroup compared with IGRT in univariate and multivariate analysis of different predictive factors as seen in table 3.

However, in subgroup analysis , this notice was only observed in patients with favorable criteria [composed 131 patients, (34%)] as seen in figure 3 ($p = 0.055$). But, in those with unfavorable criteria (257 patients, 66%), IGRT did not show a significant improvement in bFFS over the non IG EBRT as seen in figure 4. ($p=0.143$).

Patients with favorable criteria represented 130 from 387 recorded patients (33.5%) whereas those with unfavorable criteria represented 247 / 387 (64%). As seen in table 2 and figure 5, the 5 and 10 y bFFS was significantly higher in patients with favorable than unfavorable criteria (95 %; 85% versus 80% and 70% respectively; $p = 0.031$) also the hazard of BF significantly decreased with favorable criteria ($p = 0.031$) in univariate analysis as seen in table 3.

As regards the impact of predictive factors on BF, earlier T stage was associated with better 5 and 10 y bFFS compared with more advanced T stages (5 and 10 y bFFS at 90% and 78% for T1C versus 60% and 40% for T2C , $p = 0.055$ as seen in figure 6. However, on classifying the whole cohort in 2 subgroups T1C / T2A versus T2B / T2C such difference becomes not significant as seen in table 2 and figure 7 also, the hazard of BF shows no significant difference as seen in table 3.

As regards the impact of Gleason score on bFFS, a significant improvement in 5 and 10 y bFFS was associated with total Gleason score 6 compared with that at score 7 ($p = 0.039$) as seen in table 2 and figure 8 with significant decrease in the hazard of BF in uni and multivariate analysis as seen in table 3.

On the other hand, no significant difference was noticed as regards the score of primary Gleason score either 3 or 4 as seen in table 2 and 3 on BF.

Concerning the impact of percent positive biopsy cores on BF, as seen in table 2 and figure 9, percent ≤ 50% was associated with significantly longer 5 and 10 y bFFS compared with that for percent > 50% (91% and 78% versus 78% and 60% , $p = 0.002$) also with significant decrease in hazard of BF on univariate ($p = 0.002$ and multivariate analysis , $p = 0.010$ as seen in table 3.

On classifying the patients according to serum PSA at presentation, it is obvious from table 2 that no significant difference on the level of 5 and 10 y bFFS between PSA level < 10 or ≥10 ng/ml but on multivariate analysis, it shows significant decrease in hazard of BF in favor of lower level as seen in table 3.

No significant impact of ADT nor for patient's age on the BF as seen in table 2 and 3.Also no significant impact of patients" age on BF neither on the level of survival rates nor on the level of hazard ratio (HR).

Concerning the predictive factors for local recurrence, as seen in table 2, only total Gleason score (figure 10) that showed a significant impact on 5 and 10 y LFFS (100%, 100% with total score 6 versus 98% and 93% for total score 7 at 5 and 10 y respectively , $p = 0.028$) but no effect on HR as seen in table 3.

As regards the distant failure, patients treated with IGRT showed significantly longer 5 and 10 y DFFS compared with those treated with non IG EBRT on the level of the whole cohort as seen in figure 11 and table 2 (99% , 99% versus 98 and 95% respectively, $p = 0.050$) but no significant impact on HR as seen in table 3.

Unlike the case in BF, no significant difference in DFFS between IGRT and non IG EBRT was noticed whether in the favorable subgroup alone, $p = 0.270$ nor in the unfavorable subgroup alone, $p = 0.119$.

Another predictive factor that has showed an impact on 5 and 10 y DFFS was the risk group. Patients in the favorable risk subgroup showed significant longer survival compared with those with unfavorable risk (100% and 99% versus 97% and 95% respectively, $p = 0.007$) as seen in figure 12.

The impact of percent positive biopsy cores was also apparent on the level of 5 and 10 y DFFS where patients with positive cores ≤ 50% showed significantly longer rates at 99% and 99% versus 95% and 90% respectively, $p = 0.002$ as shown in table 2 and figure 13. Also the hazard of distant failure significantly decreased on univariate and multivariate analysis ($p = 0.004$ and 0.04 respectively) in favor of less positive cores as seen in table 3.

Another predictive factor that was found has significant impact on DFFS was the T stage of the tumor. As seen in figure 14 , the estimated 5 and 10 y DFFS were at 99% and 98% for T1c vs 90% and 73% for T2c (p = 0.004). However, on stratifying the whole cohort into two subcategories (T1C / T2A vs T2B / T2C), this significant difference disappears as seen in table 2 and 3.

Serum PSA although it was associated with longer 5 and 10 y DFFS in favor of PSA < 10 ng/ml versus ≥ 10 ng/ml, the difference was not significant as seen in table 2 but on the other hand, the hazard of distant failure significantly decreased (p = 0.056) in multivariate analysis in favor of lower levels as seen in table 3.

Another predictive factor of distant failure we have investigated in our study was the impact of ADT. Patients received ADT with radiotherapy showed significant lower 5 and 10 y DFFS (98% and 95%) than patients did not receive ADT (99% and 98%) with p = 0.007 as seen in table 2 and figure 15. That was associated with significant decrease in HR in univariate analysis (p = 0.011) in favor of no ADT as seen in table 3.

The last predictive factor studied in our study was that of patients" age. We did not find this factor has an impact on the 5 or 10 y DFFS as seen in table 2 and also no significant effect on HR was found as seen in table 3.

Treatment related toxicities

For rectal toxicities, according to the CTCAE version 4 (20), In non IG EBRT subgroup, 68 / 214 pts (32%) developed G1,2,3 rectal toxicity while 58 / 173 patients (33%) in IGRT subgroup developed rectal toxicities as seen in table 4. In non IG EBRT subgroup, G3 rectal toxicity was scored in 17 / 214 patients (8%) and in IGRT subgroup, 14 / 173 patients (8%) suffered from G3 rectal toxicity. No significant difference between both arms was noticed as seen in table 4.

For genitourinary toxicities, 77 / 214 patients in non IG EBRT subgroup (36%) suffered from G1,2 and 3 toxicities while 66/173 patients (38%) in IGRT subgroup suffered G1,2 and 3 toxicities as seen in table 4. G3 was observed in 2 from 214 patients in non IG EBRT (0.9%) while 3 from 197 patients in IGRT subgroup suffered from G3 toxicity (1.5%) with no significant difference as seen in table 4.

Table 1. Patients and disease characteristics

Patients and disease characteristics	**Non IG EBRT (214 pt)**	**IGRT (173 pt)**	**P**
Mean Age	68.99	66.59	**0.003**
Mean Follow up in ms	94.39	80.02	**0.005**
T1C / T2A **T2B / T2C**	160 /305 (52.5%) 54/82 (65.9%)	145/ 305 (47.5%) 28/82 (34.1%)	**0.034**
Total Gleason Score			
6	43 / 61 (70.5%)	18 / 61 (29.5%)	**0.006**
7	171 / 326 (52.5%)	155 / 326 (47.5%)	
Primary Gleason Score			
3	64 / 120 (53.3%)	56 /120 (46.7%)	0.602
4	150 / 267 (56.2%)	117 / 267 (43.8 %)	
Percentage of +ve biopsy cores			
Percentage of +ve biopsy cores ≤ 50%	141 / 269 (52.4%)	128 / 269 (47.6%)	0.076
Percentage of +ve biopsy cores > 50%	62 / 101 (61.4%)	39 / 101 (38.6%)	
PSA at presentation	9.09 ng/dl	7.67 ng/dl	**0.001**
Androgen deprivation therapy (ADT)			
Yes	68 / 97 (70%)	29 / 97 (30 %)	**0.001**
No	146 / 290 (50.3%)	144 / 290 (49.7%)	
Risk category			
Favorable	67 / 130 (51.5%)	63 / 130 (48.5%)	0.290
Unfavorable	147 / 257 (57.2%)	110 / 257 (42.8%)	

Table 2. 5 and 10 y treatment failures

Predective risk factor	Type of failure								
	Biochemical Failure Free Survival			Local Failure Free Survival			Distant Failure Free Survival		
	5 y bFFS	10 y bFFS	P	5 y LFFS	10 y LFFS	P	5 y DFFS	10 y DFFS	p
Radiotherapy tech									
IGRT	94%	78%	**0.016**	99%	95%	0.790	99%	99%	**0.050**
EBRT	85%	66%		100%	97%		98%	95%	
Age									
≤ 67 yr	88%	70%	0.918	98%	83%	0.172	99%	98%	0.344
> 67 yr	90%	70%		99%	87%		98%	95%	
Risk group									
Favorable	95	80	**0.031**	100%	97%	0.371	100%	99%	**0.007**
Unfavorable	85	70		98%	94%		97%	95%	
T stage									
T1c / T2a	90%	75%	0.205	99%	95%	0.414	99%	97%	0.075
T2b / T2c	83%	67%		100%	97%		98%	94%	
Total Gleason score									
Score 6	90%	87%	**0.039**	100%	100%	0.028	99%	97%	0.176
Score 7	88%	70%		98%	93%		96%	94%	
1ry Gleason score									
Score 3	90%	76%	0.190	99%	95%	0.756	99%	98%	0.186
Score 4	80%	70%		98%	95%		97%	93%	
% of +ve cores									
≤ 50%	91%	78%	**0.002**	100%	96%	0.548	99%	99%	**0.002**
> 50%	78%	60%		98%	92%		95%	90%	
PSA on diagnosis									
< 10 ng/ml	93%	75%	0.163	100%	95%	0.483	99%	97%	0.176
≥ 10 ng/ml	80%	68%		97%	95%		96%	94%	
ADT									
Yes	90%	75%	0.137	99%	95%	0.294	98%	95 %	**0.007**
No	80%	65%		100%	95%		99%	98%	

Table 3. Univariable and multivariable predictors of treatment failures

Predictive factor	Hazard ratio (HR) for failure in uni and multi variate analysis					
	Biochemical failure (BF)		Local failure (LF)		Distant failure (DF)	
	Univariate analysis HR (95% CI); p value	Multivariate analysis HR (95% CI); p value	Univariate analysis HR (95% CI); p value	Multivariate analysis HR (95% CI); p value	Univariate analysis HR (95% CI); p value	Multivariate analysis HR (95% CI); p value
Radiotherapy tech EBRT IGRT	1.83 (1.11 – 1.04); **0.013**	1.81 (1.07 – 3.05); **0.025**	0.88 (0.33 – 2.30); 0.791	1.04 (0.37 – 2.93); 0.936	4.04 (0.90 – 18.27); 0.069	3.23 (0.70 – 14.89); 0.132
Age ≤ 67 yr > 67 yr	1.02 (0.65 – 1.06); 0.918	1.10 (0.692 – 1.76); 0.680	1.86 (0.75 – 4.64); 0.180	2.26(0.84 – 6.02); 0.103	0.60 (0.21 – 1.74);0.350	0.55 (0.18 – 1.72);0.305
Risk group Favorable Unfavorable	0.57 (0.34 – 0.96);**0.031**	1.26 (0.63 – 2.50);0.511	0.63 (0.23 – 1.75);0.375	1.14 (0.315 – 4.14);0.840	0.25 (0.06 – 1.12);0.07	1.53(0.18 – 13.3);0.673
T stage T1c / T2a T2b / T2c	0.72 (0.44 – 1.19); 0.205	0.815 (0.47 – 1.43); 0.475	1.66(0.48 – 5.71); 0.423	1.05 (0.27 – 4.09);0.942	0.415(0.15 – 1.12); 0.084	0.65 (0.22 – 1.92); 0.444
Total Gleason score Score 6 Score 7	0.47 (0.22 – 0.98); **0.04**	0.30 (0.12 – 0.72); **0.007**	0.19(0.01 – 2.08); 0.172	0.00 (0.00 – 0.00); 0.971	0.26(0.03 – 2.01);0.20	0.25 (0.02 – 2.87); 0.267
1ry Gleason score Score 3 Score 4	0.73 (0.45 – 1.17); 0.19	0.84 (0.48 – 1.48); 0.554	1.17 (0.44 – 3.07); 0.766	1.50 (0.47 – 4.76); 0.49	1.93 (0.717 – 5.19); 0.193	0.645 (0.205 – 2.02); 0.454
% of +ve cores ≤ 50% > 50%	0.48 (0.30 – 0.77); **0.002**	2.12 (1.20 – 3.75); **0.010**	0.74 (0.28 – 1.98); 0.550	1.18 (0.33 – 3.66); 0.773	0.23 (0.08 – 0.63); **0.004**	0.27 (0.07 – 0.93); **0.04**
PSA on diagnosis < 10 ng/ml ≥ 10 ng/ml	0.72 (0.46 – 1.14); 0.165	0.45 (0.263 – 0.777); **0.004**	1.44 (0.52 – 4.00); 0.49	0.67 (0.216 – 2.10); 0.499	0.51 (0.19 – 1.37); 0.184	0.33 (0.11 – 1.02); **0.056**
ADT Yes No	0.69 (0.43 – 1.12); 0.140	1.23 (0.67 – 2.17); 0.476	1.19 (0.56 – 6.57); 0.303	2.15 (0.56 – 8.29); 0.268	0.28 (0.10 – 0.75); **0.011**	1.56 (0.50 – 4.84); 0.438

Table 4. Types and distribution of treatment related toxicities

Type of toxicity	Non IG EBRT (n/%)	IGRT (n/%)	p
Rectal toxicity			
G1/2	51/95 (53.7%)	44/95 (46.3%)	0.539
G3	17/31 (55%)	14/31 (45%)	
Genitourinary toxicity			
G1/2	75/138 (54 %)	63/138 (46%)	0.427
G3	2/5 (40%)	3/5 (60%)	

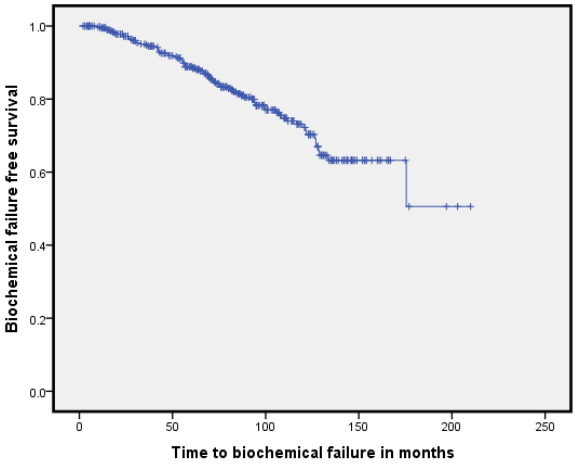

Figure 1. Biochemical failure free survival for all patients

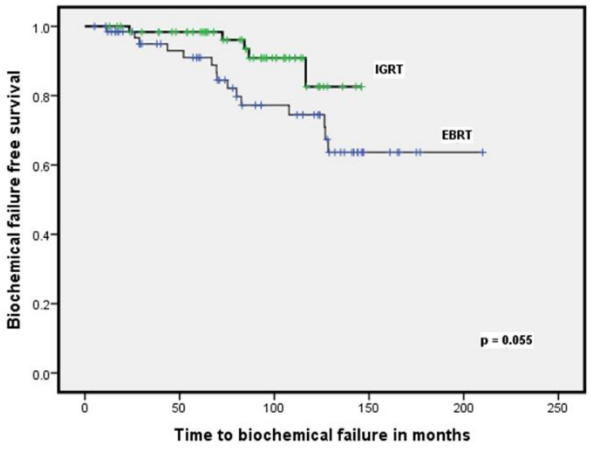

Figure 2. bFFS is significantly longer with IGRT than with non IG EBRT in all patients (favorable and unfavorable)

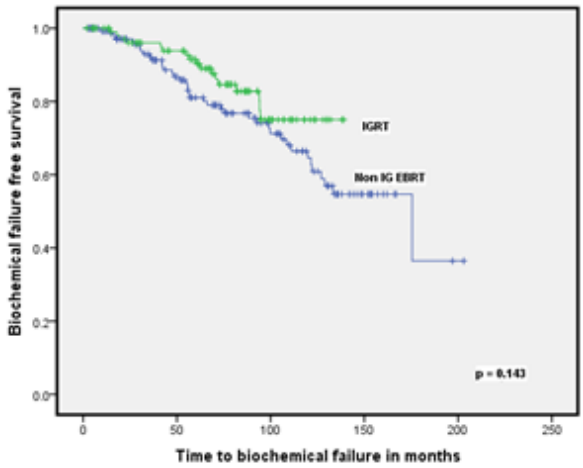

Figure 3. Longer bFFS in patients with favorable criteria treated with IGRT compared with non IG EBRT

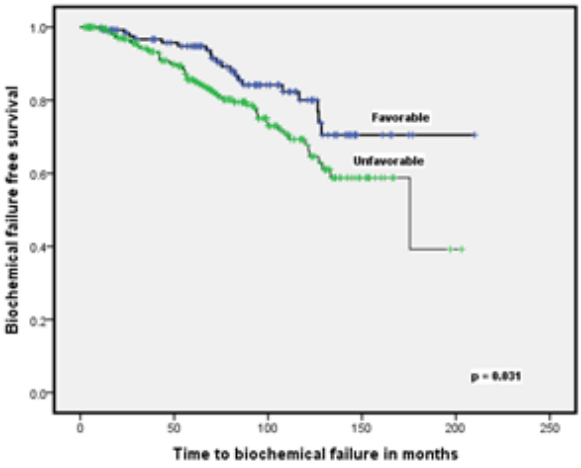

Figure 4. bFFS is not significantly different between IGRT and non IG EBRT in UIR PC patients.

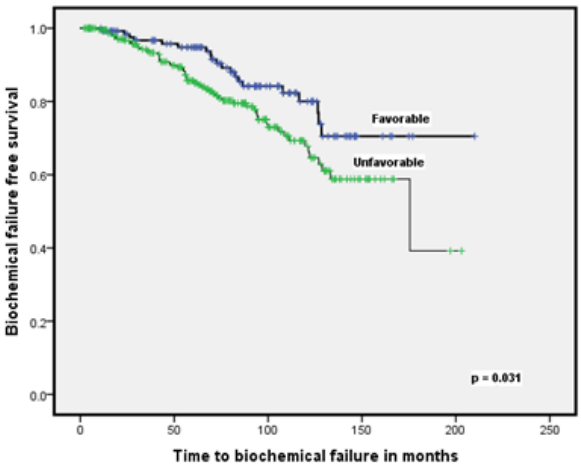

Figure 5. bFFS significantly longer with favorable vs unfavorable criteria

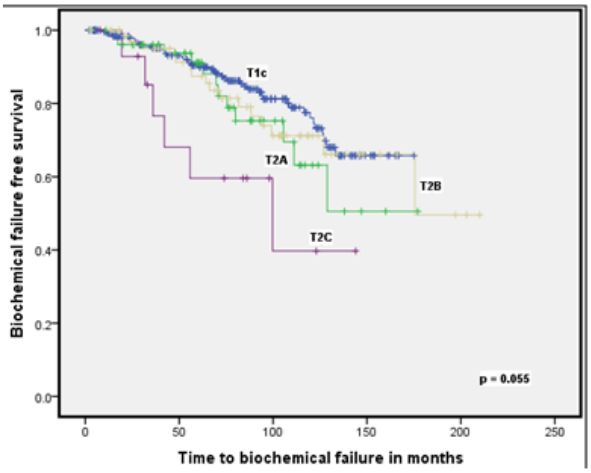

Figure 6. Significantly longer bFFS in T1C compared with T2

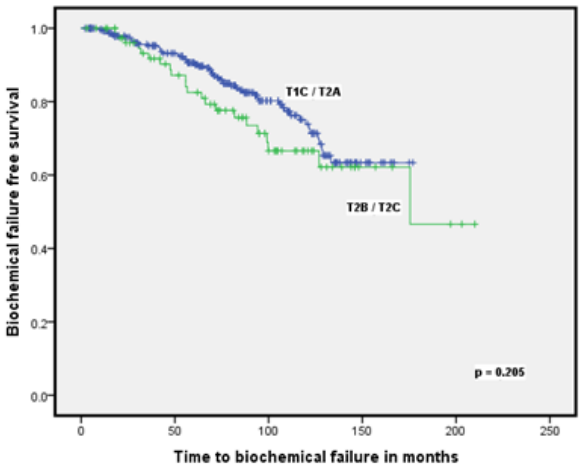

Figure 7. bFFS is not significantly different between T1A / T2A and T2B / T2C

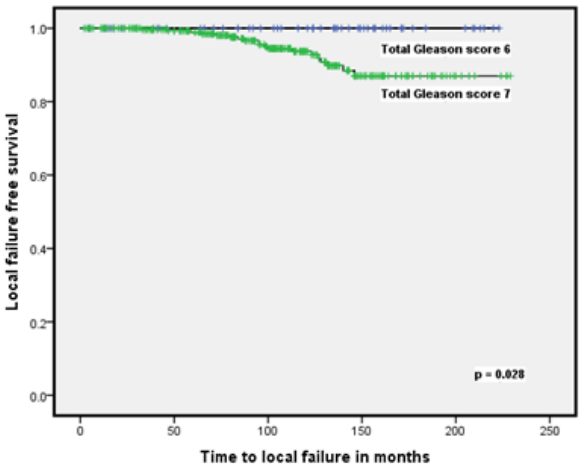

Figure 10 . LFFS is significantly longer with total Gleason score 6 vs 7

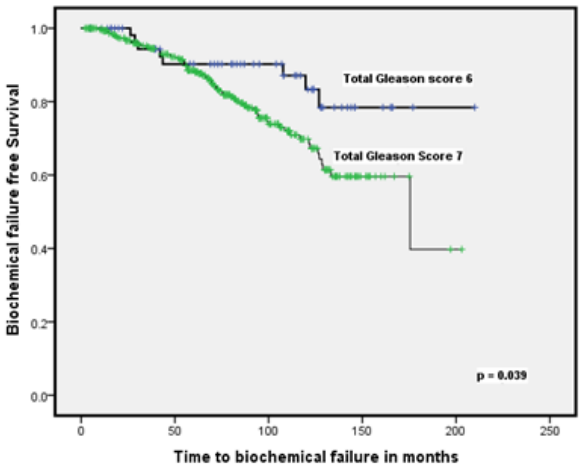

Figure 8. Total Gleason Score 6 has significantly longer bFFS than total Gleason Score 7

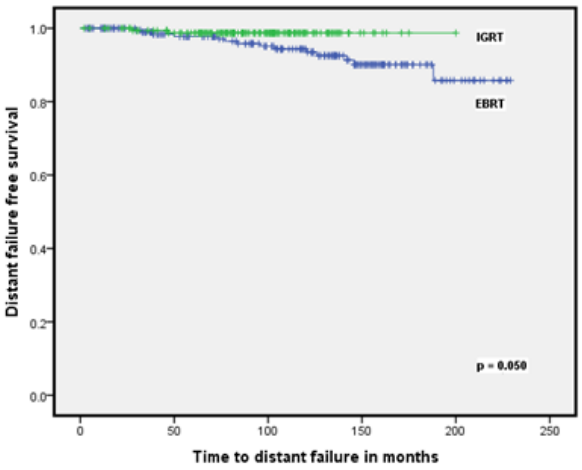

Figure 11. DFFS is significantly longer with IGRT vs EBRT

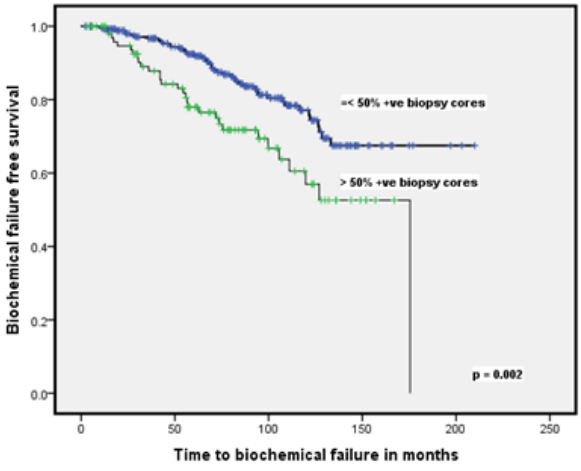

Figure 9. Significantly longer bFFS in patients with ≤ 50% +ve biopsy cores compared with > 50% +ve biopsy cores.

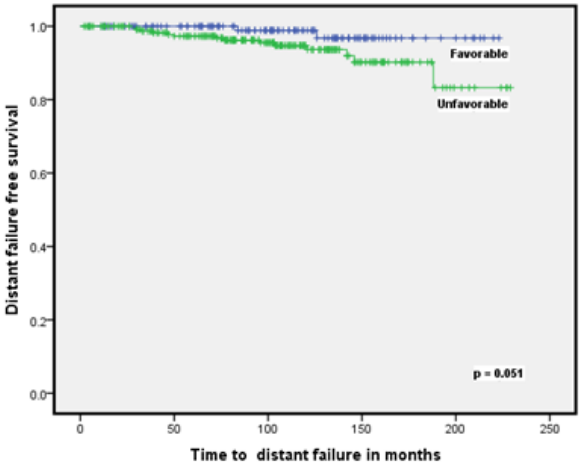

Figure 12. DFFS is significantly longer with favorable vs unfavorable criteria.

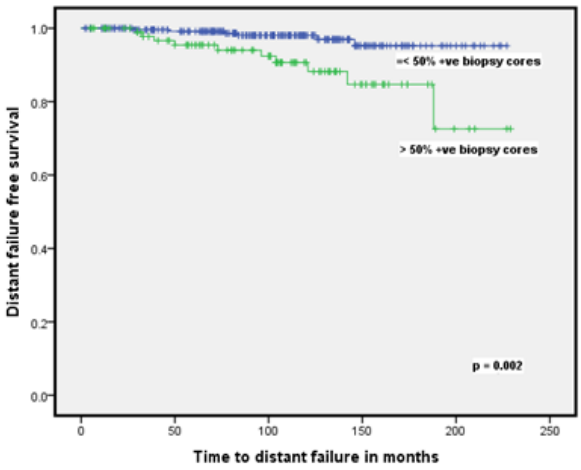

Figure 13. DFFS is significantly longer with ≤ 50% +ve biopsy cores vs > 50%

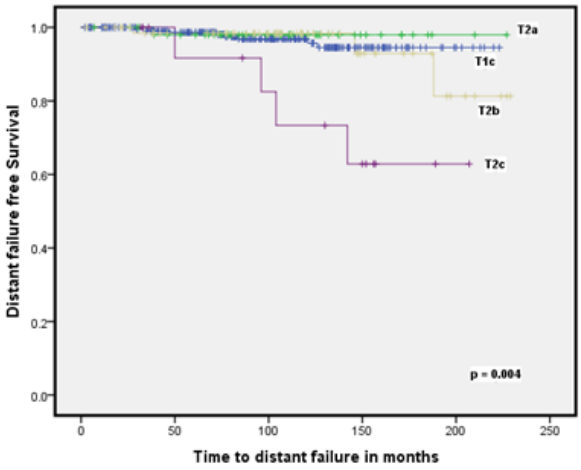

Figure 14. DFFS is significantly longer with earlier T stage

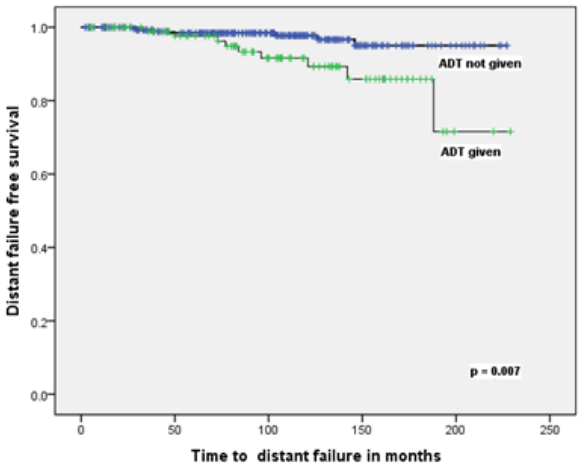

Figure 15. DFFS is significantly longer with no ADT vs with ADT

Discussion:

The advent of conformal radiotherapy and IGRT techniques has increased the precision of radiation dose delivery and permitted to safely escalate the dose in prostate cancer resulting in prolonged freedom from BF. This could be attributed to daily adjustment of the target volumes position under image guidance [9, 21, 22].

Our retrospective study demonstrates clear evidence of improvement in disease control when treating intermediate risk patients with IGRT and our results are near to those reported by other investigators.

The 5 yr bRFS reported in our series is at 88% for all intermediate risk patients whatever the technique with higher rates in patients treated with IGRT who achieved 94% and 78% bRFS at 5 and 10 y respectively vs 85% and 66% 5 and 10 y bRFS with non IG EBRT as seen in figure 2. The HR for BF decreased significantly with IGRT vs non IG EBRT both in univariate and multivariate analysis as seen in table 3. These results are even higher than results reported by other investigators such as Kupelian and colleagues who reported 5 yr bRFS rate at 86% on treatment of a similar cohort of patients with localized cancer prostate using daily image guidance [22].

Sean and colleagues in another study enrolled 962 patients of localized cancer prostate, 562 of them were categorized as intermediate / high risk, found that the 5 y biochemical control was at 89% for the entire group and 83% for intermediate/high risk with the use of IGRT and a median dose at 79.7 Gy in conventional fractionation [23].

Another study conducted by Hamid R and colleagues, 961 patients with localized cancer prostate had been treated with IGRT using intra prostatic fiducial markers and daily IG by electronic portal imaging device (EPID). Intermediate risk patients represented 653 patients (67.9%) of these patients. Three sequential institutional schedules: (A) 75.6 Gy, (B) 79.8 Gy, (C) 78 Gy, with 1.8, 1.9 and 2 Gy/fraction, respectively were used. With a median follow up period of 6.1 y. They reported BF rates at 5-year as 23%, 17% and 9% for A, B and, C respectively with HR 2.68 [95% CI 1.87–3.85] and 1.92 [95% CI 1.33–2.78] for A and B compared to C, respectively. Our results are consistent with those reported in their study for their intermediate risk subgroup. We found a bFFS at at 5 y to be at 88% for all of our cohort of intermediate risk patients with our dose at 78 Gy and even a longer bFFS (94%) in patients treated with IGRT [24].

In contrast to our results, the gain in biochemical control achieved with IGRT was not reported in intermediate risk patients in other studies in spite of using higher radiation doses. Zelefsky and colleagues in a study on 186 patients with localized cancer prostate treated to a dose at 86.4 Gy in conventional fractionation by IGRT and implanted prostatic fiducial markers reported a significant improvement at 3 years in PSA relapse-free survival for high risk patients compared with non-IGRT (97% vs. 77.7%; p = 0.05).

But for low- and intermediate risk patients, no differences were observed between IGRT and non-IGRT [16]. Not only the bFFS that has improved with IGRT in our study but also distant disease control as well. As seen in figure 11 and table 2, the 5 and 10 y DFFS with IGRT were at 99% and 99% vs 98% and, 95% for non IG EBRT (p=0.050). However, on calculating the HR, it appears that although there was a marked increase in the hazard of distant failure in the subgroup treated with non IG EBRT compared with those treated with IGRT in uni and in multi variate analysis, such difference was not significant as shown in table 3.

Concerning the LFFS, neither significant difference in 5 and 10 y LFFS nor in HR were observed between both techniques as shown in table 2 and 3.

These significant findings mentioned above can be attributed to our finding which show as in table 1 that patients in IGRT arm were having significantly earlier tumor stage than those in EBRT arm [T1c / T2a represented 145 / 173 patients (84%) vs 160 / 214 patients (75%) in EBRT arm] and were having significantly lower serum PSA at presentation compared with those treated with EBRT (7.67 ng/ml vs 9.09 ng/ml in EBRT arm). However, it should not be ignored that patients treated with the more recent IGRT technique have had a shorter period of follow up than those patients treated with the older EBRT technique (median follow up period at 80.02 m vs 94.39 m respectively) that might be a leading cause for development of late events.

Pretreatment risk factors play a crucial role in the clinical management and treatment outcomes in men with localized prostate cancer. Important risk factors include tumor stage, Gleason score, serum PSA, and, percent positive biopsy cores which have been found to exert a prognostic impact on BF, CF, DF and, overall survival [25, 26].

We have also investigated in our study the influence of pretreatment risk factors such as tumor stage, Gleason score, serum PSA and, percent positive biopsy cores on bFFS, LFFS and dFFS.

As regard T stage, as seen in figure 6 we have found that patients with T1c have gained the longest bFFS compared to T2c. The estimated 5 and 10 y bFFS were at 90% and 62% vs 78% and 43% for T1c and T2c respectively (p = 0.055). On the level of DFFS, the estimated 5 and 10 y DFFS were at 99% and, 98% for T1c vs 90% and 73% for T2c (p = 0.004) as seen in figure 14.

However, on stratifying the patients into 2 categorical groups (T1c/T2a vs T2b/T2c), these findings disappear as seen in table 2 and the HR appears not significant as seen in table 3.

Long-term case series of EBRT [27, 28, 29, 30] brachytherapy [31, 32] radical prostatectomy [33] and expectant management [34] uniformly identify tumor grade as a strong predictor of disease relapse and mortality in clinically localized prostate cancer. Studies consistently demonstrate that patients with a poorly differentiated tumor (i.e., grade 4–5 or Gleason score ≥ 7) have an increased risk of metastatic disease progression, and reduced overall survival and disease-specific survival (DSS) [35].Although tumor grade is also associated with DFS and freedom from clinically evident disease relapse [27, 36, 37,38].its impact on local tumor control after EBRT is less certain, as some reports noted an association [35, 39].whereas others did not [37].

It has been reported that Gleason score 7 prostate cancer is a heterogeneous entity [40].

In our study, total Gleason score 7 was associated with significantly lower 5 and 10 y bFFS (88% and 70%) compared with total Gleason score 6 (90 % and 87%, p = 0.039) as seen in figure 8 and, it was also associated with significantly lower 5 and 10 y LFFS (98% and 93%) compared with total Gleason score 6 (100% at 5 and 10 y , p = 0.028) as seen in table 2 and figure 10. However, no significant difference was noticed on the level of DFFS as seen in table 2. The hazard of BF decreased significantly with total score 6 compared with total score 7 but the difference was not significant on the level of LF and DF as in table 3.

Although it was reported in literatures [40]. that patients with primary Gleason score 4 have a more aggressive disease compared with those with a primary Gleason score 3 and experience higher rates of BF (48% vs 38%, p <0.001) and systemic recurrence (15% vs 8%, p < 0.001), our study did not show significant difference in these outcomes whether the primary Gleason score was 4 or 3 as seen in table 2,3.

As regard the impact of pretreatment serum PSA on treatment outcomes, it was reported that serum PSA kinetics appeared to be a valuable additional predictive factor of outcome after local treatment. Pretreatment PSA velocity (PSAV) has emerged as an independent predictor of BF and CF in patients undergoing radical prostatectomy or EBRT [41, 42, 43].

Concerning the impact of pretreatment serum PSA on treatment outcome in our study, although patients with serum PSA < 10 ng/ml have gained longer 5 and 10 y bFFS, LFFS and DFFS, the differences were not significant as seen in table 2. However, the hazard of BF and DF were significantly decreased in multivariate analysis in comparison with patients with serum PSA ≥ 10 ng/ml as seen in table 3.

Concerning the influence of positive biopsy cores on the outcome of treatment, Kestin and colleagues in their study on 844 patients with T1-T3N0M0 prostate cancer treated with different radiation techniques with different median doses, found that higher percentage positive core biopsy was associated with BF, CF, LRR, DM on univariate Cox regression [44].

In our study patients with positive biopsy cores ≤ 50% have developed significantly longer 5 and 10 y bFFS compared with those with positive biopsy cores > 50% (91%, 78% vs 78% and 60% , p = 0.002) as seen in figure 9, and also significantly longer 5 and 10 y DFFS (99%, 99% vs 95% and 90% respectively, p = 0.002) as seen in figure 13. However, such difference was not significant on the level of LFFS as seen in table 2. The hazard of BF and DF have also decreased significantly in univariate and multivariate analysis as seen in table 3 with positive biopsy cores ≤ 50%.

Concerning the influence of ADT on treatment outcomes in prostate cancer, some studies have reported that adding ADT to treatment plans in patients with high risk criteria provides an advantage in terms of improvement in BF, local disease control, metastatic disease control and even overall survival [45, 46, 47,48].

But In case of intermediate-risk prostate cancer), the role of ADT combined with RT remains controversial [45, 49, 50].

Although randomized trials [4,5] have shown improved outcomes with the combination, these trials are criticized for including patients with different risk stratifications (low, intermediate and high risk) and delivering suboptimal RT doses.

In our study, as regards the impact of ADT on treatment outcomes, it was obvious that it was not uniformly administered to these patients. A short term for a total of 6 months duration was administered to 97 of 387 patients (25%). The majority of them (70%) as seen in table 1 was in the arm treated with non IG EBRT while 30% was in the arm treated with IGRT (p = 0.001). Also our findings demonstrate that among the 97 pts received hormonal treatment, 82 (84.5%) of them were in unfavorable risk criteria group while 15 ones (15.5%) were in the favorable risk criteria group (p = 0.000). Such a finding may explain why did patients receive ADT in our study (as seen in figure 15 and table 2) have demonstrated shorter 5 y and 10 y DFFS compared to those did not receive ADT (p=0.007) with significant decrease in hazard of DF in favor of not giving ADT (p = 0.011) as seen in table 3.

As regards treatment related toxicities in our study, it is obvious from table 2 that 95 / 387 patients (24.5%) have developed G1 / 2 cumulative rectal toxicities while 31 / 387 patients (8%) have developed G3 cumulative rectal toxicity. Among the 95 patients who have developed G1 / 2 rectal toxicities, 51 were treated with non IG EBRT (51 / 214; 24%) and 44 received IGRT (44 / 197; 22%). From the 31 patients suffered from G3 rectal toxicities, 17 were in the non IG EBRT subgroup (17 / 214 ; 8%) and 14 in the IGRT subgroup (14 / 197 ; 7%). Although fewer patients suffered in the arm treated with IGRT compared with those treated with non IG EBRT, such a difference was not significant.

As regards the genitourinary toxicities, 138 from 387 patients (35.6%) have developed G1 / 2 cumulative toxicities and only 5 / 387 (1%) have developed G3 toxicities. From 138 patients developed G1/2 toxicities, 75 were in the non IG EBRT (75 / 214; 35%) and 63 received treatment by IGRT (63 / 197 ; 32%). For G3 toxicities, 3 from 5 patients were in the non IG EBRT (3 / 214; 1.4%) and 2 patients in the IGRT subgroup (2 / 197; 1%). No significant difference was noticed in the distribution of all grades of genito urinary toxicities between both treatment techniques.

Conclusion:

Our retrospective study demonstrates clear evidence of improvement in disease control when treating intermediate risk cancer prostate patients with IGRT with a similar incidence of morbidity to non IG IGRT and our results are consistent with those reported by other investigators. Patients with unfavorable intermediate risk criteria should receive more intensive irradiation and more longer ADT.

Conflict of interest

None.

Authors′ contributions

First Author: Study design, writing and revision of the study.
Second author: data collection.
Third author: writing, revision, tables and figures editing.
Fourth author: Study design, writing and revision.
Fifth author: Study design and data collection.
Sixth author: writing, revision, tables and figures editing

References:

1. Jacques F, Isabelle S, Rajesh D, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer. 2015; 136(5): E359–E386.
2. Benjamin DT, Emily CC, Visalinin NS, et al. Socioeconomic differences in prostate cancer treatment: A systematic review and meta-analysis. Cancer epidemiology. 2022; 79: 102164.
3. Nils DA, Ming-Hui C, Judd W, et al. Risk of death from prostate cancer after radical prostatectomy or brachytherapy in men with low or intermediate risk disease. The Journal of Urology. 2011;186: 91– 96.
4. Felix P, Matthew RC, Juanita C, et al. Intermediate-risk Prostate Cancer: Stratification and Management. European Urology Oncology. 2020; 3 (3): 270–280.
5. Neal A, Benjamin W, Fischer-Valuck, et al. Outcomes of patients with unfavorable intermediate-risk prostate cancer treated with external-beam radiotherapy versus brachytherapy alone. J Natl Compr Canc Netw. 2022; 20(4):343–350.
6. Zachary SZ, Daniel ES, Issac PZ, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. European Urology. 2013; 64 (6): 895–902.
7. Dearnaley DP, Sydes MR, Graham JD et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomized controlled trial. Lancet Oncol 2007; 8: 475–87.
8. Zietman AL, Bae K, Slater JD et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results

from proton radiation oncology group/american college of radiology 95-09. J Clin Oncol. 2010; 28: 1106–11.

9. Peeters ST, Heemsbergen WD, Koper PC et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. J Clin Oncol. 2006; 24: 1990–6.
10. Beckendorf V, Guerif S, Le Prise E, et al. The GETUG 70 Gy vs. 80 Gy randomized trial for localized prostate cancer: feasibility and acute toxicity. Int J Radiat Oncol Biol Phys. 2004; 60: 1056–65.
11. Daniel ES, Zachary SZ, Pirus G, et al. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. BJU Int. 2014;114:360–367.
12. Dawson LA, Sharpe MB. Image-guided radiotherapy: rationale, benefits, and limitations. Lancet Oncol. 2006 Oct;7(10):848-58.
13. Bell LJ, Cox J, Eade T, et al. Determining optimal planning target volume and image guidance policy for post-prostatectomy intensity modulated radiotherapy. Radiat Oncol. 2015;10:151.
14. Stenmark MH and Hamstra DA. Image-Guided Strategies for Prostate Cancer. In: Thomas CR, editor. Radiation Medicine Rounds Prostate Cancer. Demos Medical Publishing. 2011(2:11);113-130.
15. Hemal Ariyaratne, Hayley Chesham, John Pettingell, et al. Image-guided radiotherapy for prostate cancer with cone beam CT: dosimetric effects of imaging frequency and PTV margin. Radiotherapy and Oncology. 2016 ;121: 103–108.
16. Zelefsky MJ, Kollmeier M, Cox B, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys. 2012; 84:125–9.
17. Gill S, Thomas J, Fox C, et al. Acute toxicity in prostate cancer patients treated with and without image-guided radiotherapy. Radiat Oncol. 2011; 6:145.
18. Sveistrup J, PM af Rosenschöld, Deasy JO, et al. Improvement in toxicity in high risk prostate cancer patients treated with image-guided intensity-modulated radiotherapy compared to 3D conformal radiotherapy without daily image guidance. Radiation Oncol. 2014; 9:44.
19. Patrick Kupelian, Twyla Willoughby, Arul Mahadevan, et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. Int J Radiat Oncol Biol Phys. 2007; 67 (4): 1088-1098.
20. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 4.0. National Cancer Institute. 2009 (09-5410): 19, 2016
21. Zietman AL, De Silvio ML, Slater JD, et al. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate. A randomized controlled trial. JAMA. 2005;294:1233–1239.
22. Kupelian PA, Willoughiby TR, Reddy CA, et al. Impact of image guidance on outcome after external beam radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2008 ;70(4): 1146 – 1150.
23. Sean S. Park, Di Yan, Samuel Mc Grath, et al. Adaptive Image-Guided Radiotherapy (IGRT) eliminates the risk of biochemical failure caused by the bias of rectal distension in prostate cancer treatment planning: Clinical Evidence. Int J Radiat Oncol Biol Phys. 2012 ;83 (3) : 947 – 952.
24. Hamid Raziee, Fabio Y. Moraes , Jure Murgic, et al . Improved outcomes with dose escalation in localized prostate cancer treated with precision image-guided radiotherapy. Radiotherapy and Oncology. 2017;123: 459–465.
25. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer JAMA. 1998; 280: 969-974.
26. Shipley WU, Thames HD, Sandler HM, et al. Radiation therapy for clinically localized prostate cancer: a multi-institutional pooled analysis. JAMA. 1999; 281: 1598-1604.
27. Kuban DA, Howard D Thames, Larry BLevy, et al. Long-term multi-institutional analysis of stage T1-T2 prostate cancer treated with radiotherapy in the PSA era. Int J Radiat Oncol Biol Phys. 2003; 57(4):915–928.
28. Zagars GK, von Eschenbach AC, Ayala AG, et al. Prognostic factors in prostate cancer. Analysis of 874 patients treated with radiation therapy. Cancer. 1993;72(5):1709–1725.
29. Swanson GP, Cupps RE, Utz DC, et al. Definitive therapy for prostate carcinoma: Mayo Clinic results at 15 years after treatment. Br J Radiol. 1994;67(801):877–889.
30. Jackson W, Hamstra DA, Johnson S, et al. Gleason pattern 5 is the strongest pathologic predictor of recurrence, metastasis, and prostate cancer-specific death in patients receiving salvage radiation therapy following radical prostatectomy. Cancer. 2013;119(18):3287–3294.
31. Potters L, Morgenstern C, Calugaru E, et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. J Urol. 2005; 173(5):1562–1566.
32. Zelefsky MJ, Kuban DA, Levy LB, et al. Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. Int J Radiat Oncol Biol Phys. 2007; 67(2):327–333.
33. Zincke H, Oesterling JE, Blute ML et al. Long-term (15 years) results after radical prostatectomy for clinically localized (stage T2c or lower) prostate cancer. J Urol. 1994; 152(5:2):1850–1857.
34. Chodak GW, Ronald A Thisted, Glenn S. Gerber, et

al. Results of conservative management of clinically localized prostate cancer. N Engl J Med. 1994; 330(4):242–248.

35. Zagars GK, Pollack A, von Eschenbach AC. Prognostic factors for clinically localized prostate carcinoma: analysis of 938 patients irradiated in the prostate specific antigen era. Cancer. 1997;79(7):1370– 1380.
36. Leibel SA, Hanks GE, Kramer S. Patterns of care outcome studies: results of the national practice in adenocarcinoma of the prostate. Int J Radiat Oncol Biol Phys. 1984;10(3):401–409.
37. Lee WR, Hanks GE, Hanlon A. Increasing prostate-specific antigen profile following definitive radiation therapy for localized prostate cancer: clinical observations. J Clin Oncol. 1997;15(1):230–238.
38. Pound CR, Alan W Partin, Mario A Eisenberger, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999; 281(17):1591–1597.
39. Perez CA, Henry K lee, Anastasios Georgiou, et al. Technical and tumor-related factors affecting outcome of definitive irradiation for localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys. 1993; 26(4):581–591.
40. Tollefson MK, Leibovich BC, Slezak JM, et al. Long term prognostic significance of primary Gleason pattern in patients with Gleason Score 7 prostate cancer: Impact on prostate cancer specific survival. J Urol. 2006 Feb;175(2):547-51.
41. Hanks GE, Hanlon AL, Lee WR, et al. Pretreatment prostate-specific antigen doubling time: clinical utility of this predictor of prostate cancer behavior. Int J Radiat Oncol Biol Phys, 1996 ;34: 549-553.
42. D'Amico AV, Chen MH, Roehl KA, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med, 2004 ;351: 125-135.
43. D'Amico AV, Renshaw AA, Sussman B, et al. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. JAMA. 2005; 294: 440-447.
44. Kestin LL, Vicini F, McGrath S H. et al. Percentage of Positive Biopsy Cores is a Strong Predictor of Clinical Outcome and Overall Survival in Prostate Cancer. Int J Radiat Oncol Biol Phys. 2009; 75 (3): Supplement, S 299 – 300.
45. Nabid A, Carrier N, Vigneault E, et al. Androgen deprivation therapy and radiotherapy in intermediate-risk prostate cancer: A randomized phase III trial. Eur J Cancer. 2021 Jan;143:64-74.
46. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomized study. Lancet Oncol. 2010;11(11):1066-73.
47. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. J Clin Oncol. 2015; 33: 2143-50.
48. Laverdie`re J, Nabid A, De Bedoya LD, et al. The efficacy and sequencing of a short course of androgen suppression on freedom from biochemical failure when administered with radiation therapy for T2-T3 prostate cancer. J Urol. 2004; 171(3): 1137–40.
49. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA. 2008; 299(3):289-95.
50. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med. 2011; 365(2):107-18.