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The Role of External Beam Radiotherapy With or Without Low Dose Rate Brachytherapy in Treatment of Intermediate Risk Cancer Prostate

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Abstract

Background: Patients with intermediate risk cancer prostate represent the largest risk group with remarkable clinical and biologic heterogeneity and are further subdivided into favorable intermediate risk (FIR) and unfavorable intermediate risk (UIR) subgroups with higher rates of deaths, biochemical and metastatic recurrences.

Aim of Study: To investigate the difference between external beam radiation therapy (EBRT) and EBRT plus low-dose-rate brachytherapy (combo-RT) on tumor control and toxicity profile in patients with intermediate risk cancer prostate.

Patients and Methods: A cohort of 579 patients withintermediate-risk cancer prostate were treated between 1995 and 2012 by either EBRT (n: 388) or combo-RT (n: 191). The aim of the study was to assess biochemical recurrence free survival (bRFS), distant metastasis free survival (DMFS), and cumulative incidence of genitourinary (GU) and gastrointestinal toxicity in the favorable and unfavorable subgroups.

Results: At a median follow-up period at 7.5 yr, an improvement in the 10 yr bRFS was evident in the patients treated with Combo-RT compared to those treated with EBRT alone (91.7% vs. 75.4%, *p* 5 0.014). Multivariate analysis showed that combo-RT was associated with improved bRFS with improvement of hazard ratio (HR, 0.48; 95% confidence interval: 0.25, 0.92; *p* 0.03). Such an improvement was statistically significant in unfavorable intermediate risk patients (*p* 5 0.02), but not in the favorable risk ones (*p* 5 0.37). For DMFS, no difference was found. An increase in the 6-year cumulative incidence rate of Grade 3 genitourinary toxicity was associatedwith Combo RT (HR, 3.48; 95% confidence interval: 1.1, 11.1; *p* 0.026).

Conclusions: Treatment of intermediate-risk prostate cancer with combo-RT improved bRFS but not DMFS at the expense of increased Grade 3 genito urinary toxicity. Improvement in bRFS was found in unfavorable intermediate-risk patientsbut not in the favorable risk patients.

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Key Words: *Intermediate risk cancer prostate – Brachytherapy – Escalated dose external beam radiotherapy.*

Introduction

PATIENTS with intermediate risk cancer prostate represent the largest risk group with remarkable clinical and biologic heterogeneity and are further subdivided into favorable intermediate risk (FIR) and unfavorable intermediate risk (UIR) subgroups **[1]** with higher rates of deaths, biochemical and metastatic recurrences **[2].**

Patients in UIR are those with Gleason primary pattern of 4, percentage of positive biopsy cores at ≥50% or patients with multiple intermediate risk factors [clinically T2b/T2c; prostate-specific antigen (PSA) at 10-20ng/ml or, Gleason 7] **[3].**

Radical prostatectomy (RP) with or without pelvic nodal dissection, external-beam radiotherapy (EBRT) with a short course (4-6 months) of androgen deprivation therapy (ADT) or combination EBRT with a brachytherapy (BT) boost with or without ADT are currently considered by NCCN as definitive treatment options for patients with UIR cancer prostate **[4].**

The dose applicable without unacceptable toxicity reaches 65-70Gy, which proved to be insufficient for effective treatment of prostate tumors **[5].**

Several randomized studies have shown that radio therapeutic dose escalation is associated with improvement in disease outcomes, including biochemical relapse-free survival **[6,7]** and rate of distant metastasis **[6,8]**, in intermediate and high risk prostate cancer **[8].**

In a retrospective study conducted by Anusha Kalbasi and colleagues, patients with localized cancer prostate demonstrated an improved survival with dose-escalated external beam radiotherapy (DE EBRT) at ≥75.6Gy to 90Gy compared to standard dose (from 68.4Gy to <75.6Gy) in the intermediate and high-risk groups with adjusted hazard ratio [HR], 0.84; 95% CI, 0.80-0.88; p<.001 in intermediate risk and 0.82; 95% CI, 0.78-0.85; p<.001 in high risk patients **[9]**.

The option to escalate the irradiation dose and low toxicity of the treatment warrant the inclusion of brachytherapy in the treatment of localized carcinoma of the prostate. Possible application of high irradiation doses to the target volume, while markedly lowering the dose affecting the surrounding tissue, represents a major benefit of the brachytherapy approach.

The doses applied to the rectum via the brachytherapy approach are relatively low **[10]**.

The aim of this retrospective study is to compare the tumor control outcomes and toxicity profile of combined LDR brachytherapy plus EBRT vs EBRT alone, and to investigate (if exist) differences between the favorable and unfavorable subsets of intermediate prostate cancer patients when using different treatment approaches.

Patients and Methods

Patients:

A cohort of 579 patients with biopsy proven intermediate risk prostate cancer treated between May 1995 and March 2012, in the University of Michigan [UM], and Providence Hospital with either EBRT alone (388 patient, all of them received treatment at UM) or EBRT plus LDR brachytherapy (191 patient, all of them received treatment in Providence hospital) are collected in this study.

Patients eligible for the study were those with histologically proven prostate cancer, intermediate risk according to the National Comprehensive Cancer Network (NCCN) risk stratification (clinical stage T2B/T2c, and/or Gleason score 7, and/or PSA 10-20ng/ml). While patients with extracapsular extension, nodal metastasis, distant metastasis and patients treated with hypofractionated regimen, Stereotactic prostate radiotherapy (SPRT) or High dose rate brachytherapy (HDR) were excluded from the study.

As a routine work before starting the treatment, all patients had undergone complete blood count testing, kidney function tests, PSA, digital rectal examination. Staging was done using computed tomography (CT) of the chest, abdomen and pelvis. Bone scan was done according to the patients' complaint, but generally it was asked only for selected group of patients with unfavorable intermediate-risk category.

Treatment methods:

In case of EBRT, planning was done either by means of three dimensional technique in 238 of 388 patients or intensity-modulated radiation therapy technique in 150 of 388 patients. In both techniques, the patient underwent CT simulation in the treatment position and the target volume including the prostate and seminal vesicles is delineated. The planning target volume received a median dose at 77.5Gy in conventional fractionation (1.8-2.0Gy/fraction), 5 fractions a day. In 173 of 388 (45%) of patients, either Calypso markers (68 patients) or gold seeds (105 patients) are used in image guidance.

For patients received combo - RT, they underwent permanent interstitial LDR brachytherapy implant. Both prostate and proximal seminal vesicles (the clinical target volume) were identified while the patient is under general anesthesia using transrectal ultrasound guidance. Iodine-125 seeds (90-108Gy) were implanted using template-based transperineal catheter approach.

Postimplant dosimetry was performed approximately 3 weeks after the treatment aiming to achieve D90 (dose covering 90% of the prostate volume) is ≥90% and V100 (fractional volume of the prostate receiving 100% of the prescription dose) is ≥90%.

Nearly 6 weeks following the implant, patients received IMRT in 25-30 fractions over 5-6 weeks using three dimensional conformal technique or IMRT with gold seed image guidance. Dose delivered by brachytherapy was imported into the IMRT calculation as background, and the final dose was a full integration of IMRT and brachytherapy to deliver 90Gy external equivalent to the 3-5mm expansion of the prostate. This amounted to a 90-108Gy implant, plus EBRT doses of 45-55.8Gy in 1.8-2.0Gy per fraction.

Androgen deprivation therapy (ADT) was administered at the treating physicians' discretion for a total of 6 months with both EBRT and combo-RT.

During follow-up after treatment, patients were evaluated with physical examination and PSA level

every 3 months for the first 2 years, then every 6 months thereafter. Biochemical recurrence free survival bRFS, local progression free survival LPFS, distant metastasis free survival DMFS end points were investigated as well as genito urinary and intestinal toxicities. PSA progression was defined as nadir PSA + 2ng/mL based on the Phoenix consensus definition **[11]**. Toxicity was scored using the Common Terminology Criteria for Adverse Events, version 4.0 **[12]**.

Statistical analysis:

We investigated the differences between categorical variables including treatment type (EBRT vs. combo-RT), baseline PSA (<10 vs. 10-20ng/mL), T-stage (T1c/T2a vs. T2b/T2c), percent positive cores (≤50% vs. >50%), treatment era (1995 - 2004 vs. 2005 - 2012), ADT received or not and, grade group (1 [≤6], 2 [3+4] and, 3 [4+3]).

Chi-square and Wilcoxon rank sum test were used to detect significant differences between categorical and continuous variables respectively in baseline characteristics in both EBRT and combo-RT groups.

End points including bRFS, LPFS and DMFS were evaluated using the Kaplan-Meier method with the pair wise log-rank test to compare between them. Cox regression modeling was used for univariate and multivariate analysis.

Treatment associated adverse events were scored using the Common Terminology for adverse events version 4.0 and rates of grade 3 toxicities were compared using Chi square test. For all analyses, two-sided *p*-values of 0.05 or less were considered statistically significant and performed using SPSS, version 24.0. Subgroup analysis was performed for unfavorable and favorable intermediate risk groups based on Zumsteg et al., definition of favorable and unfavorable criteria **[13]**.

Results

Demographic and disease characteristics:

The median age of patients was 67 yrs (34-83). Some risk factors differed significantly between groups as seen in Table (1). Patients in EBRT group had significantly lower percentage of grade group 2 (Gleason 3+4), and grade group 3 (Gleason 4+3), *p* 0.025. While patients in EBRT had significantly higher base line PSA than those in the combo group (*p* 0.005). No significant difference noticed between the percentage of favorable and unfavorable risk in both groups (*p* 0.31).

ADT was more present in combo-RT group vs EBRT group (*p* 0.008) but was not significantly different between unfavorable risk patients in both EBRT and combo -RT groups (*p* 0.56).

EBRT vs. combo - RT:

Median follow-up was not significantly different (*p* 0.72). Biochemical failure occurred in 20% of patients in the EBRT group vs 7% of patients in combo-RT group.

Significant improvement in 5 and 10 yrs b RFS rates were noticed in combo RT vs EBRT groups that was 94.1% vs 89.2% and 91.7% vs 75.4% respectively (*p* 0.014) as seen in Table (2) and Fig. (1).

On Univariate analysis, treatment with EBRT, T2b/T2c, percent of positive cores ≥50%, higher grade group and, treatment era from 1995 to 2004 all has been marginally associated with increased hazard of PSA progression (all $p<0.1$). On multivariate analysis, treatment with combo-RT was associated with significant decrease in the hazard of biochemical recurrence compared with treatment with EBRT (hazard ratio [HR]: 0.48; 95% CI: 0.25, 0.92; *p* 0.03). Patients treated in the era 2005 - 2012 showed significant lower hazard of biochemical recurrence than those treated earlier (HR: 0.61; 95% CI: 0.38, 1.00; *p* 0.05). A significant association between hazard of biochemical failure and grade group 3 (Gleason 4 + 3) relative to grade group 1 (HR: 2.47 95% CI: 1.17, 5.22; *p* 5 0.02) as seen in Table (3).

Patients in the combo RT arm also showed improvement in LPFS compared with those in EBRT with a 10 year at 100% vs 94.9% [95% CI: 92.2, 97.6]; *p* 0.042). On the level of DRFS, no significant difference seen between both treatment groups that is, 4% in EBRT and an equal percent in combo RT group have developed distant failures (*p* 0.21) as seen in Table (2). That was evident in both univariable and multivariable analysis.

Favorable vs. unfavorable intermediate-risk patients:

Fig. (2) shows the actuarial bRFS rates for patient with favorable and unfavorable intermediate risk disease (186 and 392 patients respectively). In the favorable intermediate risk subgroup, no significant difference in the estimated 10 year bRFS between those treated with combo RT and EBRT (91.8% vs 82.3%, *p* 0.37) as seen in Fig. (2A). In contrast, patients in the unfavorable intermediate risk group a significant improvement in 10 years bRFS was encountered with combo RT

compared with EBRT (91.5% vs 71.7% respectively, *p* 0.017) as seen in Fig. (2B).

Urinary and intestinal toxicities:

As seen in Fig. (3A), a significant increase in the cumulative incidence of grade 3 urinary toxicity was associated with combo RT treatment compared to EBRT (6-year rates of 3.6% vs. 1.4% and 10-year rates of 7.5% vs. 1.4%; *p* 0.026).

In 57% of patients, grade 3 urinary toxicities had resolved, in 29% of patients, partial improvement was encountered, and only 1 patient had developed persistent grade 3 toxicity.

Concerning intestinal toxicities, no significant difference in the cumulative incidence of grade 2 toxicities between the two treatment groups was noticed (*p* 0.45) as shown in Fig. (3B).

Table (1): Patient characteristics.

Characteristic	EBRT		EBRT /Brachy		Total cohort		*p*
	N=388	%	N=191	%	N=579	%	
Median age (y)	66.8		66.7		66.7		0.35
Median follow-up (y)	7.5		7.6		7.5		0.72
Baseline PSA:							
<10	263	67.8	151	79.1	414	72	0.005
10-20	125	32.2	40	20.9	165	28	
T-stage:							
T1c/T2a	306	78.9	154	80.6	460	79	0.62
T2b/T2c	82	21.1	37	19.4	119	21	
Gleason Grade Groups:							
1 (≤6)	62	16.0	15	7.9	77	13	0.025
2 (3+4)	206	53.1	112	58.6	318	55	
3 (4-3)	120	30.9	64	33.5	184	32	
Positive cores, %:							
≤ 50%	218	56.2	96	50.3	314	54	0.26
>50%	153	39.4	83	43.5	236	41	
Risk group:							
Favorable	130	33.5	56	29.3	186	32	0.31
Unfavorable	258	66.5	135	70.7	393	68	
ADT (6 mo):							
No	291	75.0	123	64.4	414	72	0.008
Yes	97	25.0	68	35.6	165	28	
Year:							
1995 - 2004	236	60.8	62	32.5	298	51	<0.001
2005 - 2012	152	39.2	129	67.5	281	49	

Table (2): Tumor control outcomes by treatment type.

Treatment	Biochemical progression free survival			Local progression free survival			Distant metastasis free survival		
	95% CI								
	Low	High	*p*, 0.014	Low	High	*p*, 0.042	Low	High	*p*, 0.21
					5 y				
EBRT	89.2	85.9	92.5	99.4	98.6	100.0	98.3	96.9	99.7
EBRT brachy	94.1	90.4	97.8	100.0	100.0	100.0	95.2	91.7	98.7
					10 y				
EBRT	75.4	70.1	80.7	94.9	92.2	97.6	95.3	92.8	97.8
EBRT brachy	91.7	86.8	96.6	100.0	100.0	100.0	95.2	91.7	98.7

Table (3): Univariable and multivariable predictors of biochemical recurrence free survival.

Treatment	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
EBRT vs. combo-RT	0.47 (0.26 - 0.87)	0.02	0.48 (0.25 - 0.92)	0.03
Baseline PSA <10 vs. 10-20	1.40 (0.90 - 2.16)	0.13		
T-stage T1c/T2a vs. T2b/T2c	1.53 (0.96 - 2.43)	0.07	1.41 (0.86 - 2.32)	0.18
		Grade group (Gleason score)		
1 (≤6)	Ref.		Ref.	
2 (3+4)	1.36 (0.66 - 2.80)	0.41	1.50 (0.71 - 3.15)	0.29
3 (4+3)	2.29 (1.11 - 4.74)	0.03	2.47 (1.17 - 5.22)	0.02
Positive cores, % ≤50% vs. >50%	1.48 (0.97 - 2.26)	0.07	1.40 (0.90 - 2.17)	0.14
ADT with EBRT No vs. yes	1.18 (0.75 - 1.85)	0.47		
Treatment era 1995 - 2004 vs. 2005 - 2012	0.62 (0.39 - 0.98)	0.04	0.61 (0.38 - 1.00)	0.05

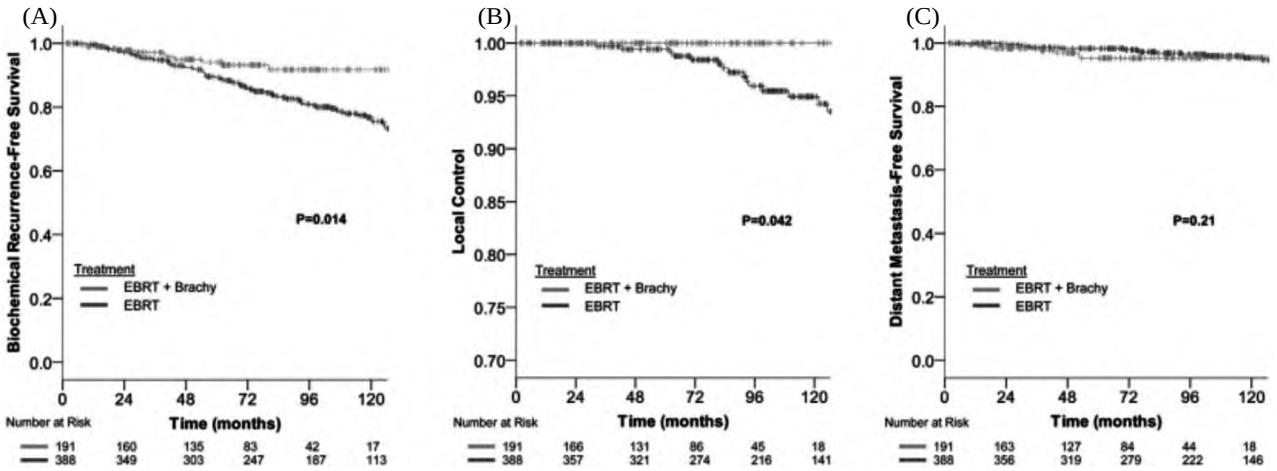

Fig. (1): (A) Biochemical recurrence-free survival, (B) Local progression-free survival, and (C) Distant metastasis-free survival for patients treated with EBRT + brachy and EBRT = external radiation therapy; EBRT + brachy = combination EBRT plus brachytherapy boost.

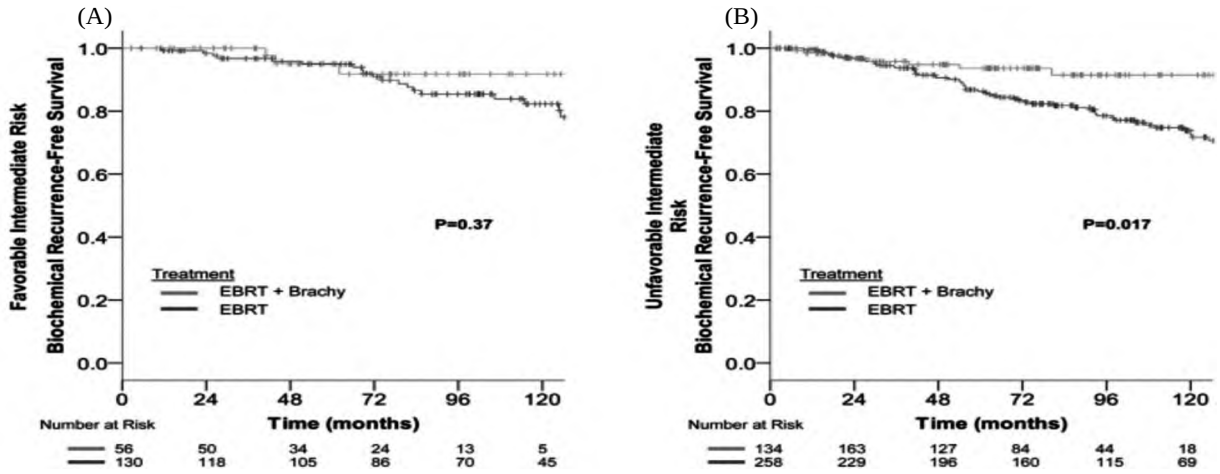

Fig. (2): Biochemical recurrence-free survival in (A) Favorable intermediate-risk patients and (B) Unfavorable intermediate-risk patients. EBRT=external beam radiation therapy; EBRT + brachy=combination EBRT plus brachytherapy boost.

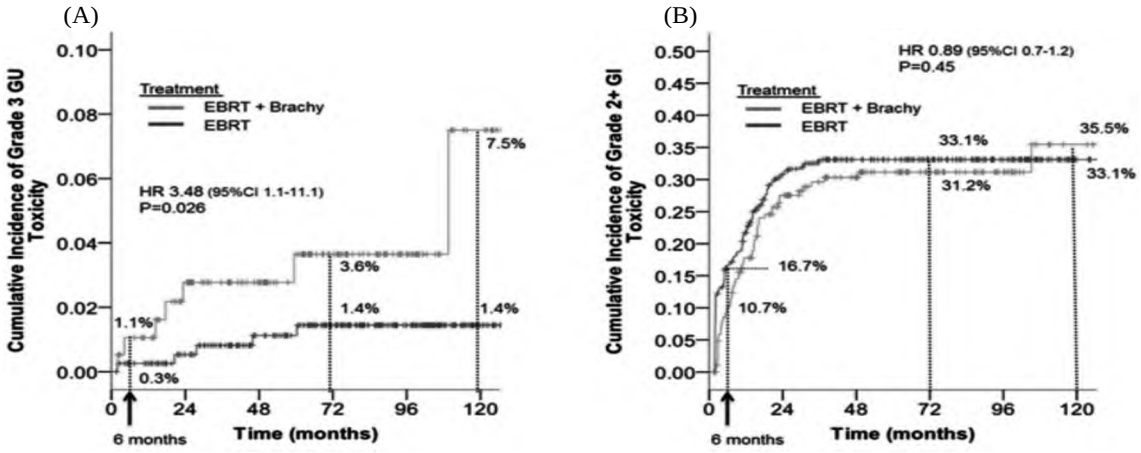

Fig. (3): The cumulative incidence of (A) Grade 3 GU toxicity and (B) Grade 2 + GI toxicity. GU = G; GI = Gastrointestinal; EBRT = External beam radiation therapy; EBRT + brachy = Combination EBRT plus brachytherapy boost; HR = Hazard ratio.

Discussion

In this study on intermediate risk prostate cancer patients, an improvement in bRFS was achieved in favor of combo RT compared to DE EBRT. On multivariate analysis, treatment with combo RT significantly reduced the hazard of biochemical recurrence compared to DE EBRT (HR: 0.5, *p* 0.03). During follow-up, 20% of patients in the group treated with DE EBRT (388 patients) developed biochemical recurrence versus 7% in the group treated with combo RT (191 patients). A statistically significant improvement in 5- and 10-year actuarial bRFS rate was achieved in the combo RT group compared with the DE EBRT one (94.1%; (95% CI: 90.4 - 97.8) vs. 89.2%; (95% CI: 85.9 - 92.5) and 91.7% (95% CI: 86.8 - 96.6) vs. 75.4% (95% CI: 70.1 - 80.7), respectively (*p* 0.014; Table 2, Fig. 1). The estimated 7 year bRFS in our study showed improvement in the combo RT vs DE EBRT (92% vs 83%). A similar result was also reported by James Morris and colleagues in the ASCENDE RT trial published in 2015. In their study, patients with high and intermediate risk prostate cancer treated with DE EBRT and those treated with EBRT plus LDR BT boost achieved 7 year bRFS at 71% and 86% respectively **[14]**.

Another study conducted by Spratt and colleagues on patients with intermediate risk prostate cancer found an improvement in bRFS in favor of combo RT compared to DE EBRT with 7-year bRFS at 92% vs. 81%; *p* 0.001). However no one of the previous two studies assessed the benefit of combo-RT within the favorable and unfavorable intermediate-risk groups separately **[15]**.

In our study as shown in Fig. (2), in the favorable subgroup, there was no statistically significant difference in bRFS between the combo-RT and DE EBRT groups (10-year estimated bRFS of 91.8% vs. 82.3%; *p* 0.37; Fig. 2A). However, in the unfavorable subgroup, combo-RT was associated with a significantly improved bRFS (10-year estimated bRFS of 91.5% vs. 71.7%; *p* 5 0.017; Fig. 2B).

The association between unfavorable criteria in intermediate risk cancer prostate and outcome was also reported in another study published by Ovidiu Marina and colleagues in 2014 and enrolled intermediate risk prostate cancer patients treated either with CT-based off-line adaptive image guided radiotherapy (IGRT) using 3D-conformal or intensity-modulated radiation therapy or EBRT with HDR brachytherapy boost. In intermediate risk patients with unfavorable criteria defined by percent.

Positive prostate biopsy cores >50%, perineural invasion, or stage T2b-c, treatment with EBRT plus HDR BT boost there was associated with a significant improvement in the 5-year biochemical control compared with IGRT with a rate at 96% vs 87% respectively, (*p* 0.002).

On the other side, lack of significant difference between DE EBRT and combo RT on the level of tumor control in patients with favorable intermediate risk that found in our study was also reported by Prestidge BR and colleagues in their study published in 2016. In this study a cohort of predominantly favorable intermediate risk population (T1c/T2b, Gleason 7 with PSA <10, or Gleason 6 with PSA 10-20ng/ml) received either combined EBRT and transperineal interstitial permanent BT or BT alone. Their results suggested that the addition of EBRT to BT did not achieve superior freedom from progression compared with BT alone **[17]**.

As regards the impact of treatment modality on distant disease control, our study was consistent with the ASCENDE-RT in reporting no significant difference on the level of DMFS with the use of combo RT vs DE EBRT in spite of the relatively long median follow up time in our study (7.5 yrs). However, in the study of Spratt mentioned above, with a median follow-up period at 5.3 year, a significantly improved DMFS with the combo-RT group was attained (7-year estimate of 97% vs. 93%; *p* 0.04).

As regards treatment related toxicities in our study, we demonstrated a significantly higher cumulative incidence in G3 GU toxicities in the combo RT arm compared with DE EBRT arm (6-year 3.6% vs. 1.4%, *p* 0.002). Such a significant increase in G3 GU toxicities in patients treated with combo RT versus DE EBRT was also reported by James Morris and colleagues in the ASCENDE RT trial mentioned before (18.4% versus 5.2% in the EBRT arm, *p* 0.001).

A higher incidence of late grade >3 genitourinary and/or gastrointestinal toxicity (15%) was also reported in a phase II study conducted by Lawton CA and colleagues and enrolled 131 patients with intermediate risk cancer prostate **[18]**.

Such higher rates of incidence of late toxicities in both studies conducted by James M and Lawton CA compared to ours could be attributed to lack of MRI in the planning process of EBRT.

On the other hand, Mark D. Hurwitz and colleagues reported a lower incidence (3%) of G3 late toxicities excluding sexual dysfunction in a cohort of 63 patients with intermediate risk cancer prostate treated with ADT and combination of EBRT and BT boost **[19]**.

Conclusions:

Although our study is a retrospective one with many limitations such as lack of randomization between both treatment arms, non consistent administration of ADT, irregular reporting of treatment related toxicities, our findings provide an evidence that treatment of intermediate risk cancer prostate with unfavorable risk factors by combination of ADT, EBRT and BT boost is more effective than treatment with ADT and DE EBRT in terms of bRFS with acceptable incidence of late genitourinary and intestinal toxicities.

Conflict of interest:

None.

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دور العلاج الاشعاعى الخارجى بدون أو بالاشتراك مع العلاج الاشعاعى عن قرب ذى الخرج الاشعاعى المنخفض فى علاج سرطان البروستاتا متوسط الخطورة

الغرض من البحث : لدراسة الاختلاف بين العلاج الاشعاعى الخارجى والعلاج الاشعاعى الخارجى مصحوباً بالعلاج الاشعاعى عن قرب ذى الخرج الاشعاعى المنخفض من حيث السيطرة على سرطان البروستاتا متوسط الخطورة ومن حيث الاعراض الجانبية المترتبة على استخدام كلتا الطريقتين.

المرضى وطرق البحث : شملت هذه الدراسة عدد ٥٧٩ مريض من مرضى سرطان البروستاتا متوسط الخطورة والذين تم علاجهم فى الفترة من ١٩٩٥ إلى ٢٠١٢ أما بواسطة العلاج الاشعاعى الخارجى (٣٨٨) مريض والمرضى الذين تم علاجهم بالعلاج الاشعاعى الخارجى مصحوباً بالعلاج الاشعاعى عن قرب ذى الخرج الاشعاعى المنخفض (١٩١) مريض لمعرفة مدى تأثير كلتا الطريقتين فى التأثير على متوسط فترة البقاء بدون ارتجاع كيميائى ومتوسط فترة البقاء بدون ارتجاع عن بعد وكذلك التفاوت بين الطريقتين على مستوى الاعراض الجانبية البولية التناسلية والاعراض الجانبية المعدية المعوية وذلك فى الحالات متوسطة الخطورة بشقيها المبشر والغير مبشر.

النتائج : بعد فترة متابعة متوسطها ٧.٥ عام ظهر أن معدل البقاء بدون ارتجاع كيميائى على مستوى ١٠ سنوات أعلى مع العلاج الاشعاعى المشترك مقارنة بالعلاج الاشعاعى الخارجى فقط وكان هذا التحسن ملحوظاً فقط فى الحالات متوسطة الخطورة بشقها المبشر فقط ولم نسجل أى فروق بين الطريقتين على مستوى متوسط فترة البقاء بدون ارتجاع عن بعد وكان هذا على حساب زيادة ملحوظة فى معدل حدوث أعراض جانبية بولية تناسلية من الدرجة الثالثة مع استخدام العلاج الاشعاعى المشترك.

الخلاصة من البحث : العلاج الاشعاعى المشترك يقدم نتائج أفضل من العلاج الاشعاعى الخارجى فى علاج سرطان البروستاتا متوسط الخطورة على مستوى متوسط فترة البقاء بدون ارتجاع كيميائى وليس على مستوى متوسط فترة البقاء بدون ارتجاع عن بعد وذلك فى الحالات متوسطة الخطورة بشقها المبشر فقط وذلك مصحوباً بزيادة ملحوظة فى معدل حدوث أعراض جانبية بولية تناسلية.