RESULTS

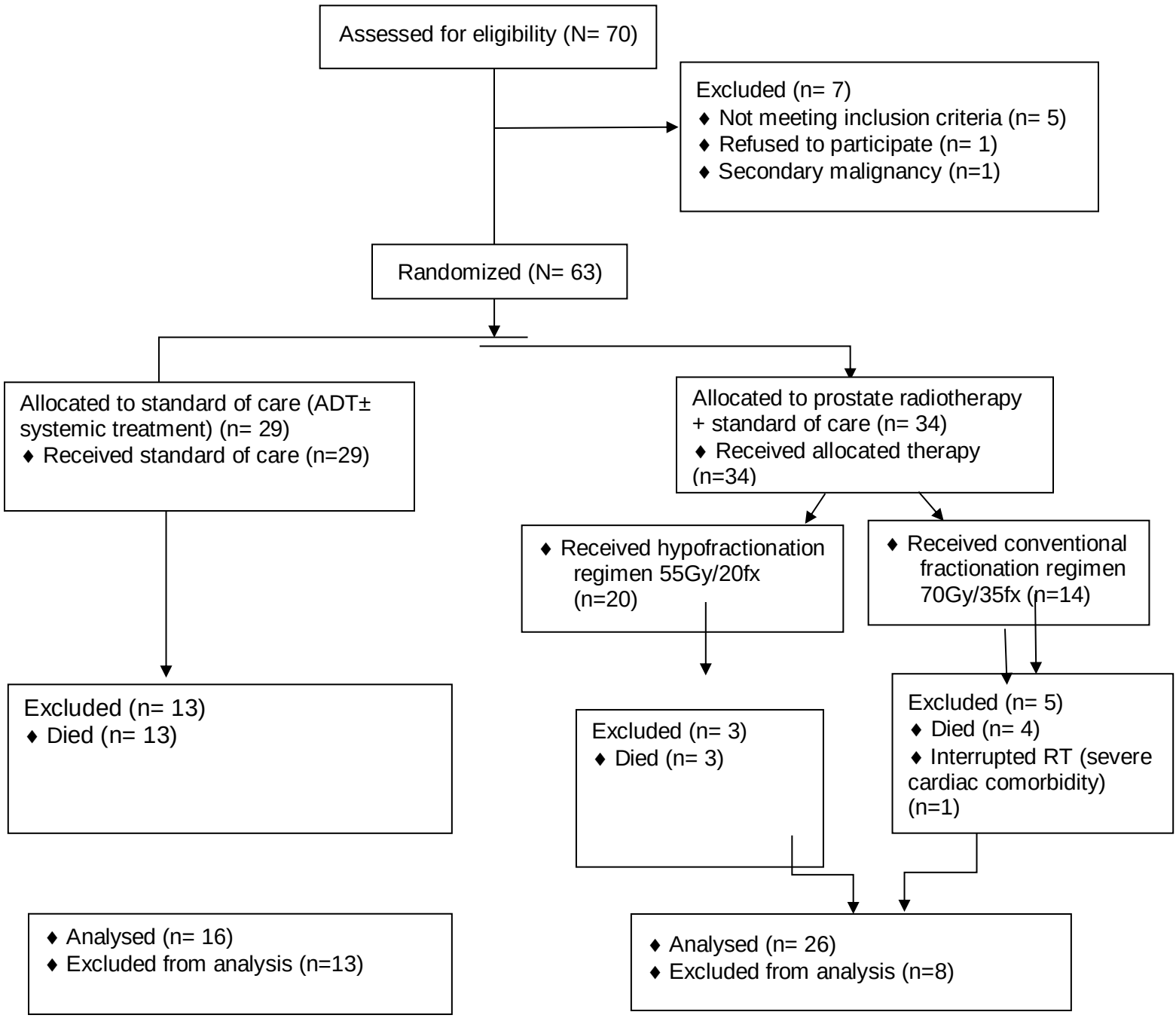


Figure 1. Flow chart of the study.

Table 1. Sociodemographic characteristics among study groups.

Variables	Prostate RT group n = 34 (54%)	Control group n = 29 (46%)	*P*-value
Age (years)			
• **< 65**	**10 (29.4%)**	**4 (13.8%)**	**0.224** [f]
• **> 65**	**24 (70.6%)**	**25 (86.2%)**	
• **Median (IQR)**	**68 (64 -72)**	**73 (68.5 -79.5)**	
Residence			
• **Rural**	**10 (29.4%)**	**11 (37.9%)**	**0.478**
• **Urban**	**24 (70.6%)**	**18 (62.1%)**	
Marital status			
• **Married**	**24 (70.6%)**	**14 (48.3%)**	**0.071**
• **Single**	**10 (29.4%)**	**15 (51.7%)**	

[f]. Fisher's exact test. RT: radiotherapy, IQR: Interquartile range

Table 1 shows that there were no statistically significant differences between the prostate radiotherapy group and the control group regarding their sociodemographic characteristics and that their distribution was balanced between both study groups. The median age of patients in the prostate radiotherapy group was 68 years compared to 73 years in the control group. Most study population (66.7%) were living in urban areas compared to 33.3% who were living in rural areas. Regarding marital status, 60.3% were married while 39.7 % were singles.

Table 2. Clinicopathological characteristics, prognostic features among study groups.

Variables	Prostate RT group n = 34 (54%)	Control group n = 29 (46%)	*P*-value
Histopathological variant			
• **Acinar adenocarcinoma**	**32 (94.1%)**	**24 (82.8%)**	**0.233** [f]
• **Others**	**2 (5.9%)**	**5 (17.2%)**	
Gleason score			
• **≤ 7**	**12 (35.3%)**	**4 (13.8%)**	**0.081** [f]
• **8 – 10**	**22 (64.7%)**	**25 (86.2%)**	
T (Stage)			
• **T2**	**13 (38.2%)**	**8 (27.6%)**	**0.115**
• **T3**	**9 (26.5%)**	**15 (51.7%)**	
• **T4**	**12 (35.3%)**	**6 (20.7%)**	
N (Stage)			
• **N0**	**17 (50%)**	**22 (75.9%)**	**0.035***
• **N+**	**17 (50%)**	**7 (24.1%)**	
M (Stage)			
• **M1a (LNs)**	**3 (8.8%)**	**0 (0%)**	**0.349** [f]
• **M1b (Bones)**	**25 (73.5%)**	**24 (82.8%)**	
• **M1c (visceral)**	**6 (17.6%)**	**5 (17.2%)**	
Metastatic volume			
• **High metastatic volume**	**18 (52.9%)**	**22 (75.9%)**	**0.060**
• **Low metastatic volume**	**16 (47.1%)**	**7 (24.1%)**	
Timing of Metastases			
• **Synchronous**	**27 (79.4%)**	**27 (93.1%)**	**0.160** [f]
• **Metachronous**	**7 (20.6%)**	**2 (6.9%)**	

[f]. Fisher's exact test. LNs: lymph nodes

*. Statistically significant p value

Table 2 shows that most clinicopathological characteristics were balanced between the study groups. The most common histopathological variant among both study groups was the acinar adenocarcinoma (88.9%). The most observed histological grade was GS 8-10 (47.6%). The most common TNM stage was T3 (38.1%), N0 (61.9%) and M1b (77.8%). The nodal positive disease was significantly higher in the radiotherapy group (p=0.035). The high-volume metastatic disease includes 63.5% of patients in both groups. Most patients had synchronous metastatic disease (85.7%).

Table 3. The baseline clinical presentation among study groups.

Variables	Prostate RT group n = 34 (54%)	Control group n = 29 (46%)	*P*-value
Performance status			
• **0**	**1 (2.9%)**	**0 (0%)**	**0.285** [f]
• **1**	**24 (70.6%)**	**17 (58.6%)**	
• **2**	**9 (26.5%)**	**12 (41.4%)**	
Baseline symptoms			
• **Frequency**	**30 (88.2%)**	**25 (86.2%)**	**1.000** [f]
• **Urgency**	**32 (94.1%)**	**28 (96.6%)**	**1.000** [f]
• **Difficulty**	**27 (79.4%)**	**29 (100%)**	**0.013*** [f]
• **Drippling**	**12 (35.3%)**	**13 (44.8%)**	**0.441**
• **Hematuria**	**4 (11.8%)**	**2 (6.9%)**	**0.678** [f]
• **Dysuria**	**26 (76.5%)**	**27 (93.1%)**	**0.092** [f]
• **Urinary retention**	**10 (29.4%)**	**14 (48.3%)**	**0.124**
• **SRE**	**5 (14.7%)**	**18 (62.1%)**	**0.001*** [f]
Comorbidities	**22 (64.7%)**	**19 (65.5%)**	**0.946**

[f]. Fisher's exact test. SRE: skeletal-related events, RT: radiotherapy
*. Statistically significant p value

Table 3 shows that most baseline clinical characteristics were balanced between the two study groups. Most patients in both study groups had performance scores of 1 (65.1%). Most patients in both study groups presented clinically with frequency (87.3%), urgency (95.2%), difficulty (88.9%) and dysuria (84.1%). Patients in the control group had statistically significantly more skeletal-related events than patients in the prostate radiotherapy group (62.1%, p=0.001). Besides, 65.1% of patients in both arms had concurrent comorbidities.

Table 4. Treatment characteristics among study groups.

Variables	Prostate RT group n = 34 (54%)	Control group n = 29 (46%)	*P*-value
Duration of androgen deprivation (months)			
• **Median (IQR)**	**4.25 (2.5-9)**	**2.8 (1.9-8)**	**0.073**
Prior hormonal treatment			
• **LHRH agonist only**	**3 (8.8%)**	**5 (17.2%)**	**0.453** [f]
• **Bicalutamide only**	**6 (17.6%)**	**3 (10.3%)**	**0.488** [f]
• **Combined**	**25 (73.5%)**	**21 (72.4%)**	**0.921**
Type of Castration			
• **Medical**	**28 (82.4%)**	**23 (79.3%)**	**0.759**
• **Surgical**	**6 (17.6%)**	**6 (20.7%)**	
Response to androgen deprivation			
• **Castration naïve/sensitive**	**24 (70.6%)**	**19 (65.5%)**	**0.666**
• **Castration resistant**	**10 (29.4%)**	**10 (34.5%)**	
Prior systemic treatment			
• **Docetaxel**	**7 (20.6%)**	**9 (31%)**	**0.342**
• **Abiraterone acetate**	**10 (29.4%)**	**4 (13.8%)**	**0.224** [f]
• **Enzalutamide**	**2 (5.9%)**	**1 (3.4%)**	**1.000** [f]
Palliative bone directed RT*	**9 (26.5%)**	**25 (86.2%)**	**< 0.001***
Bisphosphonates			
○ **Zoledronic acid**	**25 (73.5%)**	**27 (93.1%)**	**0.124** [f]
○ **Denosumab**	**4 (11.8%)**	**0 (0%)**	
○ **Both**	**1 (2.9%)**	**0 (0%)**	
○ **None**	**4 (11.8%)**	**2 (6.9%)**	

[f]. Fisher's exact test. RT: radiotherapy, IQR: Interquartile range

*. Statistically significant p value

Table 4 shows that most characteristics of prior hormonal and systemic treatment were balanced between the two study groups. The median duration of androgen deprivation therapy was 4.25 months for the prostate radiotherapy group and 2.8 months for the control group. Most patients in both groups received combined LHRH agonist and bicalutamide (71.4%). The minority of patients received either bicalutamide only (15.9%) or LHRH agonist only (14.3%). Most patients in both groups underwent medical castration (81%) whereas 19% underwent surgical castration. Most patients in both groups were castrate sensitive (68.3%) while 31.7% were castrate resistant. Docetaxel chemotherapy was received in 25.4% of patients in both groups whereas 22.2% received abiraterone acetate. Very few patients received enzalutamide (4.8%). Most patients in both groups were symptomatically treated with zoledronic acid (82.5%).

Table 5. Main characteristics of intervention in prostate radiotherapy group.

Variables	Conventional fractionation group n= 14	Hypofractionation group n=20
Dose, fraction size, duration	**70Gy/35fx, 2Gy/fx, 7weeks**	**55Gy/20fx, 2.75Gy/fx, 4weeks**
BED1.5	**163.3Gy**	**155.8Gy**
BED3	**116.67Gy**	**105.4Gy**
Finished treatment	**13 (92.9%)**	**20 (100%)**
Stopped/interrupted treatment	**1 (7.1%) ***	**0 (0%)**

* Interrupted due to decompensated heart failure. BED: Biologically effective dose

Table 5 shows that the hypofractionation regimen was received in 20 patients whereas the conventional fractionation was received in 14 patients. The characteristics of radiotherapy regimen given in each regimen were illustrated as shown in table 5. Only 1 patient in the conventional fractionation group stopped treatment after receiving 11 sessions due to severe cardiac comorbidity.

Table 6. The dropout analysis among study groups.

Variables	Prostate RT group n = 34 (54%)	Control group n = 29 (46%)	*P*-value
Dropouts	**8 (23.5%)**	**13 (44.8%)**	**0.074**
Cause of dropouts			
• **Death**	**7 (87.5%)**	**13 (100%)**	
• **Heart failure**	**1 (12.5%)**	**0 (0%)**	

RT: radiotherapy

Table 6 shows that that most patients in the prostate radiotherapy group completed their radiotherapy course and their follow-ups without interruptions (76.5%) whereas 8 patients dropped out (23.5%). On the other hand, 55.2% of patients in the control group maintained their follow up whereas 44.8% dropped out. Death was the most obvious cause of dropouts in both groups (95.2%). Heart failure was another cause (4.8%). The dropout rate was not statistically significantly different between the two study groups where p=0.074.

Table 7. Significant acute genitourinary and gastrointestinal toxicities among patients receiving prostate radiotherapy according to fractionation regimen.

Acute toxicity	Fractionation type		*P*-value
	Conventional n= 14 (41.2%)	Hypofractionation n= 20 (58.8%)	
GU toxicity G2+	12 (85.7%)	19 (95%)	0.555 [f]
Cystitis, bladder spasm G2	9 (75%)	11 (57.9%)	0.452 [f]
G3+	3 (25%)	8 (42.1%)	
Hematuria G2	6 (66.7%)	7 (46.7%)	0.423 [f]
G3+	3 (33.3%)	8 (53.3%)	
Obstruction G2	0 (0%)	1 (12.5%)	1.000 [f]
G3+	4 (100%)	7 (87.5%)	
GI toxicity G2+	7 (50%)	9 (45%)	0.774
Diarrhea G2	3 (100%)	0 (0%)	0.100 [f]
G3+	0 (0%)	3 (100%)	
GI upset G2	4 (100%)	1 (25%)	0.143 [f]
G3+	0 (0%)	3 (75%)	
Proctitis, Abdominal pain G2	6 (85.7%)	5 (55.6%)	0.308 [f]
G3+	1 (14.3%)	4 (44.4%)	
Fissure/ fistula G3+	2 (14.3%)	1 (5%)	0.555 [f]
Rectal bleeding G3+	2 (14.3%)	1 (5%)	0.555 [f]

[f]. Fisher's exact test. GU: Genitourinary, GI: Gastrointestinal, G2+: Grade 2 or higher, G3+: Grade 3 or higher

Table 7 shows that there was no statistically significant difference between patients who received either conventional fractionation or hypofractionation regimens in-terms of early GU and GI events assessed during radiotherapy or first 90 days post-radiation. The most observed significant acute GU toxicity in both fractionation arms was cystitis (G2 in 58.8% and G3+ in 32.3%). Acute G2 hematuria developed in 38.2% and G3+ in 32.3% of patients. Acute G2 urinary obstruction occurred in 2.9% and G3+ in 32.3% of patients. Meanwhile, the most common acute GI toxicity in both fractionation arms were acute proctitis and abdominal pain (G2 in 32.3% and G3+ in 14.7%). Acute G2 diarrhea developed in 3 patients (8.8%) and G3+ in 3 patients (8.8%) of patients. Of note, higher grade acute (G3) diarrhea was found only in patients who received the hypofractionation regimen. Acute anal fissure/fistula was detected in 3 patients in both fractionation arms (8.8%); 2 patients developed acute anal fissure and one patient developed acute perianal fistula. Acute G3+ rectal bleeding developed in 3 patients (8.8%).

Table 8. Significant late genitourinary and gastrointestinal toxicities among patients receiving prostate radiotherapy according to fractionation regimen.

Late toxicity	Fractionation type		*P*-value
	Conventional n= 12 (38.7%)	Hypofractionation n= 19 (61.3%)	
GU toxicity G2+	**2 (16.7%)**	**3 (17.6%)**	**1.000** [f]
Cystitis, bladder spasm G2	**1 (33.3%)**	**1 (33.3%)**	**1.000** [f]
G3+	**2 (66.7%)**	**2 (66.7%)**	
Hematuria G2	**0 (0%)**	**1 (33.3%)**	**1.000** [f]
G3+	**2 (100%)**	**2 (66.7%)**	
Obstruction G3+	**2 (16.7%)**	**2 (11.8%)**	**1.000** [f]
Erectile dysfunction	**11 (100%)**	**17 (100%)**	**----**
GI toxicity G2+	**1 (9.1%)**	**1(5.9%)**	**1.000** [f]
Proctitis, Abdominal pain G2	**0 (0%)**	**1 (100%)**	**1.000** [f]
G3+	**1 (100%)**	**0 (0%)**	
Fissure/ fistula G3+	**1 (9.1%)**	**0 (0%)**	**0.393** [f]

[f]. Fisher's exact test. GU: Genitourinary, GI: Gastrointestinal, G2+: Grade 2 or higher, G3+: Grade 3 or higher

Table 8 shows that there was no statistically significant difference between patients who received either conventional fractionation or hypofractionation regimen in-terms of late genitourinary events assessed 90 days post-radiation. The most observed late GU toxicity in both fractionation arms was late cystitis and bladder spasm (G2 in 6.4% and G3+ in 12.9%). Late hematuria occurred as G2 in 3.2% and G3+ in 12.9% of patients. Four patients developed late G3+ urinary obstruction (12.9%). Of note, all patients in both arms developed erectile dysfunction. Meanwhile, the most noticed late GI toxicity in both fractionation arms was proctitis and abdominal pain (G2 in 3.2% and G3+ in 3.2%). Late rectovesical fistula developed in 1 patient (3.2%).

Table 9. Comparison of the quality-of-life domains scoring between study groups.

QLQ-PR25 Variables	Prostate RT group Mean (SD)	Control group Mean (SD)	*P*-value
QoL Urinary functions			
○ **Baseline**	**78.19 (15.11)**	**77.44 (14.58)**	**0.844**
○ **3 months**	**18.75 (20.25)**	**62.19 (15.67)**	**<0.001***
○ **6 months**	**15.19 (17.33)**	**59.24 (18.20)**	**<0.001***
○ **9 months**	**12.5 (14.96)**	**61.04 (20.56)**	**<0.001***
○ **12 months**	**11.22 (15.17)**	**59.29 (22.89)**	**<0.001***
QoL Bowel functioning			
○ **Baseline**	**15.44 (11.26)**	**8.33 (8.34)**	**0.707**
○ **3 months**	**12.5 (9.7)**	**13.58 (14.83)**	**0.738**
○ **6 months**	**11.02 (8.97)**	**11.96 (13.02)**	**0.756**
○ **9 months**	**8.63 (5.78)**	**13.33 (13.63)**	**0.108**
○ **12 months**	**15.38 (20.93)**	**14.08 (17.12)**	**0.114**
QoL Incontinence aid			
○ **Baseline**	**16.67 (83.34)**	**31.03 (44.48)**	**0.147**
○ **3 months**	**13.54 (30.36)**	**25.93 (38.49)**	**0.173**
○ **6 months**	**11.83 (29.25)**	**20.29 (31.37)**	**0.313**
○ **9 months**	**10.71 (28.77)**	**21.67 (34.67)**	**0.239**
○ **12 months**	**11.54 (29.73)**	**28.21 (38.12)**	**0.142**
QoL ADT symptoms			
○ **Baseline**	**58.33 (16.08)**	**68.01 (10.46)**	**0.006***
○ **3 months**	**62.33 (17.04)**	**75.72 (6.19)**	**<0.001***
○ **6 months**	**64.87 (17.36)**	**77.05 (4.53)**	**<0.001***
○ **9 months**	**65.87 (18.31)**	**78.61 (4.52)**	**0.001***
○ **12 months**	**64.96 (18.51)**	**79.06 (5.15)**	**0.001***
QoL Sexual activity			
○ **Baseline**	**28.92 (18.03)**	**12.64 (12.32)**	**<0.001***
○ **3 months**	**16.40 (13.96)**	**9.88 (11.56)**	**0.058**
○ **6 months**	**14.78 (13.56)**	**8.7 (12.17)**	**0.095**
○ **9 months**	**13.1 (10.5)**	**6.67 (11.34)**	**0.053**
○ **12 months**	**13.46 (10.56)**	**7.69 (11)**	**0.121**
QoL Sexual functioning			
○ **Baseline**	**12.26 (11.83)**	**2.3 (5.41)**	**<0.001***
○ **3 months**	**2.86 (5.44)**	**2.47 (4.51)**	**0.765**
○ **6 months**	**2.96 (5.51)**	**1.89 (3.57)**	**0.431**
○ **9 months**	**3.27 (5.71)**	**0.83 (2.56)**	**0.081**
○ **12 months**	**3.53 (5.86)**	**0.64 (2.31)**	**0.097**

*. Statistically significant p value derived from independent samples t-test, SD: standard deviation.
QoL: quality of life, RT: radiotherapy, QLQ: quality of life questionnaire, ADT: Androgen deprivation therapy

Table 9 compares the patient-reported quality-of-life domains between the two study groups. Patients in the prostate radiotherapy group had a statistically significantly lower scores of urinary symptoms and ADT related symptoms than patients in the control group at 3 months, 6 months, 9 months, and 12 months, p <0.001.

Table 10. Comparison of clinical response between study groups.

Clinical response	Prostate RT group	Control group	*P*-value
6 months	**n= 31**	**n=25**	**0.011***
○ **Improved**	**13 (41.9%)**	**3 (12%)**	
○ **Stable**	**13 (41.9%)**	**10 (40%)**	
○ **Deteriorated**	**5 (16.2%)**	**12 (48%)**	
12 months	**n=26**	**n=16**	**<0.001*** [f]
○ **Improved**	**1 (3.8%)**	**0 (0%)**	
○ **Stable**	**25 (96.2%)**	**4 (25%)**	
○ **Deteriorated**	**0 (0%)**	**12 (75%)**	

[f]. Fisher's exact test. RT: radiotherapy
*. Statistically significant p value

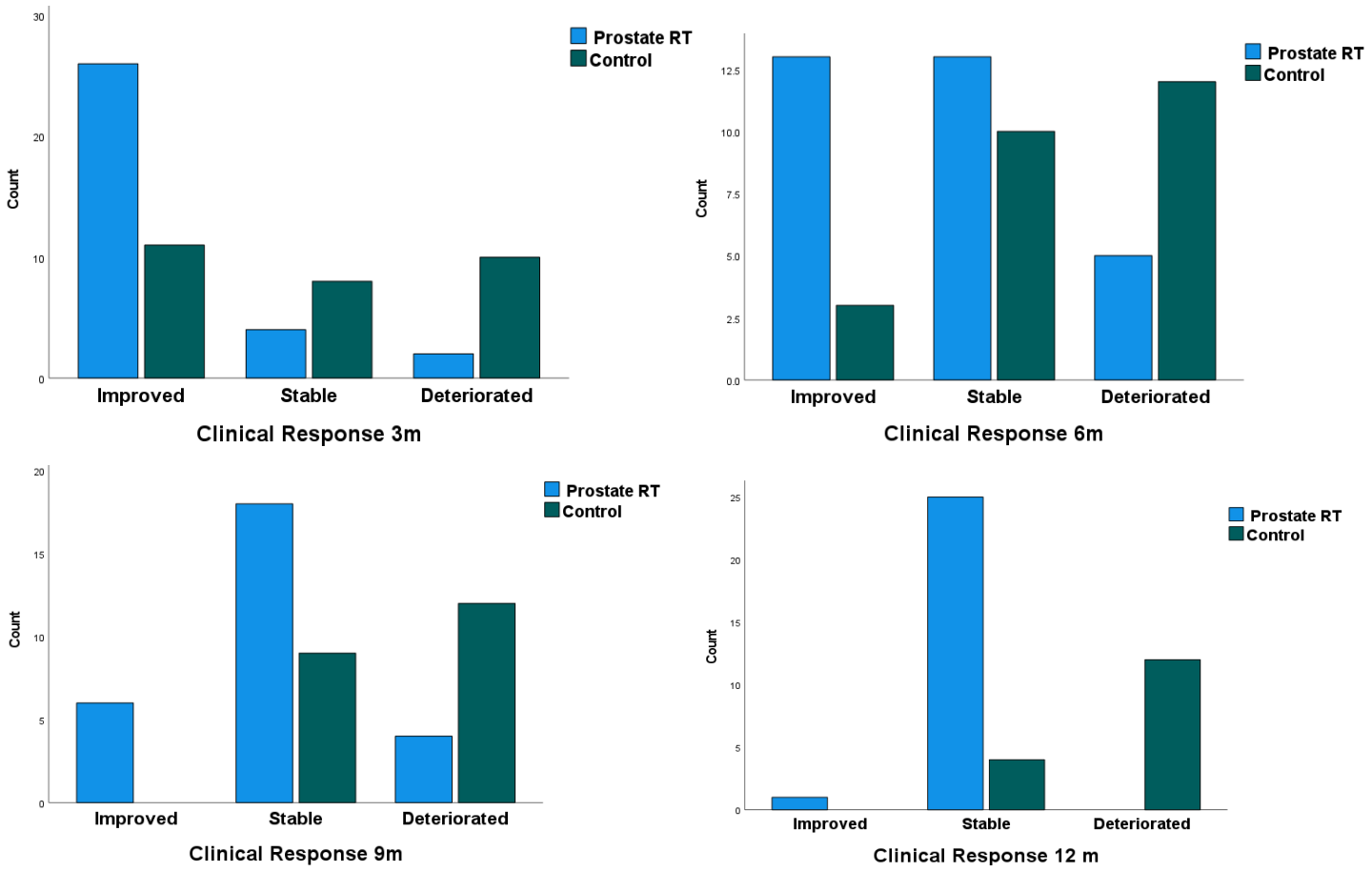


Figure 2. The clinical response among study groups.

Table 10 and figure 2 shows that the prostate radiotherapy group had a statistically significantly better clinical response at 6 months (41.9% vs 12%, p=0.011) and more stable clinical response at 12 months (96.2% vs 25%, $p < 0.001$) compared to the control group. The control group had a statistically significantly worse clinical response at 6 months (48% vs 16.2%, p=0.011) and 12 months (75%% vs 0%, p <0.001).

Table 11. Comparison of clinical response between high metastatic volume and low metastatic volume subgroups in prostate radiotherapy group.

Clinical response	Low metastatic volume	High metastatic volume	*P*-value
6 months	**n=14**	**n=17**	**0.445** [f]
○ **Improved**	**7 (50%)**	**6 (35.3%)**	
○ **Stable**	**4 (28.6%)**	**9 (52.9%)**	
○ **Deteriorated**	**3 (21.4%)**	**2 (11.8%)**	
12 months	**n=14**	**n=12**	**0.462** [f]
○ **Improved**	**0 (0%)**	**1 (8.3%)**	
○ **Stable**	**14 (100%)**	**11 (91.7%)**	

[f]. Fisher's exact test.

Table 11 shows that there was no statistically significant difference in-terms of clinical response between low metastatic volume and high metastatic volume subgroups at 6 months and 12 months after receiving prostate radiotherapy.

Table 12. Comparison of clinical response between castration resistant and castration sensitive/naïve patients in prostate radiotherapy group.

Clinical response	Castration sensitive	Castration resistant	*P*-value
6 months	**n=21**	**n=10**	**0.036*** [f]
○ **Improved**	**12 (57.1%)**	**1 (10%)**	
○ **Stable**	**7 (33.3%)**	**6 (60%)**	
○ **Deteriorated**	**2 (9.5%)**	**3 (30%)**	
12 months	**n=20**	**n=6**	**1.000** [f]
○ **Improved**	**1 (5%)**	**0 (0%)**	
○ **Stable**	**19 (95%)**	**6 (100%)**	

[f]. Fisher's exact test. *. Statistically significant p value

Table 12 shows that there was no statistically significant difference between the metastatic castration sensitive/naïve and the metastatic castrate resistant subgroups at 6 months and 12 months after receiving prostate radiotherapy. The metastatic castration sensitive subgroup had a statistically significantly better clinical response at 6 months (p=0.036).

Table 13. Comparison of clinical response among patients in the prostate radiotherapy group according to fractionation regimen.

Clinical response	Hypofractionation	Conventional fractionation	*P*-value
6 months	**n=19**	**n=12**	**0.883** [f]
○ **Improved**	**7 (36.8%)**	**6 (50%)**	
○ **Stable**	**9 (47.4%)**	**4 (33.3%)**	
○ **Deteriorated**	**3 (15.8%)**	**2 (16.7%)**	
12 months	**n=17**	**n=9**	**0.346** [f]
○ **Improved**	**0 (0%)**	**1 (11.1%)**	
○ **Stable**	**17 (100%)**	**8 (88.9%)**	

[f]. Fisher's exact test

Table 13 shows that there was no statistically significant difference regarding clinical response among patients who received the conventional fractionation regimen and patients who received the hypofractionation regimen at 6 months and 12 months.

Table 14. Comparison of local radiological response between study groups.

Radiological response	Prostate RT group	Control group	*P*-value
1 month	**n=32**	**n=29**	**<0.001*[f]**
○ **PR**	**30 (93.8%)**	**8 (27.6%)**	
○ **SD**	**2 (6.3%)**	**17 (58.6%)**	
○ **PD**	**0 (0%)**	**4 (13.8%)**	
6 months	**n= 31**	**n=25**	**0.016*[f]**
○ **PR**	**11 (35.5%)**	**4 (16%)**	
○ **SD**	**20 (64.5%)**	**16 (64%)**	
○ **PD**	**0 (0%)**	**5 (20%)**	
12 months	**n=26**	**n=16**	**0.004*[f]**
○ **PR**	**1 (3.8%)**	**0 (0%)**	
○ **SD**	**25 (96.2%)**	**9 (56.3%)**	
○ **PD**	**0 (0%)**	**7 (43.7%)**	

[f]. Fisher's exact test. *. statistically significant p value. PR: partial response, SD: stable disease, PD: progressive disease

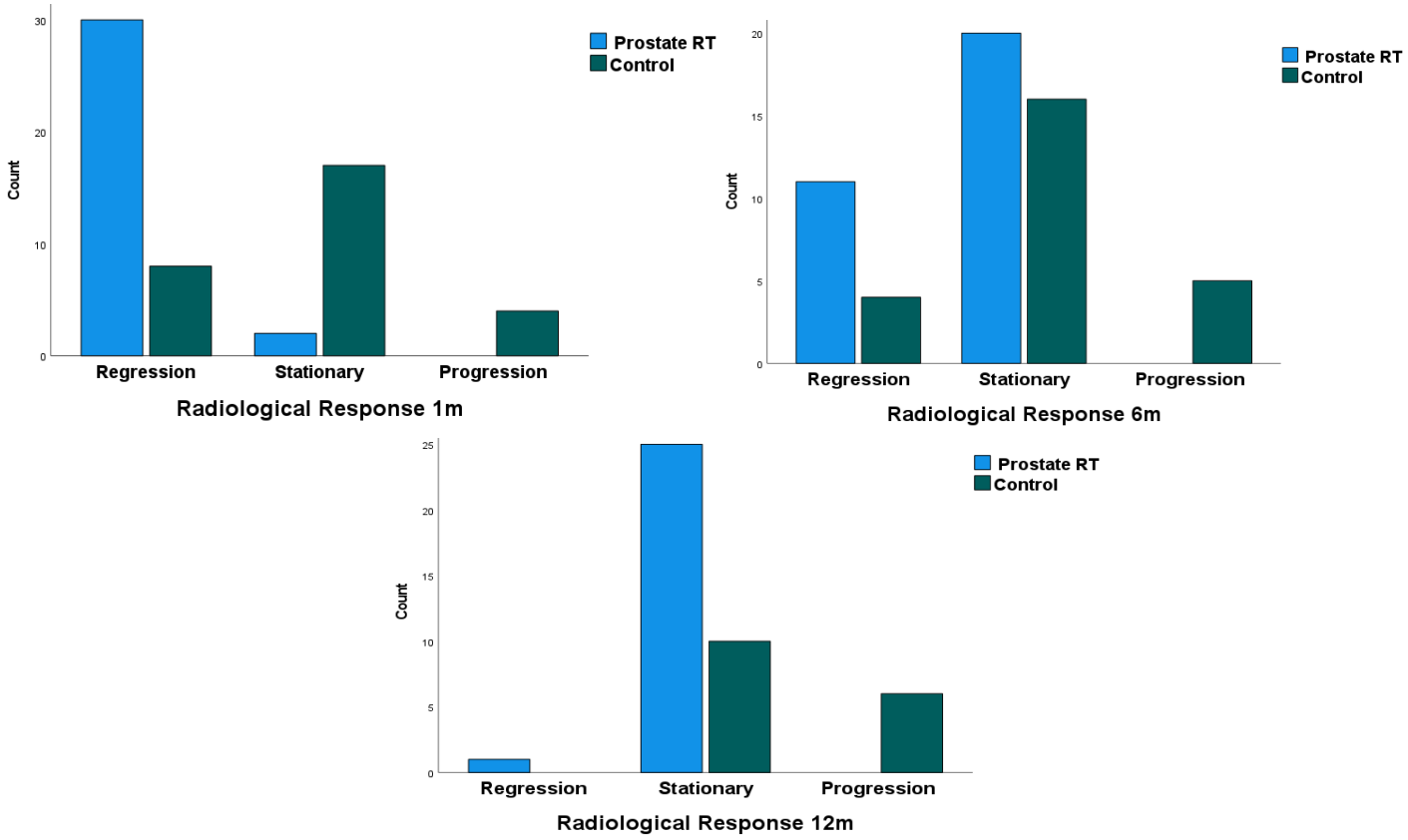


Figure 3. The local radiological response among the study groups.

Table 14 and figure 3 shows that patients in the prostate radiotherapy group experienced a statistically significant greater local radiological response assessed by bi-parametric MRI prostate compared to patients in the control group at 1-year follow up. Patients in the prostate radiotherapy group had more statistically significant radiologically regressive disease at 1 month (93.8% vs 27.6%, $p < 0.001$), 6 months (35.5% vs 16%, p=0.016) and 12 months (p=0.004) compared to patients in the control group.

Table 15. Comparison of local radiological response between subgroups receiving prostate radiotherapy.

Subgroup	Local Radiological Response								
	1 month			6 months			12 months		
	PR	SD	*P*	PR	SD	*P*	PR	SD	*P*
Low metastatic volume	13 (43.3%)	1 (50%)	1.000[f]	6 (54.5%)	8 (40%)	0.477[f]	1 (100%)	13 (52%)	1.000[f]
High-metastatic volume	17 (56.7%)	1 (50%)		5 (45.5%)	12 (60%)		0 (0%)	12 (48%)	
Castration sensitive	22 (73.3%)	0 (0%)	0.091[f]	9 (81.8%)	12 (60%)	0.262[f]	0 (0%)	20 (80%)	0.231[f]
Castration resistant	8 (26.7%)	2 (100%)		2 (18.2%)	8 (40%)		1 (100%)	5 (20%)	
Hypofractionation	19 (63.3%)	1 (50%)	1.000[f]	5 (45.5%)	14 (70%)	0.255[f]	0 (0%)	17 (68%)	0.346[f]
Standard fractionation	11 (36.7%)	1 (50%)		6 (54.5%)	6 (30%)		1 (100%)	8 (32%)	

[f]. Fisher's exact test. PR: partial response, SD: stable disease

Table 15 shows that there was no statistically significant difference regarding local radiological response between all subgroups including the high metastatic volume and the low metastatic volume as well as the metastatic castration sensitive/naïve and the metastatic castration resistant subgroups at 1 month, 6 months, and 12 months. Moreover, there was no statistically significant difference in-terms of local radiological response between patients who received either the standard fractionation regimen or the hypofractionation regimen at 1 month, 6 months, and 12 months.

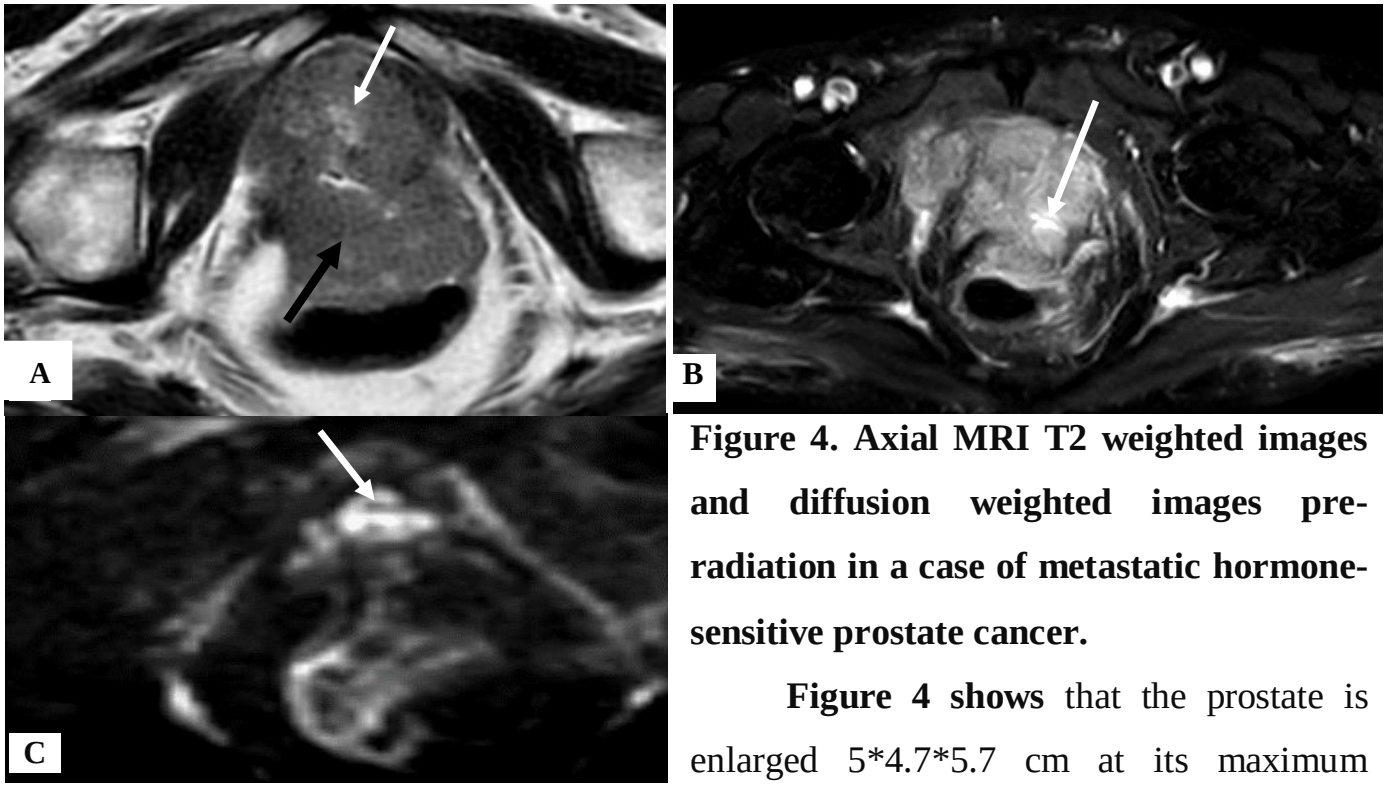


Figure 4. Axial MRI T2 weighted images and diffusion weighted images pre-radiation in a case of metastatic hormone-sensitive prostate cancer.

Figure 4 shows that the prostate is enlarged 5*4.7*5.7 cm at its maximum dimension with large extra-prostatic rectal mass lesion 7.2*6.8*7.8 cm exhibiting heterogenous signal intensity (A- white arrow) with evidence of extracapsular extension invading meso-rectal fascia (A- black arrow) showing evidence of restricted diffusion (B, C- white arrow).

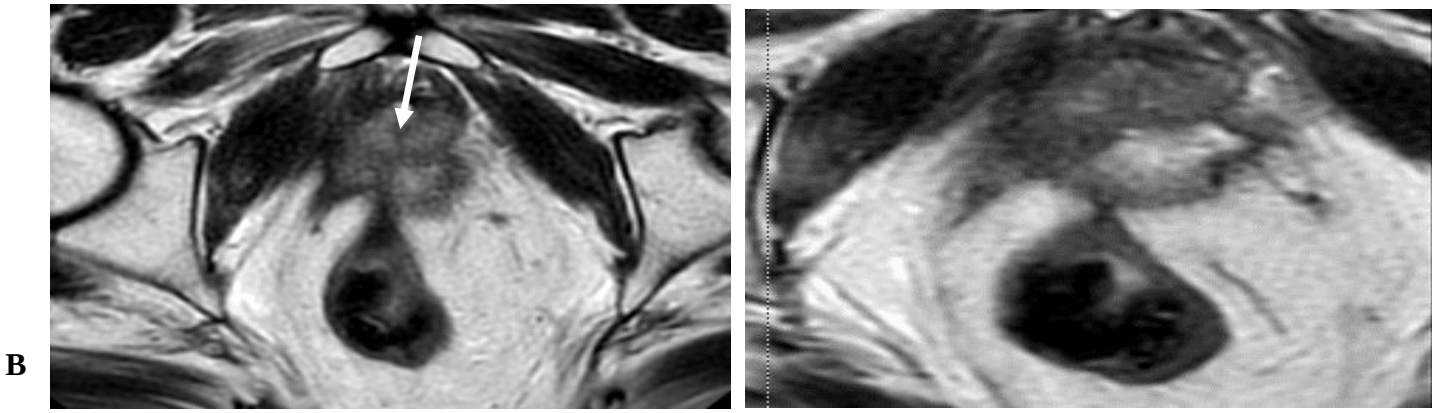


Figure 5. Axial MRI T2 weighted images post-radiotherapy of a case of advanced hormone-sensitive prostate cancer.

Figure 5 shows reduced signal intensity of prostate indicating regression (A- white arrow). The prostate is heterogenously enlarged 3.6*2.7*3.6 cm with no significant prostatic enlargement exhibiting reduced signal intensity and post-radiation shrinkage denoting regressive course and good response to radiation (B- white arrow).

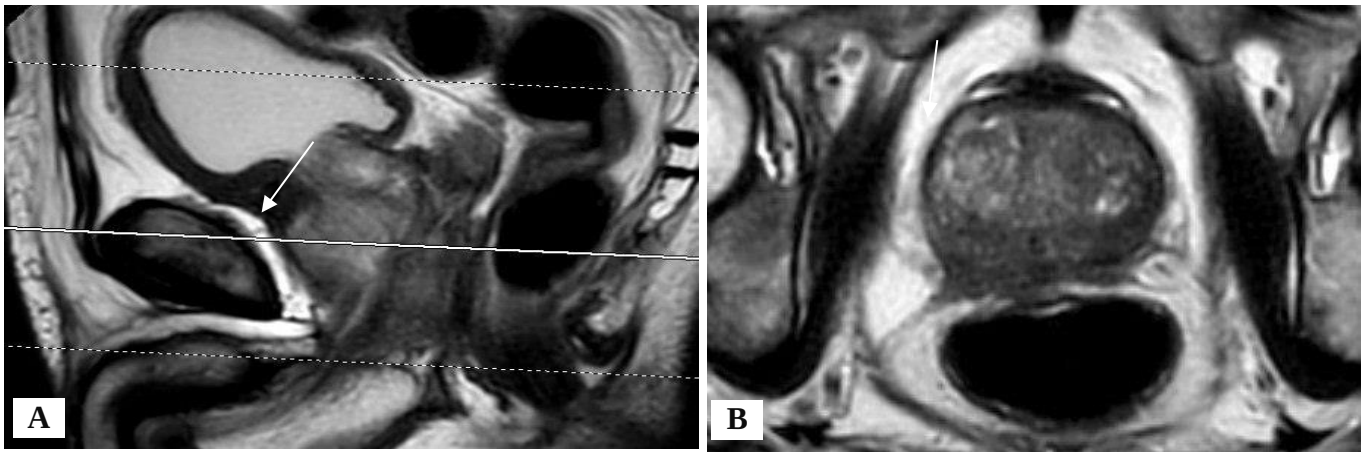


Figure 6. Sagittal and axial MRI T2 weighted images pre-radiation in a case of metastatic castrate resistant prostate cancer.

Figure 6 shows that the prostate is enlarged 5*3.7*4.3 cm with 2 suspicious nodules seen at transitional zone of base and mid-prostate PIRADS4 with evidence of extra-prostatic extension invading rectum and meso-rectal fascia (A- white arrow) and neurovascular bundle invasion (B- white arrow).

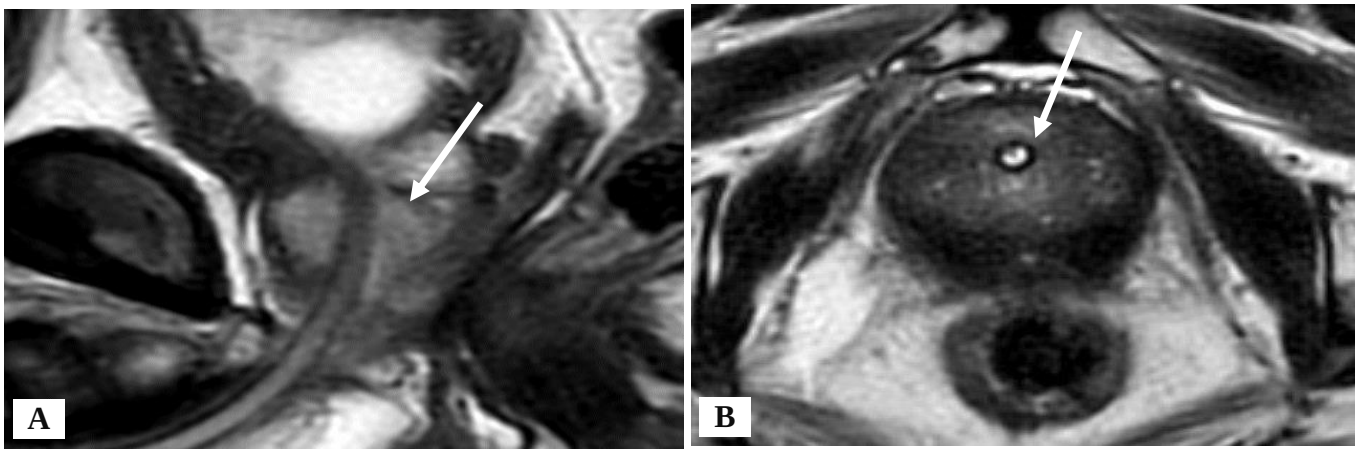


Figure 7. Sagittal and axial MRI T2 weighted images post-radiotherapy of a case of metastatic castrate resistant prostate cancer.

Figure 7 shows that the prostate had a good response to radiation measuring 4.6*3.8*3.7 cm with regression of the multiple suspicious nodules at transitional zone of base and mid-prostate (A, B- white arrow).

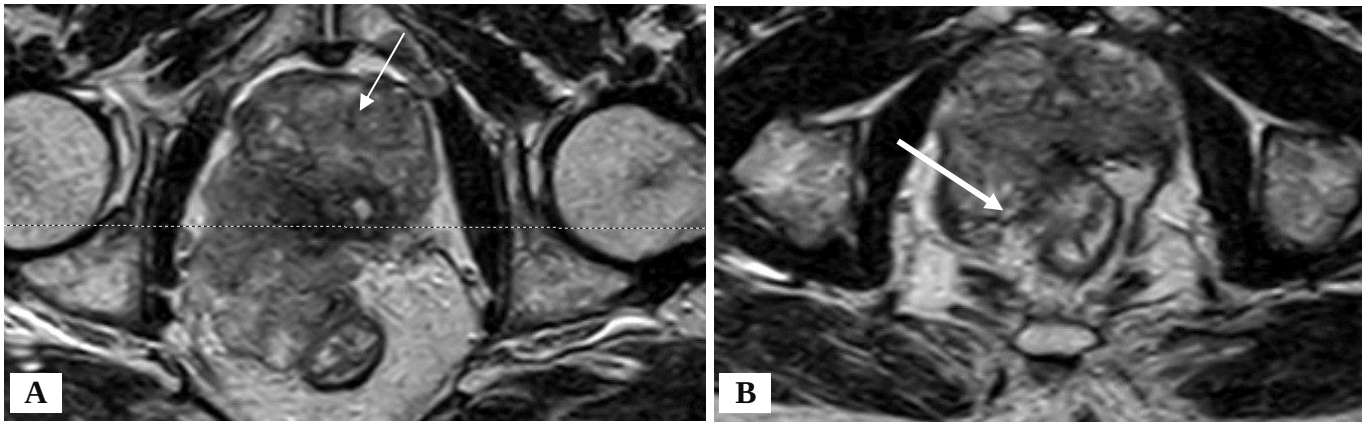


Figure 8. Axial MRI T2 weighted images pre-radiation of a case of metastatic hormonal-sensitive prostate cancer.

Figure 8 shows that the prostate is enlarged 4.7*4.5*4 cm ats maximum dimension involving prostatic mass lesion 6.4*4.2 cm PIRADS-5 seen at the peripheral zone of right side (A- white arrow) with evidence of extra-prostatic extension invading the rectum and meso-rectal fascia and neurovascular bundle (B- white arrow).

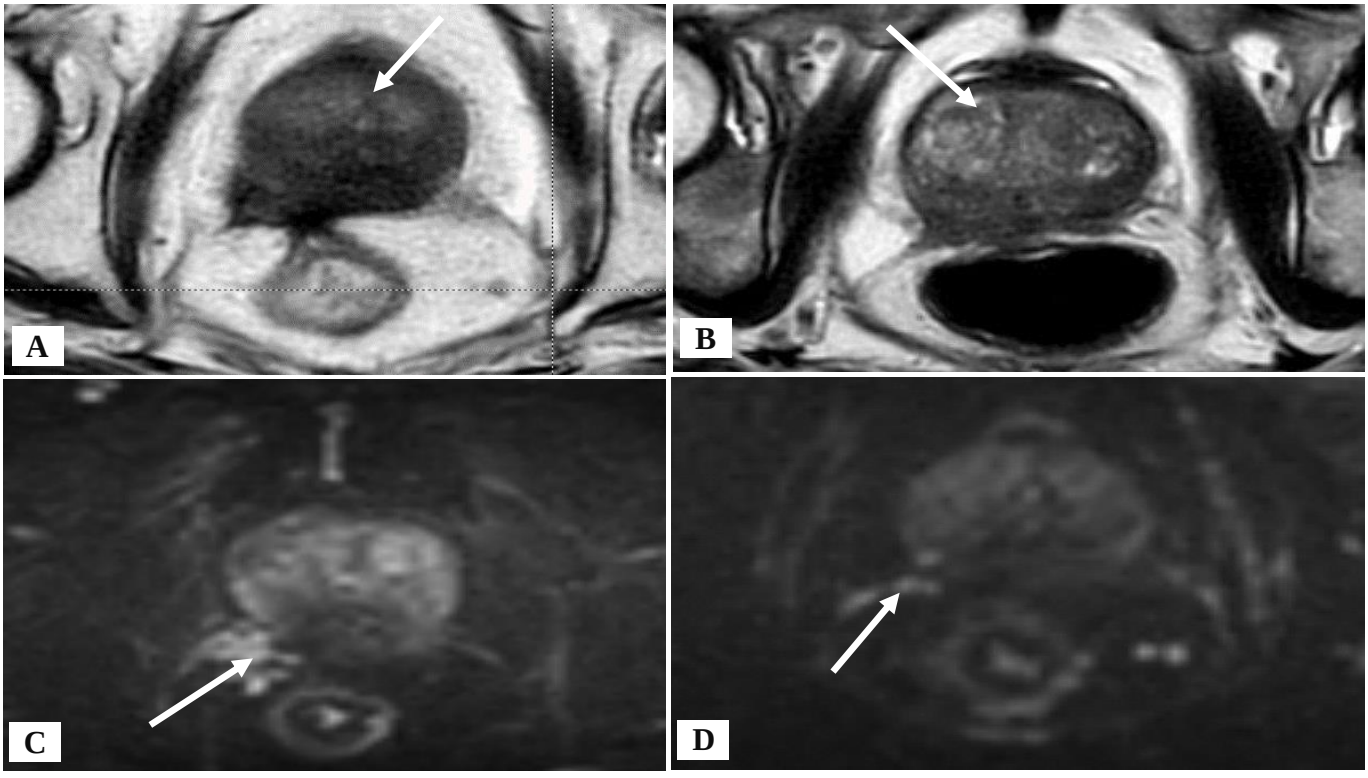


Figure 9. Axial MRI T2 and diffusion weighted images post-radiotherapy in a case of metastatic castrate resistant prostate cancer. Figure 9 shows reduced prostatic signal intensity denoting excellent radiation response (A, B- white arrow) and regression of prostatic mass 3.8*3 cm with restricted diffusion (C- white arrow).

Table 16. Comparison of progression-free survival between study groups.

Group	PFS events N (%)	Censored N (%)	Median PFS (months)	95% CI		*P*-value
				Lower	Upper	
Prostate RT group (n=33)	**11 (28.9%)**	**22 (91.7%)**	**.**	**.**	**.**	**<0.001***
Control group (n=29)	**27 (71.1%)**	**2 (8.3%)**	**4.067**	**3.290**	**4.844**	

*. Statistically significant p value. Censored: left the study before event occurs, or the study ends before event occurs
RT: Radiotherapy, CI: Confidence interval

Table 16 shows the median progression-free survival was not reached for patients in the prostate radiotherapy group compared to 4.067 months for patients in the control group ($p < 0.001$).

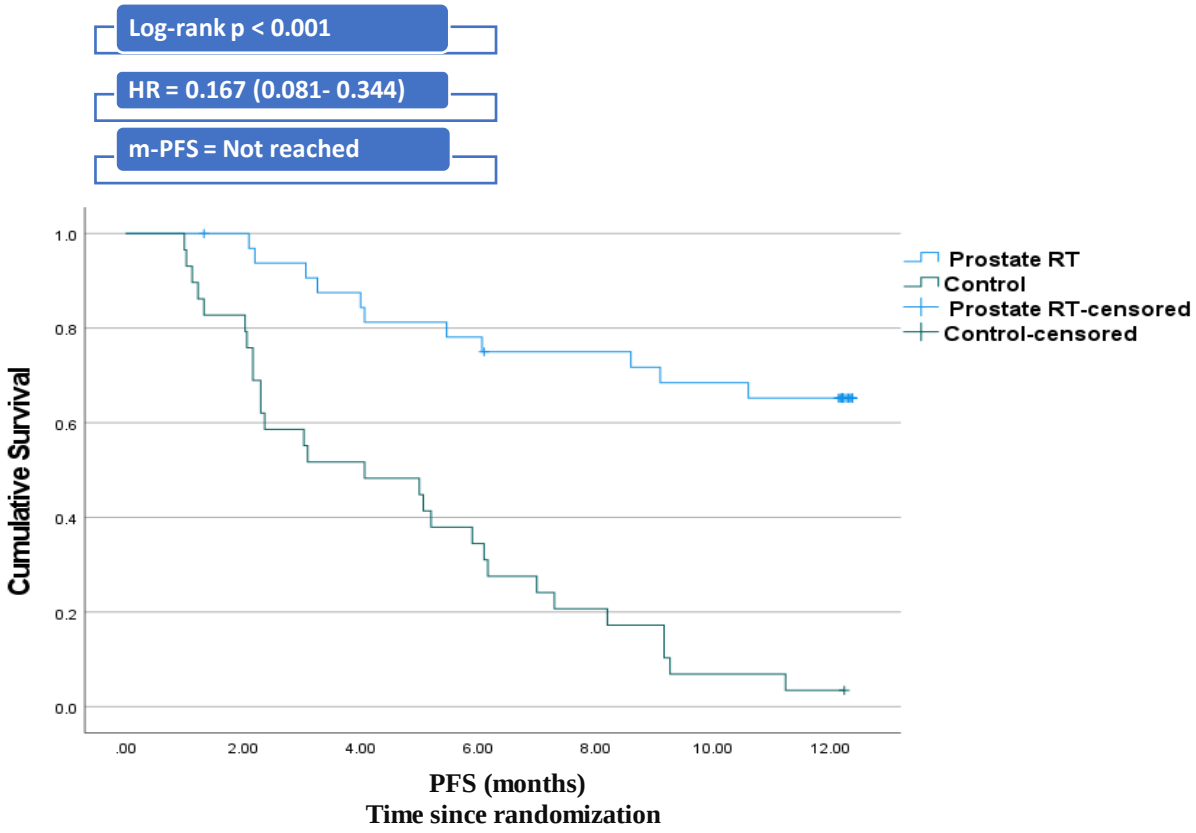


Figure 10. Kaplan-Meier curve of progression-free survival between study groups.

Table 16 and figure 10. show that the prostate radiotherapy group showed a statistically significantly greater progression-free survival than the control group (not reached vs 4.067 months, Log-rank $p < 0.001$). The risk of progression among the prostate radiotherapy group was 0.167 times the risk among the control group (i.e., 83.3% less risk of progression than the control group).

Table 17. Subgroup analysis of progression-free survival between study groups.

Subgroup	HR	*P*-value	95% CI	
			Lower	Upper
Metastatic volume				
Low metastatic volume	**0.029**	**0.004***	**0.003**	**0.244**
High metastatic volume	**0.343**	**0.006***	**0.160**	**0.739**
Response to hormonal treatment				
Castration sensitive	**0.096**	**<0.001***	**0.032**	**0.292**
Castration resistant	**0.355**	**0.05**	**0.128**	**0.987**
Total population				
Prostate radiotherapy group	**0.167**	**<0.001***	**0.081**	**0.344**

*. Statistically significant p value. HR: Hazard ratio, CI: Confidence interval

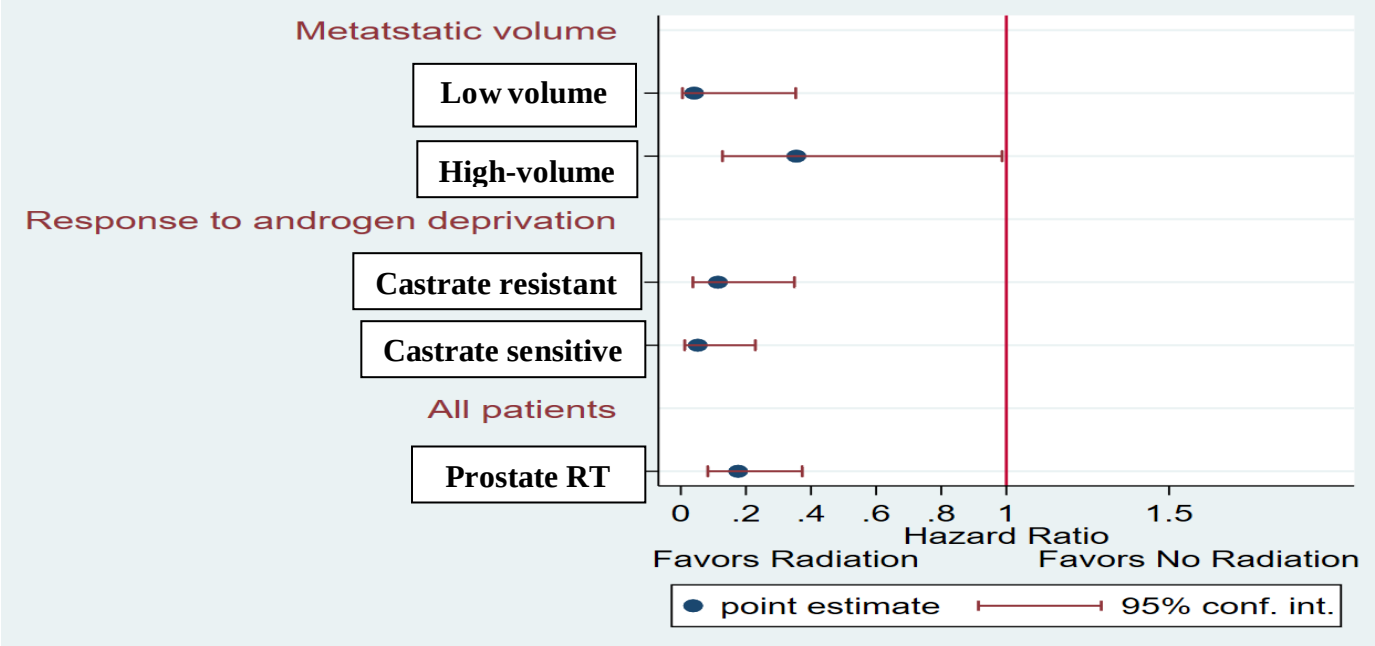


Figure 11. Forest plot for subgroup analysis of progression-free survival.

Table 17 and Figure 11 show that low metastatic volume patients in the prostate radiotherapy group had a statistically significantly lower risk of progression than low metastatic volume patients in the control group (HR:0.029, p=0.004). Besides, high metastatic volume patients in the prostate radiotherapy group had a statistically significantly lower risk of progression than the high metastatic volume patients in the control group (HR:0.343, p=0.006). Castrate sensitive patients in the prostate radiotherapy group had a statistically significantly lower risk of progression than castrate sensitive patients in the control group (HR:0.096, $p < 0.001$). Overall, patients in the prostate radiotherapy group had lower risk of progression than patients in the control group (HR:0.167, p <0.001).

Table 18. Comparison of progression-free survival between subgroups receiving prostate radiotherapy.

Subgroup	PFS events N (%)	Censored N (%)	Median PFS (months)	95% CI		*P*-value
				Lower	Upper	
Metastatic volume						
Low metastatic volume (n=15)	**1 (9.1%)**	**14 (63.6%)**	**.**	**.**	**.**	**0.004***
High metastatic volume (n=18)	**10 (90.9%)**	**8 (36.4%)**	**9.100**	**5.248**	**12.952**	
Response to hormonal treatment						
Castration sensitive (n=23)	**4 (36.4%)**	**19 (86.4%)**	**.**	**.**	**.**	**0.012***
Castration resistant (n=10)	**7 (63.6%)**	**3 (13.6%)**	**8.600**	**3.900**	**13.300**	
Fractionation regimen						
hypofractionation (n=20)	**6 (54.5%)**	**14 (63.6%)**	**.**	**.**	**.**	**0.620**
Conventional fractionation (n=13)	**5 (45.5%)**	**8 (36.4%)**	**.**	**.**	**.**	

*. Statistically significant p value. CI: Confidence interval

PFS: progression-free survival, Censored: left the study before event occurs, or the study ends before event occurs

Table 18 shows that the median progression-free survival was statistically significantly higher and not reached for the low metastatic volume subgroup compared to 9.1 months for the high metastatic volume subgroup (p=0.004). The median progression-free survival of the castration sensitive/naïve group was statistically significantly higher and not reached compared to 8.6 months for the castration resistant subgroup (p=0.012). There was no statistically significant difference between both fractionation regimens in terms of progression-free survival (p=0.620).

Table 19. The univariate analysis for progression-free survival of study groups.

Group	Univariate Cox regression			
	HR	*P*-value	95% CI	
			Lower	Upper
Prostate RT	**0.167**	**<0.001***	**0.081**	**0.344**
Control	**1**			

*. Statistically significant p value < 0.05

HR: Hazard ratio, CI: Confidence interval

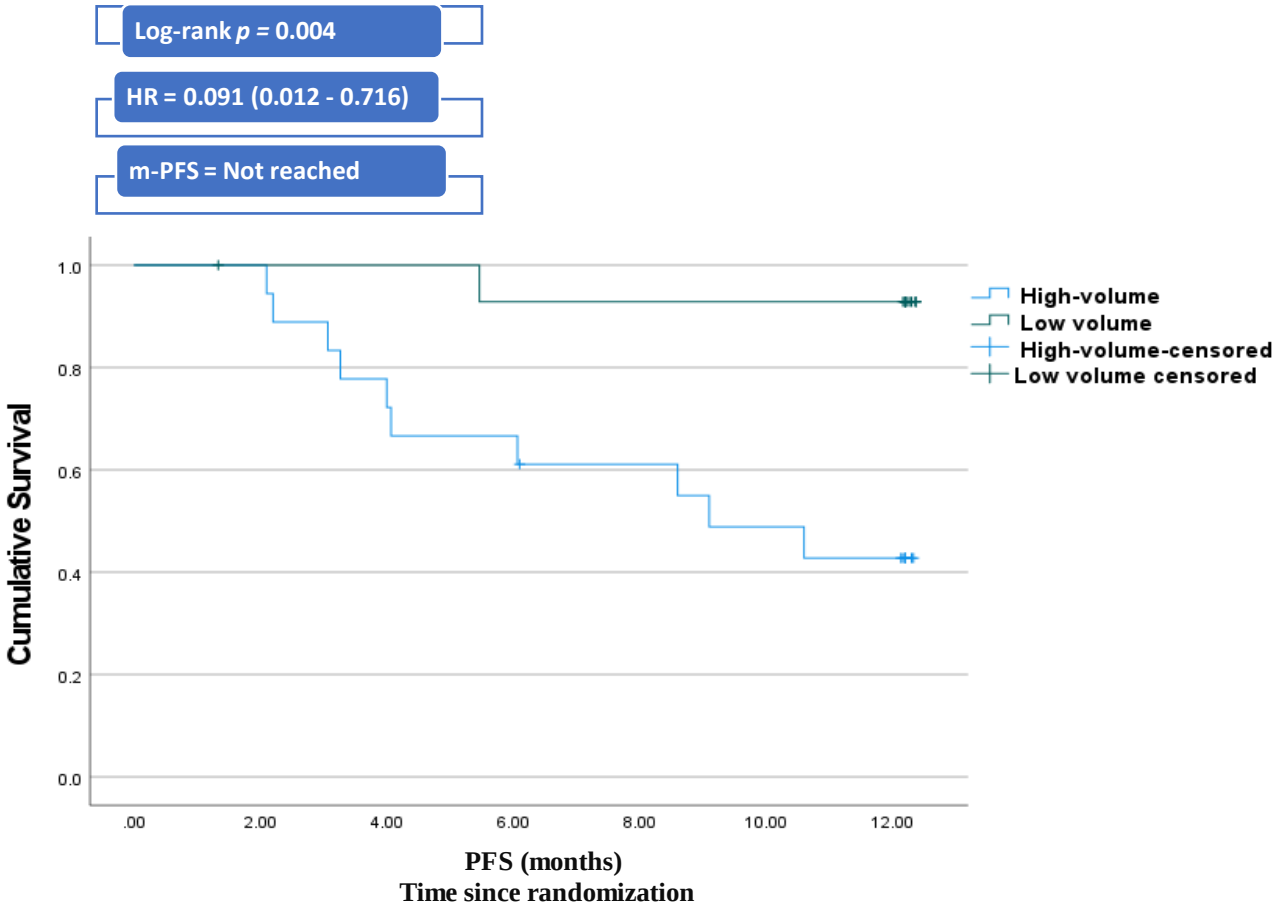
Table 19 shows that the risk of radiographic progression among patients in the prostate radiotherapy group was 0.167 times the risk among control group (i.e., 83.3% statistically significant less risk of radiographic progression than the control group).

Table 20. The univariate and multivariate subgroup analysis for progression-free survival in prostate radiotherapy group.

Subgroup	Univariate				Multivariate			
	HR	*P*-value	95% CI		HR	*P*-value	95% CI	
			Lower	Upper			Lower	Upper
Metastatic volume								
Low metastatic volume	**0.091**	**0.023***	**0.012**	**0.716**	**0.104**	**0.035***	**0.013**	**0.857**
High metastatic volume	**1**				**1**			
Response to treatment								
Castration sensitive	**0.233**	**0.021***	**0.068**	**0.805**	**0.305**	**0.073**	**0.083**	**1.117**
Castration resistant	**1**				**1**			
Fractionation								
Hypofractionation	**0.740**	**0.621**	**0.226**	**2.433**	**0.650**	**0.502**	**0.185**	**2.287**
Conventional fractionation	**1**				**1**			

*. Statistically significant p value
HR: Hazard ratio, CI: Confidence interval

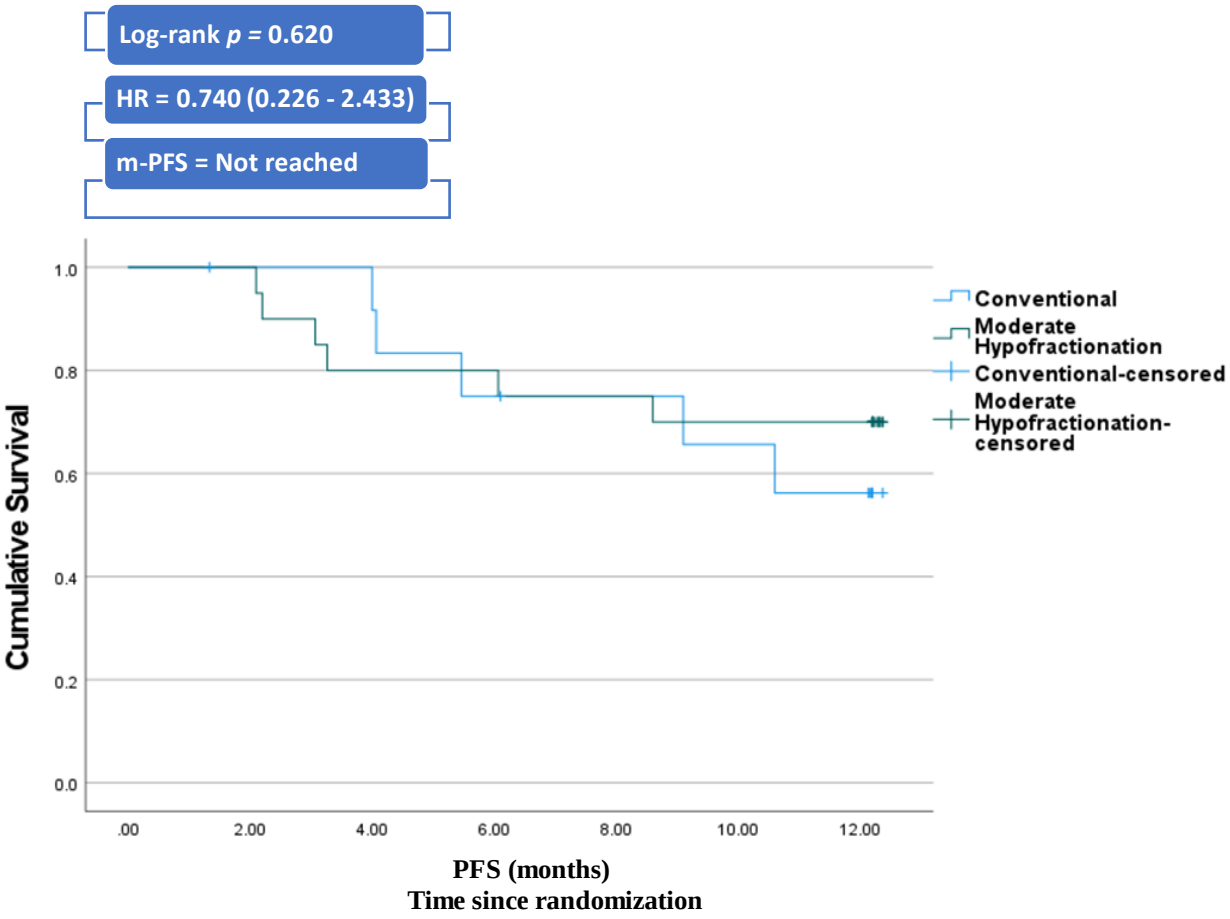
Table 20 shows the crude and the adjusted associations between the progression-free survival and subgroups who received prostate radiotherapy. The crude associations show that the progression-free survival was statistically significantly associated with low metastatic volume subgroup (HR: 0.09, p=0.023), castration sensitive subgroup (HR: 0.233, p=0.021) and non-statistically significantly associated with the hypofractionation regimen (HR: 0.740, p=0.621). The adjusted associations show that the progression-free survival was statistically significantly associated with low metastatic volume subgroup (adjusted HR: 0.104, p=0.035) but non-statistically significantly associated with castration sensitive subgroup (adjusted HR: 0.305, p=0.073) and hypofractionation regimen (adjusted HR: 0.650, p=0.502).



No at Risk	**33**	**32**	**31**	**28**	**26**
High-volume	**18**	**18**	**17**	**14**	**12**
Low volume	**15**	**14**	**14**	**14**	**14**

Figure 12. Kaplan-Meier curve and plot of progression-free survival between low metastatic volume and high metastatic volume subgroups receiving prostate radiotherapy.

Figure 12 shows that patients in the low metastatic volume subgroup who received prostate radiotherapy showed a statistically significant greater progression-free survival than the high metastatic volume subgroup (not reached vs 4.067 months, Log-rank p=0.004). The risk of progression among patients in the low metastatic volume subgroup who received prostate radiotherapy was 0.091 times the risk among patients in the high metastatic volume subgroup (i.e., 90.9% less risk of progression than the high metastatic volume subgroup).



No at Risk	**33**	**32**	**31**	**29**	**28**
Conventional	**20**	**12**	**12**	**11**	**9**
Hypofractionation	**13**	**20**	**19**	**17**	**17**

Figure 13. Kaplan-Meier curve and plot of progression-free survival between patients in the conventional fractionation and the hypofractionation subgroups.

Figure 13 shows that there was no statistically significant difference between patients who received either the conventional fractionation or the hypofractionation regimens in terms of progression-free survival (Log-rank p=0.620). The risk of progression among patients who received the hypofractionation regimen was 0.74 times the risk among patients who received the conventional fractionation regimen.

Table 21. Comparison of overall survival between study groups.

Group	OS events N (%)	Censored N (%)	Median OS (months)	95% CI		*P*-value
				Lower	Upper	
Prostate RT group (n=33)	**8 (24.2%)**	**25 (75.8%)**	**16.33**	**8.61**	**24.05**	**0.003***
Control group (n=29)	**26 (89.7%)**	**3 (10.3%)**	**11.33**	**7.70**	**14.97**	

*. Statistically significant p value. Censored: left the study before event occurs, or the study ends before event occurs
OS: Overall survival, CI: Confidence interval

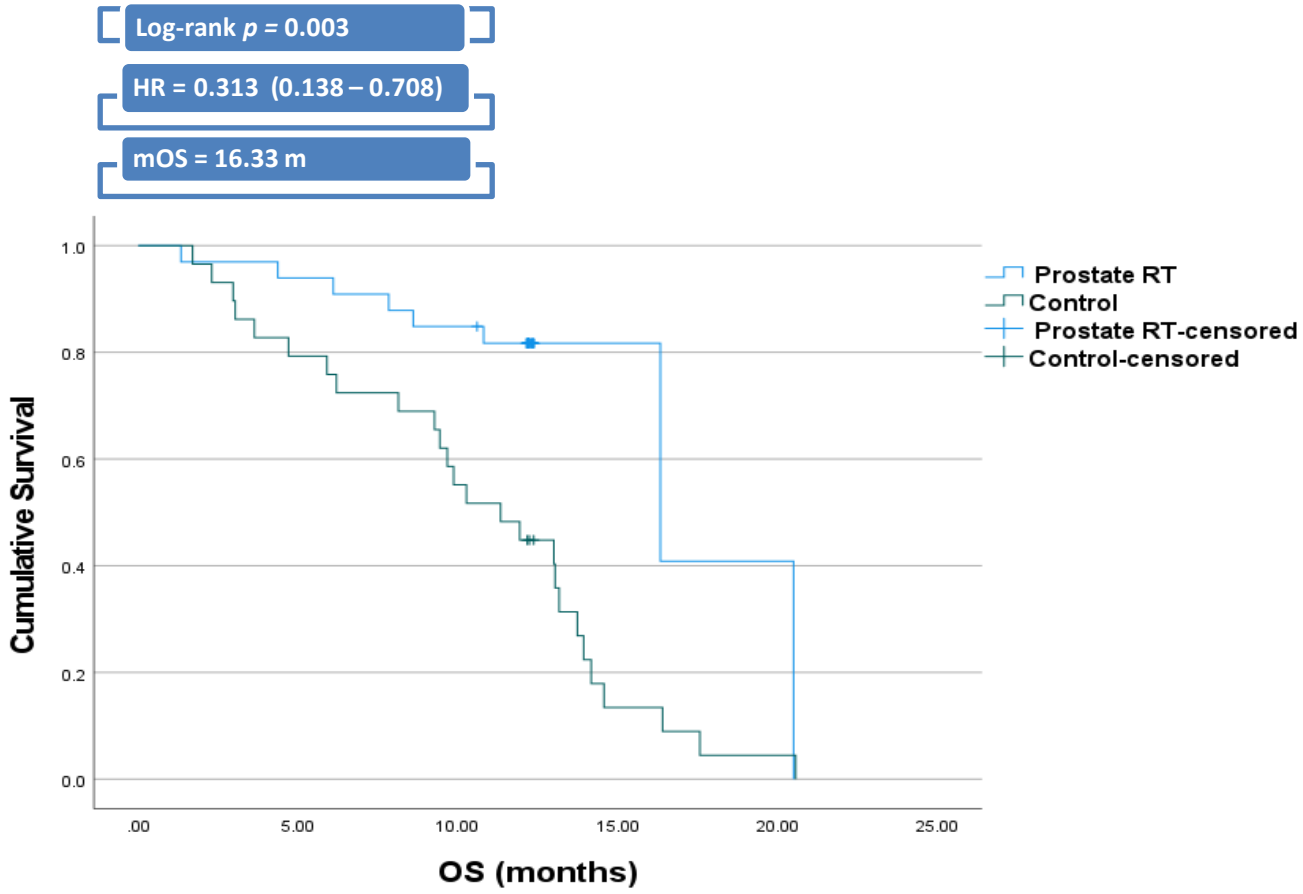


Figure 14. Kaplan-Meier curve and plot of overall survival between study groups.

Table 21 and figure 14 compare the overall survival between patients in the prostate radiotherapy group and patients in the control group. The prostate radiotherapy group showed a statistically significantly greater median overall survival than control group (16.33 vs 11.33 months, Log-rank p=0.003). The risk of death among patients in the prostate radiotherapy group was 0.313 times the risk among patients in the control group (i.e., 68.7% less risk of death than the control group).

Table 22. Subgroup analysis of overall survival between study groups.

Subgroup	HR	P-value	95% CI	
			Lower	Upper
Metastatic volume				
Low metastatic volume	**0.152**	**0.025***	**0.029**	**0.788**
High metastatic volume	**0.513**	**0.172**	**0.197**	**1.336**
Response to hormonal treatment				
Castration sensitive	**0.235**	**0.030***	**0.064**	**0.871**
Castration resistant	**0.335**	**0.066**	**0.104**	**1.074**
Total population				
Prostate RT group	**0.313**	**0.005***	**0.138**	**0.708**

*. Statistically significant p value

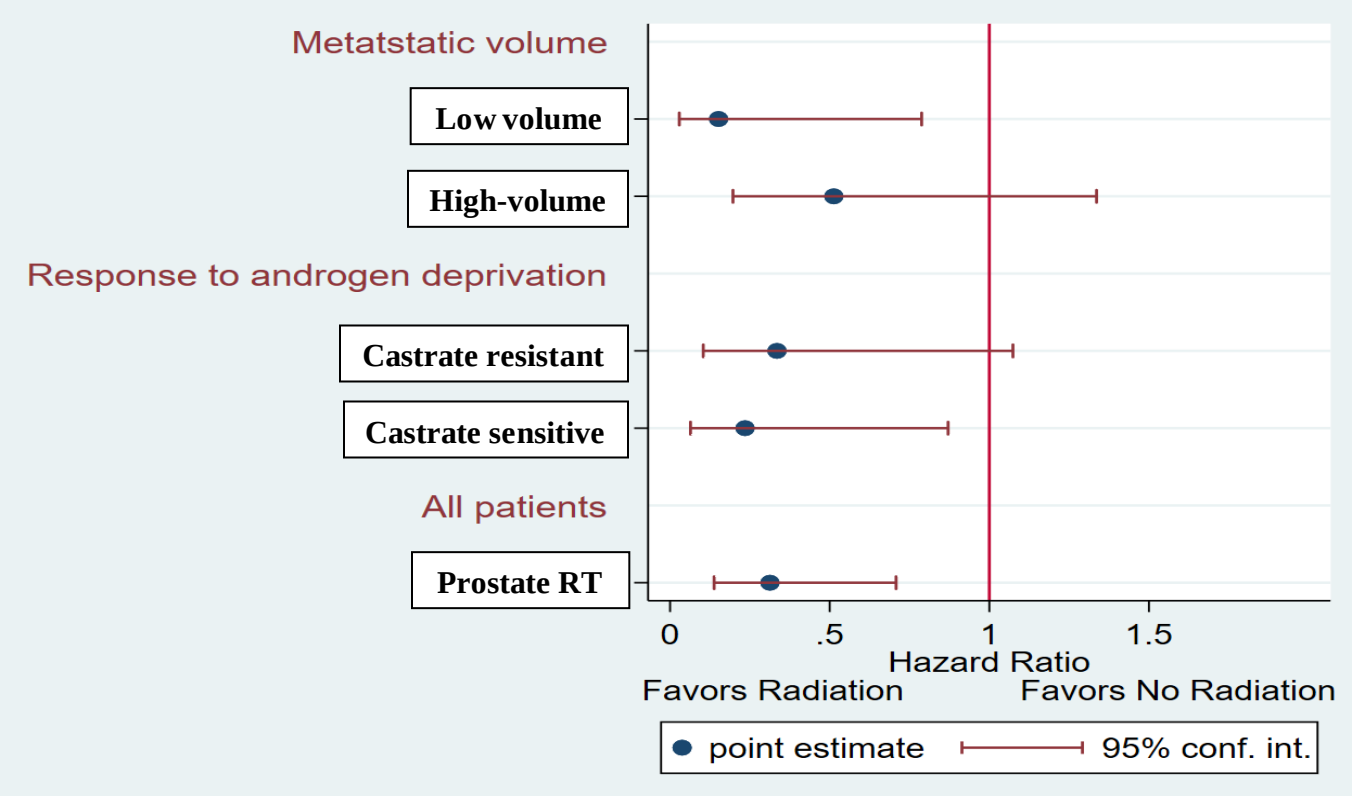


Figure 15. Forest plot for subgroup analysis of overall survival.

Table 22 and Figure 15 show that low metastatic volume patients in the prostate radiotherapy group had a statistically significantly lower risk of death than the low metastatic volume patients in the control group (HR: 0.152, *p*=0.025). Besides, castrate sensitive patients in the prostate radiotherapy group had a statistically significantly lower risk of death than castrate sensitive patients in the control group (HR: 0.235, *p*=0.030). Overall, patients in the control group had a statistically significant lower risk of death than patients in the control group (HR: 0.313, *p*=0.005).

Table 23. Comparison of overall survival between subgroups receiving prostate radiotherapy.

Subgroup	OS events N (%)	Censored N (%)	Median OS (months)	95% CI		*P*-value
				Lower	Upper	
Metastatic volume						
Low metastatic volume (n=15)	**2 (25%)**	**13 (52%)**	**20.55**	**.**	**.**	**0.080**
High metastatic volume (n=18)	**6 (75%)**	**12 (48%)**	**16.33**	**.**	**.**	
Response to hormonal treatment						
Castration sensitive (n=23)	**3 (37.5%)**	**20 (80%)**	**.**	**.**	**.**	**0.304**
Castration resistant (n=10)	**5 (62.5%)**	**5 (20%)**	**16.33**	**8.299**	**24.368**	
Fractionation regimen						
Hypofractionation (n=20)	**3 (15%)**	**17 (85%)**	**.**	**.**	**.**	**0.540**
Conventional fractionation (n=13)	**5 (38.5%)**	**8 (61.5%)**	**16.33**	**8.474**	**24.192**	

OS: Overall survival, CI: Confidence interval

Table 23 shows that there was no statistically significant difference in terms of overall survival between low volume and high-volume metastatic subgroups, castration sensitive and resistant subgroups and between conventional and hypofractionation regimens.

Table 24. The univariate analysis for overall survival between study groups.

Group	Univariate Cox Regression			
	HR	*P*-value	95% CI	
			Lower	Upper
Prostate RT	**0.313**	**0.005***	**0.138**	**0.708**
Control	**1**			

*. Statistically significant p value. HR: Hazard ratio, CI: Confidence interval

Table 24 shows the risk of death among patients in the prostate radiotherapy group was 0.313 times the risk of death among patients in the control group (i.e., 68.7% statistically significant less risk of death than the control group).

Table 25. The univariate and multivariate subgroup analysis for overall survival in prostate radiotherapy group.

Subgroup	Univariate				Multivariate			
	HR	*P*-value	95.0% CI		HR	*P*-value	95% CI	
			Lower	Upper			Lower	Upper
Metastatic volume								
Low metastatic volume	**0.185**	**0.118**	**0.022**	**1.538**	**0.206**	**0.150**	**0.024**	**1.77**
High metastatic volume	**1**				**1**			
Response to hormonal therapy								
Castration sensitive	**0.442**	**0.318**	**0.089**	**2.193**	**0.589**	**0.533**	**0.111**	**3.115**
Castration resistant	**1**				**1**			
Fractionation regimen								
Hypofractionation	**0.609**	**0.544**	**0.123**	**3.021**	**0.855**	**0.853**	**0.163**	**4.505**
Conventional fractionation	**1**				**1**			

HR: Hazard ratio, CI: Confidence interval

Table 25 shows the crude and adjusted associations between the overall survival and subgroups receiving prostate radiotherapy. The crude associations show that the overall survival was non-statistically significantly associated with low metastatic volume subgroup (HR: 0.185, p=0.118), castration sensitive subgroup (HR: 0.442, p=0.318) and hypofractionation regimen (HR: 0.609, p=0.544). The adjusted associations show that the overall survival was non statistically significantly associated with low metastatic volume subgroup (adjusted HR: 0.206, p=0.150), castration sensitive subgroup (adjusted HR: 0.585, p=0.533) and hypofractionation subgroup (adjusted HR: 0.855, p=0.853).

SUMMARY

Prostate Cancer (PCa) is an aggressive malignancy currently ranked as the fourth most common malignancy and the fifth leading cause of all cancer related deaths. Nearly 10% of PCa patients typically present with metastatic disease. In fact, management of metastatic prostate cancer has witnessed major changes over the last decade with the introduction of novel agents and newly adopted treatment strategies.

There are several prognostic stratification models for metastatic hormonal-sensitive prostate cancer that can predict the disease outcomes and define the optimal management of the disease. According to CHAARTED definition, the high-volume disease was defined as presence of visceral metastasis or ≥ 4 bone metastases with ≥ 1 beyond the vertebral bodies and pelvis.

Recently, there has been strong evidence which suggests the benefits of cytoreductive local radiotherapy of the primary tumor in metastatic prostate cancer. Radical prostate radiotherapy doesn't only inhibit the development of distant disease, yet it also avoids the progression of existing metastases. Several retrospective analyses have recognized an association between adding prostate radiotherapy and overall survival improvement. Cytoreductive prostate-radiotherapy in metastatic prostate cancer patients has been tested in a few prospective randomized studies. STAMPEDE was a practice changing trial which concluded that the addition of prostate radiotherapy to standard systemic treatment improves OS for de-novo metastatic prostate cancer patients with low metastatic burden. Therefore, prostate radiotherapy has been currently adopted as a new standard of care in management of oligometastatic hormonal-sensitive prostate cancer.

We conducted a phase III randomized controlled study on 63 metastatic prostate cancer patients attending clinics at the department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Suez Canal university aiming to evaluate the efficacy and tolerability of adding local cytoreductive prostate directed radiotherapy to the standard treatment

compared to the standard treatment alone in metastatic prostate cancer patients.

After a median follow-up of 1 year, we found that treating metastatic prostate cancer patients with prostate-directed radiotherapy added to the standard of care improved clinical response, local radiological response and significantly impacted upon different quality-of-life domains. The addition of cytoreductive prostate radiotherapy to the standard treatment was significantly associated with better progression free survival and overall survival.

Our exploratory subgroup analysis demonstrated that low volume and hormonal-sensitive metastatic prostate cancer patients who received prostate radiotherapy had better progression-free survival time than high-volume and castration-resistant metastatic disease. Additionally, prostate radiotherapy improved progression-free survival and overall survival particularly in low volume hormonal-sensitive metastatic prostate cancer patients. Our findings also realized that the hypofractionated prostate radiotherapy renders similar disease response and survival outcomes to the conventional prostate radiotherapy with comparable GI and GU toxicity.

The main limitations of this study were the short duration of follow up which could underestimate the potential benefits of prostate radiotherapy. Besides, the small sample size and the single institution experience can limit the generalizability of the study findings to all metastatic prostate cancer patients. Moreover, the high dropout rate which can affect the power of the study and can be a source of bias. Consequently, this study can better be replicated in a multicentric larger study design with more extended durations of follow up.