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Original Article

A prospective longitudinal study to evaluate bone health, implication of FRAX tool and impact on quality of life (FACT-P) in advanced prostate cancer patients

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Abstract: Background: Androgen-deprivation therapy (ADT) as a treatment modality in advanced prostate cancer has deleterious effect on bone mineral density (BMD) and quality of life (QOL). Using FRAX (Fracture Risk Assessment) model, candidates at high risk of fractures can be predicted and appropriate treatment can be initiated at early step to prevent skeletal-related events. Objectives of the present study were to evaluate bone health, implication of FRAX tool in advanced prostate cancer and to see the impact of ADT and Bone-directed therapy (BDT) on FRAX and FACT-P QOL scores. Material & method: We conducted a prospective longitudinal study of 83 localized and metastatic prostate cancer patients from March 2017 to Dec 2020. FRAX tool using BMD femoral neck (GE-Lunar) was used to compute the probability of 10-year Major osteoporotic fracture (MOF) and hip fracture risk %. Patients who received monthly Zolendronic acid with or without Vitamin-D/calcium supplementation were classified as BDT group. FRAX and FACT-P were measured at baseline and 12 months follow-up and compared between different therapeutic modalities to see the impact on clinical outcomes. Results: Majority of patients had skeletal metastasis (78.3%) and high-grade disease at presentation. Secondary osteoporosis was the most commonly (82.05%) observed clinical risk factor (CRF) followed by smoking (19.23%). Hip fracture risk ≥3% accounted for larger proportion of patients than did MOF risk ≥20% (21.2% and 2.5%, respectively). Statistically significant reduction was observed in both MOF and hip fracture risk in BDT group, while worsening on ADT. ADT duration correlated positively with both MOF and hip fracture risk (R^2=0.148, P<0.001 and R^2=0.164, P<0.001, respectively). FRAX score accurately predict future fracture events in majority (80%) of high-risk patients. Statistically and clinically significant worsening in PWB, EWB, PCS, FACT-P Total, FACT-P TOI and FAPSI scores were observed in patients on ADT. Statistically and clinically significant improvement was noted in physical well-being in BDT group. However, other QOL domains and FACT-P total scores remained stable. Conclusions: ADT caused duration depended worsening of FRAX and FACT-P score in these patients while improvements of FRAX were seen on BDT. FRAX tool is advantageous in identifying the patients who require early intervention or therapy to decrease skeletal-related events.

Keywords: Prostate cancer, FRAX score, bone health, bone mineral density, quality of life, bone directed therapy, androgen deprivation therapy

Introduction

Prostate cancer (PC) has the highest incidence of bone metastases among all urological malignancies [1]. Bone metastasis causes some of the most worrisome symptoms of advanced staged cancer, with 22% of patients requiring therapy for pathological fractures, 7% for spinal-cord compression and 3-4% for paresis or hemi-paresis [2]. Unfortunately, maintaining the optimum bone health and quality of life (QoL) in these patients usually remains neglected even today [3].

Androgen deprivation therapy (ADT) as a treatment modality has deleterious effect on bone mineral density (BMD) and QoL. Development of osteoporosis in these patients appears to increase steadily with duration of ADT with an annual bone loss of 0.6 to 9.6% and most significant loss occurs within 1-year of initiation of ADT [4, 5]. Maintaining an optimum bone health

and estimation of BMD at the time of instituting ADT for metastatic and locally advanced prostate cancer is recommended by several speciality groups and expert panels [6-8]. The National Osteoporosis Foundation (NOF) guidelines recommend initiation of therapy to prevent fractures in patients with the T score ≤2.5, past history of hip or vertebral fracture and 10-year hip fracture risk ≥3%, or Major Osteoporotic Fracture (MOF) ≥20% by FRAX (Fracture Risk Assessment) model [9].

Appropriate use of imaging modalities like DEXA scan can detect osteoporosis at an early stage and scrutinize patients who need therapy to improved bone health. Unfortunately, there has been no proven definitive method for predicting pathologic fracture in patients with bony metastasis so far. Using a computer-based FRAX model, candidates at high risk of fractures can be predicted accurately and appropriate treatment can be initiated at an early step to prevent skeletal related events and to improve QoL. FRAX tool is recommended by WHO to predict fracture risk according to clinical risk factors (CRF) alone or in combination with bone mineral density at the femoral neck [9-12]. FRAX provides 10-year probability of MOF (spine, forearm or shoulder) and hip fractures according to age, sex, BMI, and CRF [6, 9-12]. The factors which may affects FRAX score include age, ethnicity, type and duration of ADT, mode of radiotherapy and CRF [10-12]. Further studies are needed to ascertain the role of this new investigating tool (FRAX) in these patients. The objectives of present study is to evaluate the bone health, implication of FRAX tool in locally advanced and metastatic prostate cancer and to see the impact of ADT and Bone-directed therapy on FRAX score and QoL.

Material & methods

We conducted a prospective longitudinal study of locally advanced and metastatic prostate cancer [13] at our institute (Tertiary care center) from March 2017 to Dec 2020 after getting institutional ethical clearance [1737/Ethics/R.Cell-17]. Study was registered in Central Trial Registry of India (CTRI/2017/08/00945). Patients who presented with locally advanced and metastatic prostate cancer were included into the study after getting informed consent. Patients with metabolic or congenital bone disease, prostate secondaries, other active malignancy, central nervous disorders, and moribund status were excluded from the study.

Baseline demographic characteristics of all the patients were recorded. Initial work-up as per EAU guideline was performed to confirm the diagnosis and stage the disease [6]. Treatment of prostate cancer was decided as per stage, recent EAU guideline and patient's personal preference [6]. Base level bone health was assessed by DEXA scan; BMD (GE-Lunar) in g/cm^2 and T score measurement done at spine, femur neck, femur total and radius in gm/cm^2. Mode with duration of ADT and skeletal related events (SRE) were recorded. Dichotomised CRF (**Table 2**) were noted for FRAX score calculation.

FRAX tool (www.shef.ac.uk/FRAX/) was used to compute the probability of a 10 year MOF and hip fracture risk %. Numbers of patients who have 10-year probability of major osteoporotic fracture ≥20% and 10-year probability of hip fracture ≥3% (considered as risk threshold for treatment) were noted. Monthly intravenous infusion of 4 mg Zolendronic acid (ZA) was initiated in patients on ADT with either positive bone scan or with high fracture risk on DEXA or FRAX model. Patients who received Zolendronic acid with or without vitamin D and calcium supplementation were classified as bone directed therapy (BDT) group. DEXA scan was repeated at 12 months follow up to look for changes in bone health, BMD and FRAX scores.

Patient's QoL was measured using English or validated Hindi version [14] of Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire at baseline and at 12 months after enrolment in the study [15]. It includes five independent subscales measuring 7-items physical well-being (PWB), 6-items emotional well-being (EWB), 7-items social well-being (SWB), 7-items functional well-being (FWB) and 12-items prostate cancer subscale (PCS) [15]. FACT-P total score is measured by addition of these 5 subscales and ranges from 0 to 156. FACT-P Trial Outcome Index (TOI) is based on the sum of PWB, FWB and PCS. FACT Advanced Prostate Symptom Index (FAPSI) includes 8-items from the FACT-P questionnaire [16]. A higher score indicates better QoL. FRAX and

FACT-P scores were measured and compared at baseline and at 12 months between different therapeutic modalities like ADT versus Non-ADT and BDT versus non-therapy groups to evaluate the impact on clinical outcome in these patients.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 21.0 software (IBM Co., Armonk, NY, USA, 2013). T score at baseline and post-therapy was compared using Wilcoxon Signed Ranks. Paired t-test was used to compare baseline and follow-up FRAX scores. Bone health of patients in different groups (ADT, BDT and non-therapy) were compared using the Mann-Whitney test. The independent samples t-test, Chi-square test and Fisher's exact test were used to test for level of significance with confidence interval of 95%. *P* value less than 0.05 was considered statistically significant.

Results

Eighty three patients of metastatic and locally advanced prostate carcinoma were enrolled in the study and analyzed in results. The baseline characteristics of study subjects are shown in **Table 1**.

Secondary osteoporosis was the most commonly (82.05%) observed CRF followed by smoking (19.23%). Other CRF were recorded in less than 10% cases (**Table 2**). Baseline and follow up FRAX scores are depicted in **Table 3**. Hip fracture risk (≥3% i.e. treatment threshold) accounted for larger proportion of patients than did major osteoporotic fracture risk (≥20%) [21.2% and 2.5%, respectively]. FRAX scores (both MOF & Hip fracture risk) were strongly influenced by age of patients on Scatter plot and worsening of scores were seen with advancing age.

Statistically significant reduction was observed in both MOF and hip fracture risk in BDT group, while worsening of FRAX score was noted in non-treatment group. When FRAX of ADT versus Non-ADT group was compared, statistically significant increase was noted in both MOF and hip fracture in ADT group, while no significant changes were seen in non-ADT group (**Table 4**; **Figure 1**). The ADT duration correlated positively with both MOF and hip fracture risk (R^2=0.148, *p* value <0.001 and R^2=0.164, *p* value <0.001, respectively). Comparison of the ADT versus non-ADT groups showed that the MOF ≥20% and the hip fracture ≥3% were higher in ADT subjected group than in non-ADT group (ADT -6.8% and 55.4%, non-ADT -3.4% and 35.2%, *p* value <0.001 & *p* value <0.001, respectively).

BMD comparison as T-Score of pre and post-ZA therapy group at various bone sites showed statistically significant improvement at all bone sites except radius in patients on BDT (P<0.05). The baseline and follow up T scores of different bone sites in patients who received ADT without BDT were also compared with Mann Whitney test. It showed statistically significant decrease in T score at all bone sites except radius at follow up (P<0.05) (**Figure 2**).

Skeletal related events (SRE) including fracture, occurrence of spinal cord compression and need of radiation or surgery for skeletal metastasis [17] were seen in 10 patients (13.7%). Eight of these (80%) who developed SRE were found to have baseline FRAX score above the risk thresholds value. Therefore, FRAX score accurately predict future fracture events in majority (80%) of high risk patients, while 20% patients had score below the risk threshold value and could not be predicted (P<0.05). Six patients (12.5%) of BDT and 4 patients (16%) of non-therapy group developed SRE. SREs were significantly more common in non-therapy group than BDT group. In our series, 15 patients (18.1%) died within the study period of 2 years.

In ADT group, statistically significant decrease or worsening of QOL in PWB, EWB, prostate cancer subscale, total FACT-P, FACT-P TOI and FAPSI scores were seen at follow-up. However, functional well-being domain score improved significantly at follow-up, while no statistically significant difference was noted in social well-being domain in ADT group. No statistically significant difference was noted in any domain/scale in non-ADT group at follow-up. When these differences in FACT-P scores were compared with established minimal clinically important difference (MCID) [16, 18], all these differences were found to be clinically significant. Statistically and clinically significant improvement was noted in physical well-being in BDT group while worsening of FAPSI observed in patients who did not receive bone directed

Table 1. Baseline demographical characteristics

Baseline Characteristics (N=83)		Average ± SD	Range
Age (years)		69.3 ± 10.0	49-99
BMI (kg/m^2)		22.69 ± 3.43	16-31
Serum PSA (ng/dl)		60.2 ± 32.1	0.04-1929
ADT Duration (Months)		19.6 ± 11.3	1-128
ECOG Performance Status	Performance Status 0	77	92.77%
	Performance Status 1	4	4.82%
	Performance Status 2	2	2.40%
Parameters		No of Patients	Percentage
Geographical Distribution	Rural	51	61.45%
	Urban	32	38.5%
Locally advanced Prostate Cancer		18	21.68%
Metastatic Prostate Cancer (+Bone Scan)		65	78.31%
Pattern of Bony Involvement*	Spine	47	72.30%
	Pelvis	40	61.53%
	Ribs	35	53.84%
	Shoulder	16	24.61%
	Skull	10	15.38%
	Sternum	5	7.69%
	Clavicle	2	3.07%
	Other Bones	5	7.69%
Gleason Grading	High (G>7)	41	49.39%
	Intermediate (G=7)	30	36.14%
	Favourable (G<7)	12	14.45%
Treatment Modality*	Orchidectomy	54	72.30%
	LHRH Agonist	17	20.48%
	LHRH Antagonist	4	4.8%
	Bicalutamide	46	54.42%
	Docetaxel Chemo	5	6.02%
	Abiraterone	18	21.68%
	Enzalutamide	2	2.4%
	No Therapy	3	3.6%
Baseline Serum Vit D (ng/ml) (N=80)	Deficiency (<10)	4	5%
	Insufficiency (10-30)	64	80%
	Sufficiency (30-100)	12	15%
Baseline T Score and Stratification	Normal	7	8.43%
	Osteopenia	52	62.65%
	Osteoporosis	24	28.91%

BMI-Basal Metabolic Index, PSA-Prostate Specific Antigen, *Total number may exceed 100% as some patients had more than one bone involvement or received more than one treatment modality.

therapy. However, other QOL domains/scales and FACT-P total scores remained stable (**Tables 5** and **6**).

Discussion

Most (61.45%) of our study subjects were from rural background and presented with high grading (Gleason score >7 in 49.4% cases), signifying the aggressive nature of disease. Incidence of skeletal metastases is quite high in India [19, 20] and in our series, metastases were seen in 78.3% of patients compared to 80% localized disease at presentation in western countries [21].

ADT is commonly used in our setting because most patients present to us in advance stage

Table 2. Pattern of distribution of clinical risk factors (CRF)

Clinical Risk factors (CRF)*	No. of patients	Percentage %*
Previous Fracture	6	7.69
Parental Hip Fracture	3	3.85
Currently Smoking	15	19.23
Steroid Use	3	3.85
Rheumatoid Arthritis	3	3.85
Secondary Osteoporosis	64	82.05
Alcohol Intake ≥3 units	3	3.85
No of CRF in particular patient	No. of patients	Percentage %*
None	10	13.7
1 CRF	44	60.23
2 CRF	14	19.18
3 CRF	3	4.11
4 CRF	1	1.37
5 CRF	1	1.37

*Total number may exceed 100% as some patients had more than one CRFs.

and are not the suitable candidates for radical prostatectomy or active surveillance. Most commonly used treatment modality was orchidectomy (72.3%) followed by GnRH therapy in 25% cases. Most of the patients are from poor socioeconomic background and cannot afford the costly treatment of GnRH analogue and hence chose surgical castration. Saylor et al [22] in a cross-sectional study of 363 prostate cancer patients on ADT (GnRH agonist, mean duration 1.6 years) showed that clinical fracture risk or FRAX score positively correlated with advancing age and longer duration of ADT. Our study results also depicted positive correlation of advancing age and duration of ADT with FRAX scores.

In our study, T scores at spine, femur neck and femur total except radius improved in Zolendronate group patients. While significant deterioration in T scores at all the sites except radius were observed in patients on ADT. Kapoor A et al [23] concluded in a study of 41 non metastatic prostate cancer patients on ADT, that quarterly administration of Zoledronate for 1 year improved vertebral and left femur-neck BMD in men on GnRH analogue. Saad et al [17] studied the effect of ZA on skeletal complications in cancer prostate patients with bony metastases. Administration of ZA (4 mg or 8 mg, 3 weekly) reduced the fracture events and increased the median time to first SRE in their study. We also found significant reduction of SREs in patients on Zolendronate therapy.

Distribution of CRF and their impact on FRAX in prostate cancer patients has been evaluated in limited number of studies. Saylor et al [22] in a cross-sectional study showed that daily alcohol intake was the most common (11.6%) CRF followed by prolonged steroid use (8.3%). The prevalence of each of CRFs other than alcohol consumption was less than 10%. Kawahara et al [24] in study of 1220 patients also showed that alcohol intake (31.1%) was the most prevalent CRF followed by history of previous fracture (20.9%), smoking (11.3%), and secondary osteoporosis (8.9%, respectively. These studies identified that CRF combined with BMD predicts fractures risk better than the BMD or CRF alone. However, secondary osteoporosis due to ADT was the most common (82.05%) CRF followed by current smoking (19.23%) in our study cohort. Other CRFs were recorded in less than 10% of patients.

Just handful of studies were identified in literature related to implication of FRAX tool for prostate cancer and all are from USA except one from Japan [11, 12, 22, 24-26]. Patients in these studies varied in respect to enrollment of localized, metastatic, CRPC, with or without ADT and patients on photon or radiotherapy. Saylor et al [22] found that FRAX model recognized more men at skeletal fracture risk than BMD alone. Mean 10 years hip and major osteoporotic fracture probability from CRF including ADT as secondary osteoporosis were 3.1% and 12%, respectively. Another study by Adler et al [12] showed that FRAX score calculation using femur neck BMD or without BMD identified different populations at fracture risk. A retrospective study by Dhanapal et al [25] of 174 patient who received injection leuprolide (97.7% cases) for a mean duration of 13.8 months showed that baseline MOF and hip fracture risk increased from 4% to 5.6% and 1.3% to 2.2%, respectively after start of ADT. Worsening of FRAX scores after giving longer duration ADT was also noted in a large prospective study by Kawahara et al [24]. Com-

Table 3. Baseline and follow-up FRAX score (10 yrs MOF & Hip Fracture risk %)

Parameters	Baseline	1st Follow up	2nd Follow up
MOF Risk % (Mean ± SD)	4.49 ± 2.87	4.35 ± 2.80	4.23 ± 2.72
MOF Risk % (Range)	1.1-21	0.9-22	1.2-22.7
No. of Patients with ≥20% MOF risk	2 (2.5%)	1 (1.37%)	2 (3.6%)
Hip Fracture risk % (Mean ± SD)	1.68 ± 1.56	1.60 ± 1.52	1.52 ± 1.47
Hip Fracture risk % (Range)	0.1-17.9	0.08-18.1	0.1-18.8
No. of Patients with ≥3% Hip fracture risk	17 (21.25%)	15 (21.42%)	12 (20.8%)

Table 4. Comparison of baseline and follow up FRAX score in different therapy groups

	FRAX Score	Baseline	Follow up	Difference	*P* value	Sig
A: Effects on FRAX Score in patients who received bone directed therapy (BDT)						
MOF Risk % (Mean ± SD)	BDT Group (N=48)	4.93 ± 3.07	4.10 ± 1.82	-0.76 ± 1.94	0.009	Sig
	Non-treatment Group (N=25)	3.66 ± 2.63	4.49 ± 2.74	0.83 ± 0.47	0.02	Sig
HF Risk % (Mean ± SD)	BDT Group (N=48)	1.77 ± 1.86	1.29 ± 1.11	-0.48 ± 0.38	0.003	Sig
	Non-treatment Group (N=25)	1.52 ± 1.51	1.97 ± 1.74	0.45 ± 1.86	0.001	Sig
B: Effects on FRAX score in patients receiving ADT versus No ADT						
MOF Risk % (Mean ± SD)	ADT Group (N=68)	4.13 ± 1.27	4.90 ± 1.89	+0.77 ± 1.86	0.002	Sig
	Non-ADT Group (N=15)	3.46 ± 2.04	3.54 ± 2.69	0.08 ± 0.58	0.08	NS
HF Risk % (Mean ± SD)	ADT Group (N=68)	1.57 ± 1.64	2.39 ± 1.21	+0.82 ± 0.97	0.003	Sig
	Non-ADT Group (N=15)	1.32 ± 1.22	1.38 ± 1.69	0.45 ± 0.76	0.09	NS

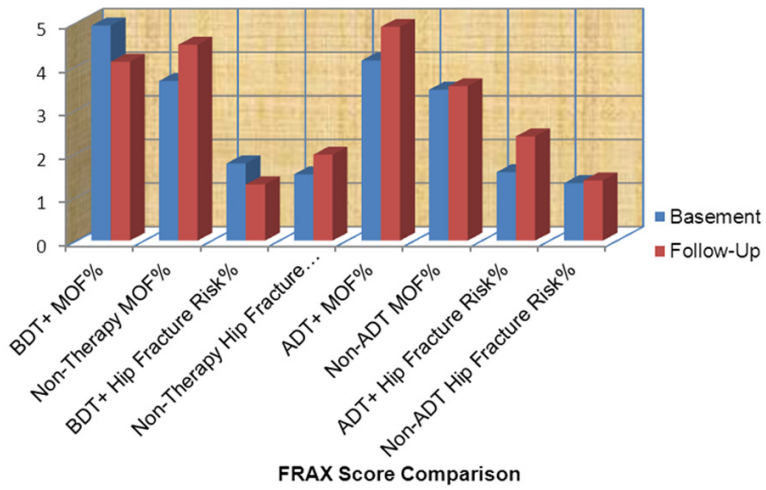

Figure 1. Baseline and post treatment FRAX Score in Bone therapy versus No-treatment and ADT versus Non-ADT group.

parison of ADT and non-ADT groups in that study proved that the MOF ≥20% and hip fracture risk ≥3% were more common in patients who received ADT (5.3% and 63.1%) than in the non-ADT group (3.3% and 47.4), respectively. In our series, baseline MOF and hip fracture risk were 4.49 and 1.68, respectively. Reduction of both MOF and hip fracture risk % were seen in bone-therapy group, while worsening was noted in non-therapy and ADT group. These results show that patients on ADT had higher chances of future fracture risk than patients who didn't receive ADT. Hip fracture risk (≥3% i.e. treatment threshold) accounted for larger proportion of patients than did major osteoporotic fracture risk (≥20%) [21.2% and 2.5%, respectively].

Few studies have evaluated the impact of ADT on QoL of advanced prostate cancer patients. Various adverse effects associated with ADT like erectile dysfunction, hot flashes, osteopenia, fatigue, breast tenderness and impairment of cognitive function lead to worsening of quality of life in these patients. Dacal et al showed that those patients receiving ADT had significantly poor QoL including physical function [27]. Green et al in a study of 65 patients underwent ADT also showed significant decrease in QoL scores [28]. We also observed statistically and clinically significant worsening of QoL in PWB, EWB, prostate cancer subscale, FACT-P Total, FACT-P TOI and

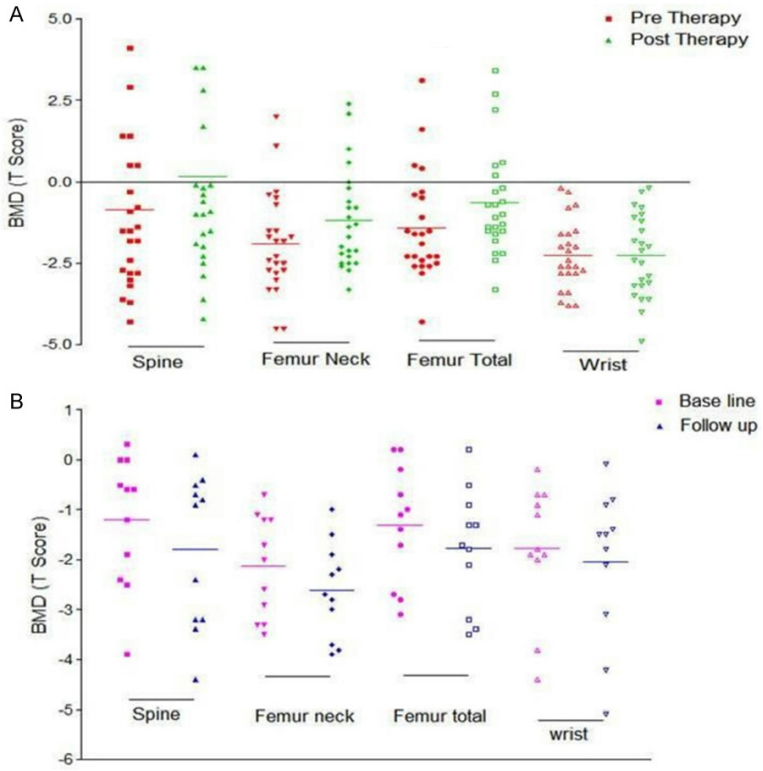

Figure 2. A: Standard error plot showing comparison of T-Score (BMD) between pre and post bisphosphonate therapy. B: Comarison of baseline and follow up T-Score (BMD) in patients on ADT without bisphosphonate therapy.

Table 5. Baseline QoL (FACT-P) questionnaire and related index scores

FACT-P Domain Score	No of Items	Theortical Range	Baseline (Mean ± SD)	Established MCID range
PWB Score	7	0-28	17.19 ± 5.52	2-3a,b
SWB Score	7	0-28	14.93 ± 2.78	2-3a,b
EWB Score	6	0-24	14.39 ± 5.06	2-3a,b
FWB Score	7	0-28	14.34 ± 4.71	2-3a,b
PCS Score	12	0-48	27.28 ± 5.18	2-3a
FACT-P Total	39	0-156	87.73 ± 19.88	6-10a
FACT P TOI Score	26	0-96	56.57 ± 14.21	5-9a
FAPSI	8	0-32	20.96 ± 13.23	2-3a

Abbreviation: FACT-P: Functional Assessment of Cancer Therapy-Prostate; PWB: Physical Well Being; SWB: Social Well Being; EWB: Emotional Well Being; FWB: Functional Well Being; FACT-P TOI: Functional Assessment of Cancer Therapy-Trial Outcome Index; PCS: Prostate cancer subscale; FAPSI: FACT Advanced Prostate Symptom Index; MCID: Minimal clinically important difference; Reference: a-Cella et al [18], b-Yost and Eton [16].

FAPSI scores in our study subjects who received androgen deprivation therapy.

Saad et al conducted a study to evaluate impact of Zolendronic acid administration (3 weekly for 15 months) on quality of life in 643 patients with hormone-refractory metastatic cancer prostate [17]. Total FACT-G and EURO-QOL scores deteriorated from baseline to last measurement with no statistically significant differences among all three groups (ZA 4 mg/ZA 8 mg/placebo). In the present study, statistically and clinically significant improvement was noted in physical well-being domain in BDT group but overall FACT-P scores remained same.

To the best of our knowledge, this is the first study which focuses collectively on bone health, implication of FRAX tool and QoL in prostate cancer patients. Optimal bone health management and maintaining better QoL is important for this population subgroup as we found that most of the patients presenting to us have a high burden and stage disease.

Conclusion

FRAX tool for predicting fracture risk in prostate cancer is better modality than BMD or T score alone, as it includes CRF, age, ethnicity and BMI. It accurately predicts future skeletal related events in majority (80%) of cases. The patients on the ADT had significantly higher FRAX score or more chances of future fracture risks. The FRAX tool is advantageous in identifying the patients who require early intervention or bone directed therapy to decrease skeletal related events. Administration of ADT has deleterious effects on patient's quality of life (FACT-P). Statistically and clinically significant improvement was noted in physical well-being domain in BDT group but overall FACT-P scores remained stable.

Table 6. Impact of ADT and BDT on QoL FACT-P questionnaire scores

FACT-P (Mean ± SD)		Baseline	Follow-Up	Difference	*p* Value
Impact of Androgen Deprivation Therapy on QoL (FACT-P)					
PWB	ADT	17.41 ± 5.62	12.96 ± 5.65	-4.45 ± 2.88#	<0.001*
	Non-ADT	15.87 ± 6.22	15.25 ± 5.77	-0.62 ± 2.19	0.5
SWB	ADT	14.98 ± 2.79	13.92 ± 3.08	-1.06 ± 1.52	0.8
	Non-ADT	12.87 ± 3.09	13.63 ± 3.77	+0.76 ± 0.70	0.7
EWB	ADT	15.64 ± 5.02	11.66 ± 4.80	-3.98 ± 2.98#	<0.001*
	Non-ADT	12.50 ± 5.80	12.87 ± 5.56	+0.37 ± 1.76	0.56
FWB	ADT	14.22 ± 4.95	16.80 ± 4.65	+2.58 ± 2.81#	<0.05*
	Non-ADT	14.75 ± 5.41	15.87 ± 5.61	+1.12 ± 1.75	0.07
PCS	ADT	28.26 ± 5.19	24.12 ± 4.49	-4.14 ± 3.08#	<0.001*
	Non-ADT	26.0 ± 5.52	24.62 ± 5.18	-1.38 ± 1.59	0.09
FACT-P Total	ADT	90.51 ± 20.03	79.46 ± 19.89	-11.05 ± 3.86#	<0.001*
	Non-ADT	81.99 ± 14.24	82.24 ± 14.64	-0.25 ± 4.74	0.9
FACT P TOI	ADT	59.89 ± 14.15	53.88 ± 18.71	-6.01 ± 3.67#	<0.001*
	Non-ADT	56.62 ± 9.63	55.75 ± 9.33	-0.87 ± 3.64	0.52
FAPSI	ADT	21.53 ± 6.21	18.23 ± 5.87	+3.3 ± 2.25#	<0.05*
	Non-ADT	19.34 ± 5.11	19.95 ± 5.26	+0.61 ± 2.1	0.8
Impact of Bone Directed Therapy on QoL (FACT-P)					
PWB	BDT	16.12 ± 5.67	19.21 ± 6.12	+3.09 ± 1.89#	<0.001*
	Non-BDT	16.96 ± 5.22	15.32 ± 6.11	-1.64 ± 1.52	<0.05*
SWB	BDT	13.54 ± 2.34	14.78 ± 3.23	+1.24 ± 0.96	0.087
	Non-BDT	13.12 ± 2.55	12.86 ± 2.76	-0.26 ± 0.56	0.4
EWB	BDT	14.3 ± 5.5	15.51 ± 4.87	+1.21 ± 0.98	0.093
	Non-BDT	14.15 ± 5.19	14.22 ± 4.43	+0.07 ± 0.21	0.3
FWB	BDT	14.55 ± 5.34	16.20 ± 5.56	+1.65 ± 2.15	<0.05*
	Non-BDT	14.72 ± 4.98	13.25 ± 5.57	-1.47 ± 1.86	<0.05*
PCS	BDT	29.22 ± 6.54	27.43 ± 5.23	-1.79 ± 1.11	0.45
	Non-BDT	28.45 ± 5.98	27.22 ± 4.76	-1.23 ± 1.24	0.54
FACT-P Total	BDT	87.73 ± 16.32	93.13 ± 18.53	+5.4 ± 4.76	<0.05*
	Non-BDT	87.4 ± 17.43	82.87 ± 14.29	-4.53 ± 2.45	<0.05*
FACT P TOI	BDT	59.89 ± 15.3	62.84 ± 14.22	+2.95 ± 3.23	<0.05*
	Non-BDT	60.13 ± 10.23	55.79 ± 16.76	-4.34 ± 2.87	<0.05*
FAPSI	BDT	20.56 ± 5.14	22.13 ± 6.36	+1.57 ± 2.41	<0.05*
	Non-BDT	19.87 ± 5.02	17.28 ± 4.43	-2.59 ± 2.83#	<0.05*

**Statistically Significant*, #Clinically Significant.

Disclosure of conflict of interest

None.

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