Impact of skeletal-related events on survival in patients with metastatic prostate cancer prescribed androgen deprivation therapy

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ABSTRACT

Objective: To investigate the impact of skeletal-related events on survival in patients with metastatic prostate cancer prescribed long-term androgen deprivation therapy.

Methods: This historical cohort study was conducted in two hospitals in Hong Kong. Patients who were diagnosed with metastatic prostate cancer and prescribed androgen deprivation therapy between January 2006 and December 2011 were included. Details of skeletal-related events and mortality were examined.

Results: The median follow-up was 28 (range, 1-97) months. Of 119 patients, 52 (43.7%) developed skeletal-related events throughout the study, and the majority received bone irradiation for pain control. The median actuarial overall survival and cancer-specific survival for patients with skeletal-related events were significantly shorter than those without skeletal-related events (23 vs 48 months, P=0.003 and 26 vs 97 months, P<0.001, respectively). Multivariate analysis revealed that the adjusted hazard ratio of presence of skeletal-related events on overall and cancer-specific survival was 2.73 (95% confidence interval, 1.46-5.10; P=0.002) and 3.92 (95% confidence interval, 1.87-8.23; P<0.001), respectively. A prostate-specific antigen nadir of >4 ng/mL was an independent poor prognostic factor for overall and cancer-specific survival after development of skeletal-related events (hazard ratio=10.42; 95% confidence interval, 2.10-51.66 and hazard ratio=10.54; 95% confidence interval, 1.94-57.28, respectively).

Conclusions: Skeletal-related events were common in men with metastatic prostate cancer. This is the first reported study to show that a skeletal-related event is an independent prognostic factor in overall and cancer-specific survival in patients with metastatic prostate cancer prescribed androgen deprivation therapy. A prostate-specific antigen nadir of >4 ng/mL is an independent poor prognostic factor for overall and cancer-specific survival following development of skeletal-related events.

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New knowledge added by this study

- Skeletal-related events (SREs) in patients with metastatic prostate cancer significantly worsen their prognosis.
- The prevalence of SREs in patients with metastatic prostate cancer is high.

Implications for clinical practice or policy

- Medications such as bisphosphonate therapy and receptor activator for nuclear factor κB ligand inhibitor should be considered to prevent SREs in patients with metastatic prostate cancer.

Introduction

Prostate cancer is the most common cancer diagnosed in men in developed countries. In the United States, there were 240 890 estimated new cases in 2011, accounting for 29% of all new cancers in men and over 33 000 deaths.[1] According to the Hong Kong Cancer Registry in 2012, prostate cancer was the third most common cancer in men.[2]

The overall incidence of advanced-stage prostate cancer has declined in recent years, probably due to early detection and treatment following application of prostate-specific antigen (PSA) for prostate cancer screening.[3] Nonetheless it has been shown that approximately 4% of patients present with metastatic disease at the time of diagnosis[1] and 5% present with localised or regional disease that

eventually metastasises.[4]

Bone is the major metastatic site of prostate cancer, and has been observed in 90% of patients during autopsy.[4] Common sites of metastases include the vertebrae, pelvis, long bones, ribs, and skull. Bone metastases cause major morbidity in patients with prostate cancer. They weaken the structural integrity of bone, leading to an increased risk for skeletal-related events (SREs) such as pathological fracture, spinal cord compression, and severe bone pain requiring palliative radiotherapy or surgery to bone.[5,6]

The prognosis of localised and regional prostate cancer is excellent while that of metastatic prostate cancer is poor. The 5-year survival rate in patients with metastatic disease has been reported to be as low as 30%[1] with a mean survival of 24 to 48 months.[7,8]

Evidence of the importance of SREs for survival in metastatic prostate cancer is limited. Oefelein et al[9] evaluated men with prostate cancer who were prescribed androgen deprivation therapy (ADT) regardless of staging. The relative risk of skeletal fracture for mortality was 7.4. In another retrospective study, patients with bone metastasis from different primary tumours were analysed.[10] In the subgroup analysis, pathological fracture increased risk of death by 20% in patients with prostate cancer although the authors failed to demonstrate statistical significance.[10] A population-based cohort study demonstrated that mortality in men with metastatic prostate cancer and SREs were approximately twice that of patients with no SREs.[11] Treatments for prostate cancer were, however, not recorded or analysed in the study.[11]

The aim of this study was to investigate the impact of SREs on survival, specifically in patients with carcinoma of the prostate with bone metastasis prescribed long-term ADT. Prognostic factors of survival in patients with SREs were also investigated.

正接受雄激素阻斷治療的轉移性前列腺癌患者，其骨骼相關事件對存活率的影響

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目的：探討骨骼相關事件對正接受雄激素阻斷治療的轉移性前列腺癌患者的存活率的影響。

方法：本歷史隊列研究於香港兩間醫院內進行。2006年1月至2011年12月期間接受雄激素阻斷治療的轉移性前列腺癌患者均被列入研究範圍。檢視骨骼相關事件的詳細資料及死亡率。

結果：中位隨訪時間為28個月（介乎1至97個月）。研究期間，119名患者中有52人（43.7%）出現骨骼相關事件，他們大部分接受骨腫瘤放射治療以減輕疼痛。總生存率和癌症特異性生存率中位數方面，有骨骼相關事件發生的比沒有骨骼相關事件發生的明顯較短（總生存率：23比48個月，P=0.003；癌症特異性生存率：26比97個月，P<0.001）。多變量分析顯示有骨骼相關事件發生對於總生存率和癌症特異性生存率的調整風險比分別為2.73（95%置信區間：1.46-5.10；P=0.002）和3.92（95%置信區間：1.87-8.23；P<0.001）。骨骼相關事件發生後，最低值前列腺特異抗原（PSA）>4 ng/mL是總生存率和癌症特異性生存率的獨立不良預後因素，風險比分別為10.42（95%置信區間：2.10-51.66）和10.54（95%置信區間：1.94-57.28）。

結論：骨骼相關事件常見於轉移性前列腺癌患者身上。這是首個研究報告顯示骨骼相關事件是影響正接受雄激素阻斷治療的轉移性前列腺癌患者的總生存率和癌症特異性生存率的獨立不良預後因素。骨骼相關事件發生後，最低值前列腺特異抗原（PSA）>4 ng/mL是總生存率和癌症特異性生存率的獨立不良預後因素。

Methods

The study period was between 1 January 2006 and 31 December 2011. Patients who were diagnosed with prostate cancer and bone metastasis and who underwent either bilateral orchiectomy or were prescribed a first dose of luteinising hormone releasing hormone analogue (LHRHa) injection during the study period at either Queen Mary Hospital or Tung Wah Hospital in Hong Kong were included. Patients were followed up until death or the last follow-up taken on 31 March 2014.

Diagnosis of carcinoma of the prostate was made following transrectal ultrasound-guided prostate biopsy, incidental histological findings of transurethral resection of a prostate specimen, biochemical diagnosis of PSA of >100 ng/mL, or other histological evidence such as bone biopsy in patients who presented with pathological fracture. Presence of bone metastasis was confirmed either by bone scan or by cross-sectional imaging such as computed tomography (CT) or magnetic resonance imaging (MRI). Patients who had evidence of bone metastases at four or more sites or visceral metastasis were regarded as having high-volume disease. Patients with medical castration were prescribed regular LHRHa injection every 3 months. Patients with underlying metabolic bone disease were excluded from study. In this study, SRE was defined in patients who developed pathological fractures, cord compression related to bone metastasis, and/or those who received irradiation or prophylactic surgery to bone metastasis.[6,7] Castration-resistant prostate cancer (CRPC) was diagnosed when there were at least two consecutive rises in PSA, at least 1 week apart, with PSA of >2 ng/mL.

Data were collected from the electronic clinical management system database in the government health care system. Patients who underwent bilateral orchiectomy or received the first dose of LHRHa within the study period were shortlisted, reviewed,

TABLE 1. Baseline characteristics of and treatments received in patients with and without SREs

	SREs		P value
	Yes (n=52)	No (n=67)	
Baseline characteristic			
Mean age at diagnosis (years)	73.1	76.3	0.04‡
Median total Gleason score	9	9	-
Initial PSA (ng/mL)			0.30‡
Mean	1077.1	683.8	
Median	252.0	151	
PSA nadir (ng/mL)			0.44‡
Mean	42.7	31.0	
Median	3.0	1.5	
Mean follow-up (months)	28.5	39.1	0.02‡
Mode of ADT			0.52§
LHRH analogue	27	34	
Bilateral orchiectomy	25*	33†	
CRPC status	44 (84.6%)	44 (65.7%)	0.02§
ECOG grade 2 or above	12 (23.1%)	11 (16.4%)	0.36§
High-volume metastasis	42 (80.8%)	46 (68.7%)	0.14§
Bone pain at the start of ADT	22 (42.3%)	18 (26.9%)	0.08§
Treatment			
Chemotherapy	2 (3.8%)	0	0.18¶
Abiraterone	1 (1.9%)	1 (1.5%)	-
Bisphosphonate	4 (7.7%)	7 (10.4%)	0.75¶
RANKL inhibitor	1 (1.9%)	1 (1.5%)	-
Hormonal manipulation			
Bicalutamide	11 (21.2%)	17 (25.4%)	0.59§
Flutamide	28 (53.9%)	48 (71.6%)	0.07§
Ketoconazole	7 (13.5%)	7 (10.4%)	0.77¶
Cyproterone acetate	4 (7.7%)	5 (7.5%)	0.53¶
Calcium supplement	5 (9.6%)	12 (18.0%)	0.29¶

Abbreviations: ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; LHRH = luteinising hormone releasing hormone; PSA = prostate-specific antigen; RANKL = receptor activator for nuclear factor κB ligand; SREs = skeletal-related events

* 5 Patients in SRE-positive group changed to bilateral orchiectomy subsequently

† 2 Patients in SRE-negative group changed to bilateral orchiectomy subsequently

‡ Independent sample *t* test

§ Pearson Chi squared test

¶ Fisher's exact test

and then recruited as eligible patients according to the inclusion criteria. Data were collected from in-patient and out-patient records and included age at diagnosis; performance status; any bone pain at diagnosis; imaging such as bone scan, CT, and MRI; volume of metastasis; details of ADT and SREs; history of metabolic bone disease; CRPC status; treatment received for prostate cancer; and date and causes of death. Two authors (KW Wong and CF Tsang) abstracted the data and were not blinded to the outcomes.

Data were analysed using the Statistical Package for the Social Sciences (Windows version 21.0; SPSS Inc, Chicago [IL], US). The primary outcome was survival time, calculated from the date of start of ADT until death or the last follow-up. Survival was described with Kaplan-Meier curves. Univariate and multivariate analyses were performed with Cox regression model to predict prognostic factors for survival. The dependent variables were time to death (overall and cancer-specific), defined as the time from the start of ADT to death. Prognostic variables significant in the univariate analyses were entered into the multivariate Cox regression models.

Results

A total of 119 eligible patients were identified within the study period. The mean age at prostate cancer diagnosis was 75 (range, 49-94) years. Initial ADT was by bilateral orchiectomy or LHRHa injection in 58 and 61 patients, respectively, with seven patients subsequently switched from injection to bilateral orchiectomy. The median time of follow-up was 28 (range, 1-97) months. No patient was lost to follow-up during the study.

The baseline characteristics of patients are summarised in Table 1. When stratified according to the presence of SREs, the two groups did not differ significantly in total Gleason score of prostate cancer, PSA level at the time of diagnosis, PSA nadir, Eastern Cooperative Oncology Group (ECOG) performance status, volume of metastasis, presence of bone pain at the start of ADT, or mode of ADT. Patients with SREs were slightly younger at the time of diagnosis (73.1 vs 76.3 years; P=0.04) and had a shorter mean follow-up time (28.5 vs 39.1 months; P=0.02). More patients with SREs developed CRPC when compared with those who did not have SREs (84.6% vs 65.7%; P=0.02).

The treatment received by patients with and without SREs were compared (Table 1). Only treatments received prior to development of SREs were included in Table 1 to analyse whether the baseline characteristics of treatment differed before the development of SREs. The proportion of patients prescribed chemotherapy, bicalutamide, flutamide, ketoconazole, cyproterone acetate, and calcium supplement was statistically similar for the two groups. Only two patients in each group received abiraterone and denosumab therapy. No patient received sipuleucel-T, cabazitaxel, enzalutamide, radium-223, or other novel treatment for prostate cancer throughout the study period.

Incidence of skeletal-related events

Of 119 patients, 52 (43.7%) developed SREs. A total of 69 SREs were recorded—36 (69.2%) patients had

one SRE, 15 (28.8%) patients had two SREs, and one patient had three SREs. Irradiation to bone for pain control accounted for 47 (68.1%) events; 14 (20.3%) events were cord compression and there were eight (11.6%) events of pathological fractures without cord compression. No patient underwent prophylactic surgery for bone metastasis. With regard to timing of SRE development, 13 (10.9%) patients had SRE as the initial presentation of metastatic prostate cancer. The overall cumulative incidence of SREs at 1 year and 5 years of diagnosis was 23.5% and 42.9%, respectively (Fig 1).

Castration-resistant status and survival

The median time required to develop CRPC status from the start of ADT was 9 months (Fig 2a). When

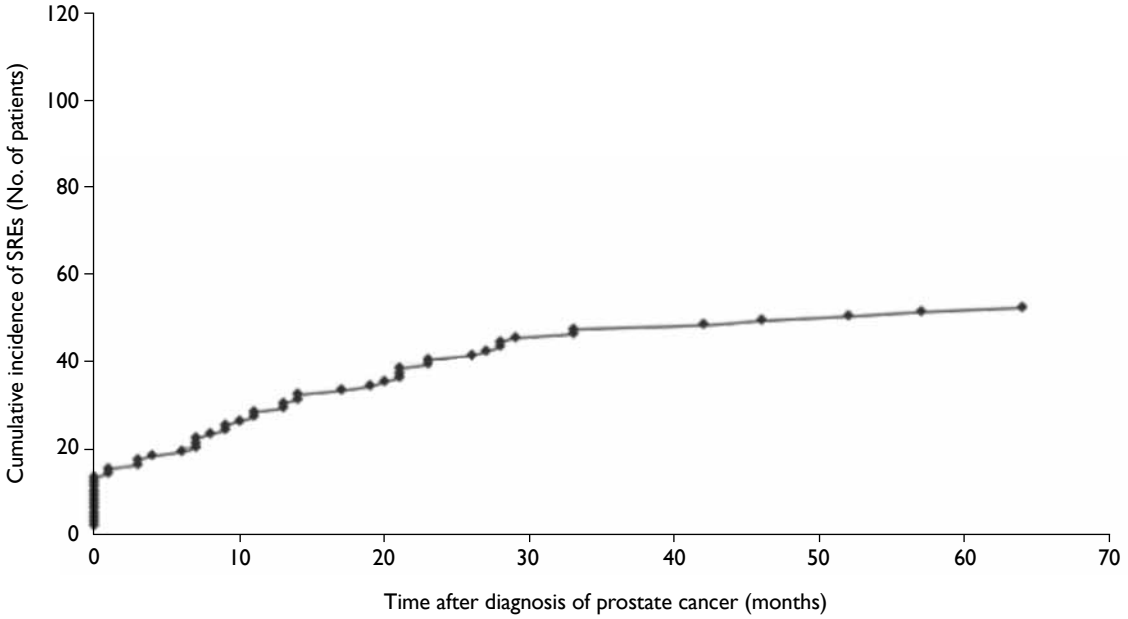

FIG 1. Cumulative incidence of skeletal-related events (SREs) in men with prostate cancer

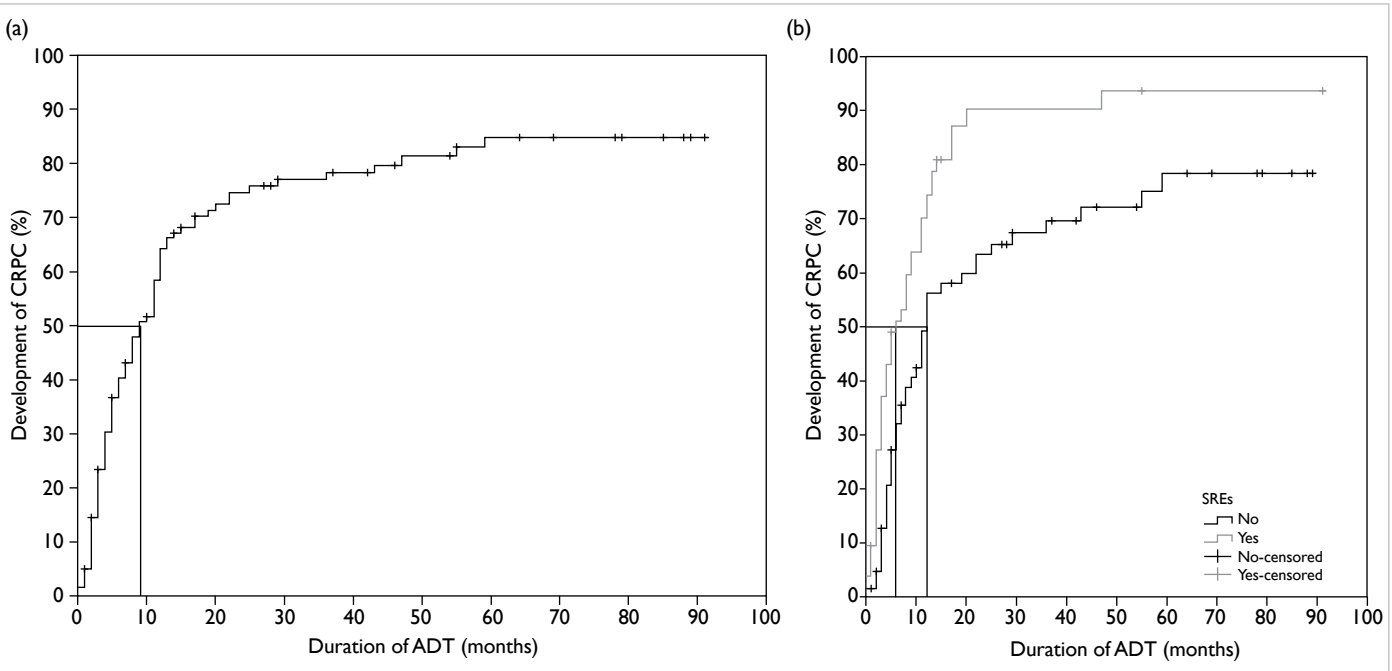

FIG 2. (a and b) Kaplan-Meier curves of patients developing CRPC status, with (b) stratified according to the presence of SREs
Abbreviations: ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; SREs = skeletal-related events

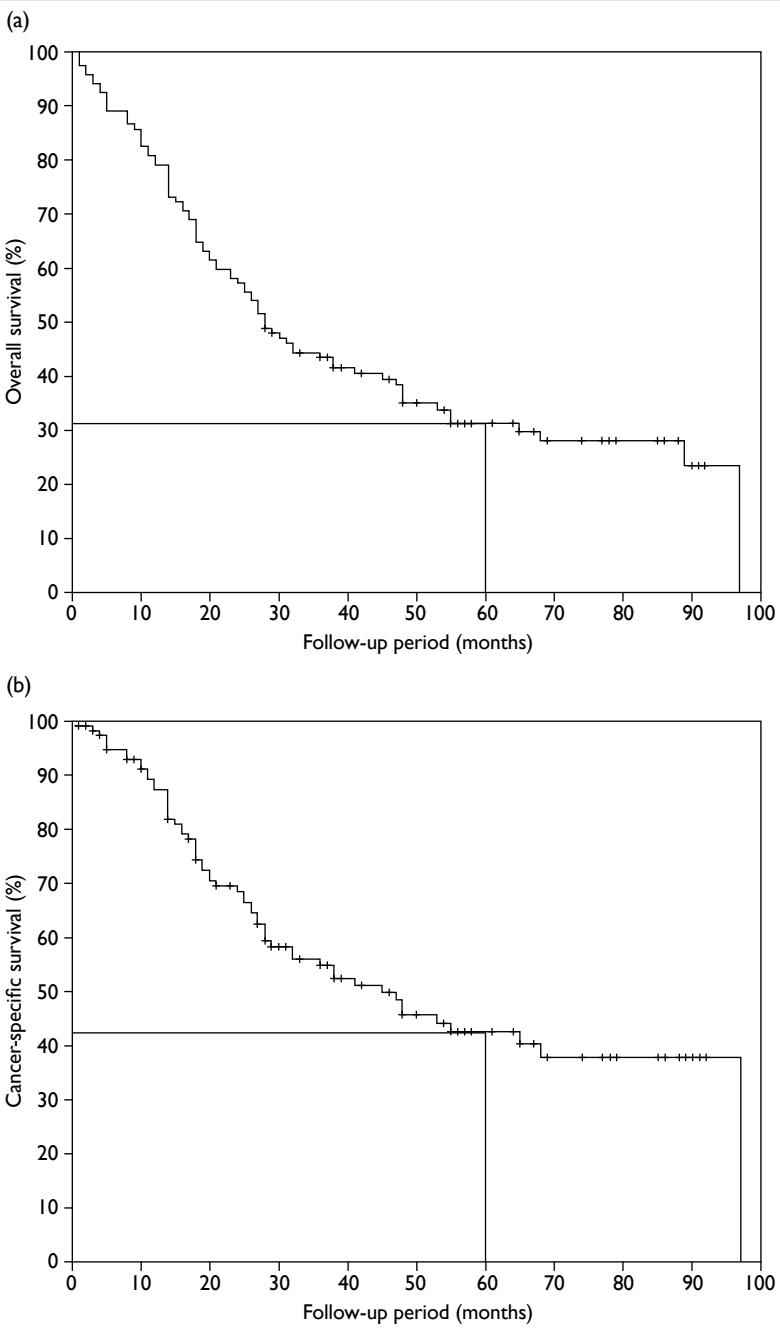

FIG 3. (a) Overall and (b) cancer-specific survival curves of all patients

stratified according to the presence of SREs, the median time to CRPC status from ADT initiation was significantly shorter in patients with SREs than in those without (6 vs 12 months, log-rank test, P=0.001; Fig 2b).

The actuarial overall survival (OS) and cancer-specific survival (CSS) curves are shown in Figure 3. The 5-year actuarial OS and CSS was 32% and 43%, respectively. Among men without SREs, 38 (56.7%) patients died, compared with 44 (84.6%) patients in the SRE group. When stratified according to presence of SREs (Fig 4), the median OS and CSS for patients with SREs were significantly shorter than that for patients without SREs (log-rank test: 23 vs 48 months, P=0.003 and 26 vs 97 months, P<0.001, respectively).

Risk factors for survival

Various possible factors that could affect survival were analysed (Table 2a). All treatments for prostate cancer received both before and after SRE were included. Univariate analysis revealed that in terms of OS, presence of SREs (P=0.003), PSA nadir of >4 ng/mL (P<0.001), ECOG grade 2 or above (P=0.01), and calcium supplement (P=0.03) were significant risk factors. On multivariate analysis, only the presence of SREs and PSA nadir of >4 ng/mL remained statistically significant, with hazard ratio (HR) of 2.73 (95% confidence interval [CI], 1.46-5.10; P=0.002) and 3.01 (95% CI, 1.54-5.90; P=0.001), respectively. In terms of CSS, presence of SREs (P<0.001), PSA nadir of >4 ng/mL (P=0.004), and ketoconazole therapy (P=0.05) remained significant risk factors on both univariate and multivariate analyses. The HR for the presence of SREs, PSA nadir of >4 ng/mL, and ketoconazole therapy was 3.92 (95% CI, 1.87-8.23; P<0.001), 2.98 (95% CI, 1.43-6.23; P=0.004), and 2.10 (95% CI, 1.01-4.38; P=0.05), respectively.

The median survival period after occurrence of SRE was 11.5 months. A post-hoc analysis for OS and CSS after SRE revealed PSA nadir of >4 ng/mL as the only independent predictor for survival after SRE in both univariate and multivariate analyses, with HR of 10.42 (95% CI, 2.10-51.66; P=0.004) and 10.54 (95% CI, 1.94-57.28; P=0.006), respectively (Table 2b).

Discussion

The importance of SREs in survival of patients with prostate cancer with different disease stage and treatments was studied[10-12] but not specifically in patients with metastatic prostate cancer prescribed ADT. This group of patients was selected because patients with metastatic prostate cancer are at risk of developing SREs.[11] In addition, ADT is the standard first-line treatment for metastatic prostate cancer.[12] It has been proven to provide a clear benefit in terms of preventing SREs.[13] Focusing on patients who are prescribed ADT can ensure that the effect of ADT in preventing SREs is balanced out during analysis. A study by Oefelein et al[9] showed that skeletal fractures negatively correlate with OS in men with prostate cancer prescribed ADT, but it included patients with localised disease and all kinds of fracture including osteoporotic fractures. Berruti et al[4] reported the

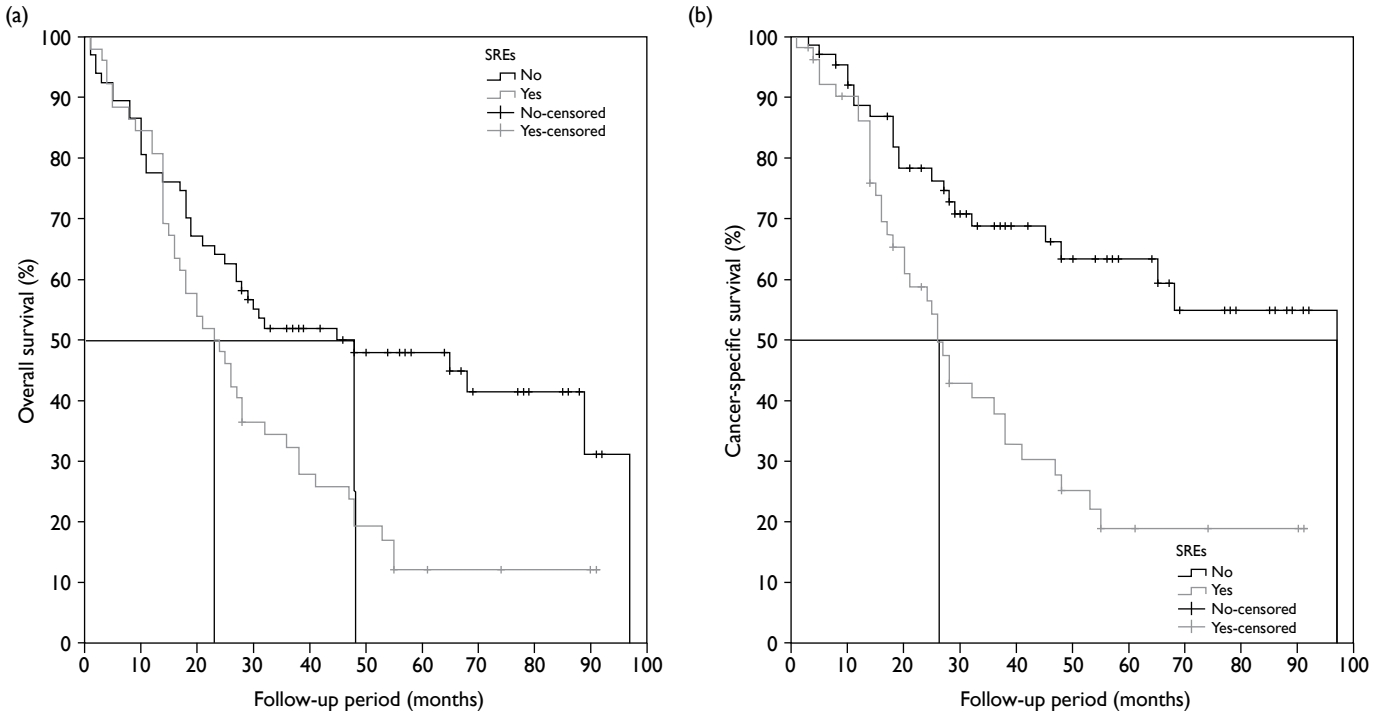

FIG 4. Kaplan-Meier survival curves of all patients on (a) overall survival and (b) cancer-specific survival, stratified according to the presence of skeletal-related events (SREs)

incidence of skeletal complications in patients with CRPC and bone metastasis, but failed to demonstrate any difference in survival between patients with and without skeletal complications. Multivariate analysis was not performed on survival either. Daniell et al[14,15] reported eight fractures in 49 patients with prostate cancer at various times following orchiectomy but did not take into account the preventive effect of ADT in SREs.[13] In our study, patients with SREs had much worse OS and CSS when compared with those without SREs (23 vs 48 months and 26 vs 97 months, respectively), and remained significantly so after multivariate Cox regression analysis. To our knowledge, this is the first reported study to investigate the impact of SREs on survival in this homogeneous group of patients.

The baseline characteristics were similar between patients with or without SREs except that those with SREs were slightly younger at diagnosis (73.1 vs 76.3 years; P=0.04). This, however, does not affect data interpretation since age at diagnosis was not a significant factor in subsequent analyses for both OS and CSS. In our targeted group of patients with metastatic prostate cancer prescribed ADT, the presence of SREs was first shown to be an independent predictive factor for OS and CSS with a notable HR of 2.73 and 3.92 respectively, taking into account baseline cancer characteristics, ECOG performance status, development of CRPC status, and different treatments received. In addition, PSA nadir was found to be another predictive factor for OS and CSS. This finding has been reported in previous studies[16] although most included patients who were heterogeneous in terms of clinical stage of prostate cancer. Kitagawa et al[16] showed that PSA nadir of >4 ng/mL was associated with HR of 5.22 (95% CI, 2.757-9.89; P<0.001) in OS in patients with prostate cancer. The cohort, however, included patients with either locally advanced non-metastatic disease or metastatic disease. Park et al[17] reported that a higher PSA nadir level correlated with shorter CSS. Similar to the previous study,[16] patients with lymph node metastasis were also included. In another retrospective study,[18] a high PSA nadir level was shown to be associated with shorter OS in a homogeneous group of patients with metastatic prostate cancer prescribed ADT. Nonetheless only 87 patients were included in the study. In our study, in patients who developed SREs, PSA nadir was the only predictive factor for both OS and CSS with HR of 10.42 and 10.54, respectively. This is previously unreported.

Various treatments have been proven to improve OS in patients with metastatic prostate cancer,

TABLE 2. Cox regression analysis of different factors on overall and cancer-specific survival in (a) all patients and (b) patients with SREs

(a)

Factor	Overall survival				Cancer-specific survival			
	P value		Hazard ratio	95% CI	P value		Hazard ratio	95% CI
	Univariate	Multivariate			Univariate	Multivariate		
Presence of SREs	0.003	0.002	2.73	1.46-5.10	<0.001	<0.001	3.92	1.87-8.23
Age at diagnosis >70 years	0.402				0.45			
Initial PSA level >100 ng/mL	0.055				0.41			
PSA nadir >4 ng/mL	<0.001	0.001	3.01	1.54-5.90	<0.001	0.004	2.98	1.43-6.23
Gleason score ≥8	0.33				0.11			
CRPC status	0.09				0.01	0.07		
ECOG grade 2 or above	0.01	0.10			0.10			
High-volume metastasis	0.31				0.27			
Bone pain at the start of ADT	0.69				0.54			
Chemotherapy	0.24				0.39			
Bisphosphonate	0.64				0.23			
Bicalutamide	0.39				0.92			
Flutamide	0.83				0.72			
Ketoconazole	0.09				0.01	0.05	2.10	1.01-4.38
Cyproterone acetate	0.88				0.77			
Calcium supplement	0.03	0.13			0.30			

(b)

Factor	Overall survival				Cancer-specific survival			
	P value		Hazard ratio	95% CI	P value		Hazard ratio	95% CI
	Univariate	Multivariate			Univariate	Multivariate		
Timing of SREs (≤12 months after commencement of ADT)	0.55				0.34			
No. of SRE >1	0.40				0.57			
Age at diagnosis >70 years	0.56				0.50			
Initial PSA level >100 ng/mL	0.60				0.87			
PSA nadir >4 ng/mL	0.001	0.004	10.42	2.10-51.66	0.02	0.006	10.54	1.94-57.28
Gleason score ≥8	0.06				0.051			
CRPC status	0.53				0.98			
ECOG grade 2 or above	0.60				0.24			
High-volume metastasis	0.06				0.14			
Bone pain at the start of ADT	0.33				0.14			
Chemotherapy	0.05	0.98			0.08			
Bisphosphonate	0.72				0.61			
Bicalutamide	0.26				0.46			
Flutamide	0.43				0.19			
Ketoconazole	0.48				0.40			
Cyproterone acetate	0.18				0.20			
Calcium supplement	0.67				0.29			
Prophylactic radiation	0.38				0.31			
Cord compression	0.61				0.72			
Pathological fracture	0.06				0.04	0.33		

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; CRPC = castration-resistant prostate cancer; ECOG = Eastern Cooperative Oncology Group; PSA = prostate-specific antigen; SRE = skeletal-related events

including docetaxel,[19] cabazitaxel,[20] abiraterone,[21-23] sipuleucel-T,[24] and enzalutamide.[25,26] Various bone-modulating agents have also been studied for patients with bone metastasis. Bisphosphonate therapy has been shown to improve bone mineral density and quality of life,[27,28] and reduce the incidence of SREs in patients with metastatic CRPC in a randomised controlled trial (RCT), although there was no proven survival benefit.[6] The receptor activator for nuclear factor κB ligand (RANKL) inhibitor denosumab is another bone-modulating agent proven to reduce the incidence of SREs in metastatic CRPC patients but also without survival benefit.[29,30] Radium-223, a bone-seeking calcium-mimicking alpha emitter, was shown in a RCT[31] to not only delay first symptomatic SRE, but also improve OS. Therefore, when investigating the incidence of SRE and survival in these groups of patients, the aforementioned treatments have to be taken into account. In our study, treatments received by patients without SREs and in patients prior to development of SREs were statistically similar (Table 1). The number of patients prescribed chemotherapy or novel hormonal agents was relatively small in our series. Sipuleucel-T, enzalutamide, and radium-223 were not available in this locality during the study period. Denosumab and abiraterone therapies were used by only two patients in each group as these medications were not subsidised by the local government and were not affordable for many patients. Docetaxel has been shown to improve bone pain and OS in a phase III RCT.[19] After development of SREs, six more patients received chemotherapy in our series. All but one patient received docetaxel. The remaining patient received estramustine and etoposide before development of SREs. The fact that all patients prescribed docetaxel were in the SRE group suggests that its potential benefit in improving OS has been offset by SREs and so this is not a confounding factor in our study.

The overall prevalence of bisphosphonate therapy was low (17%). Nine patients received bisphosphonate therapy only after development of SREs. In fact, in patients receiving bisphosphonate therapy, two out of seven patients without SREs and six out of 13 patients with SREs only received one dose of bisphosphonate due to various reasons, including side-effects of the medication, affordability, and early mortality after medication. With the heterogeneous timing of start and duration of therapy, we cannot accurately comment on the benefit of bisphosphonate in our series. No further patient received RANKL inhibitor or abiraterone after development of SREs.

Since the pre-chemotherapy era, the concept of complete androgen blockade with classic hormonal manipulation by both steroidal anti-androgen, such as cyproterone acetate,[32] and non-steroidal anti-androgen (such as bicalutamide,[33] flutamide,[34] and nilutamide[35]) has been widely adopted when patients develop CRPC status. This practice remains in use in this locality despite the fact that no associated survival benefit has ever been reported[12] due to the side-effects and availabilities of aforementioned novel treatments for CRPC. Ketoconazole, a broad-spectrum imidazole antifungal agent, was previously the hormonal treatment of choice after anti-androgen withdrawal for complete androgen blockade.[35] It works by preventing adrenal steroidogenesis with inhibition of the enzyme cytochrome P450 14 alpha-demethylase.[36] Bicalutamide, flutamide, cyproterone acetate, and ketoconazole were used in our centre for hormonal manipulation. Interestingly, ketoconazole use appeared to have a deleterious effect on CSS even with multivariate Cox regression in our study. This result contradicts that of a phase III RCT[35] which showed positive PSA and objective response but no survival benefit or harm. As our study was retrospective in nature, the implication of ketoconazole use is doubtful based on the results of this study and requires further evaluation.

With a median follow-up of 28 months, the incidence of SREs in men with metastatic prostate cancer was high (43.7%) and is comparable with 43.6% reported from the Danish group population-based cohort study with similar follow-up period.[11] The median time to CRPC status from first ADT was 9 months, which is 5.7 months shorter than the control arm of the CHAARTED trial.[37] This may be explained by the fact that the CHAARTED trial included patients prescribed ADT for less than 24 months but those with disease progression within 12 months were excluded.

We obtained local data of the natural history of metastatic prostate cancer with or without SREs and the impact of SREs on survival. A PSA nadir of >4 ng/mL was an independent poor prognostic factor for OS and CSS after development of SREs. Its clinical use in terms of predicting prognosis and patient counselling is highly feasible. Based on our results, prevention of SREs in patients with metastatic prostate cancer may translate to longer survival. Nonetheless most bone-targeting therapies, including bisphosphonate therapy and RANKL inhibitors, have failed to demonstrate survival benefit even though they prevent SREs.[6,30,34,38] Radium-223 appears to hold promise as it delays symptomatic SREs by 5.8 months and improves OS by 3.8 months in metastatic prostate cancer patients.[31] Further studies are needed in this field.

There are several limitations in this study. This was a retrospective study with small sample size so statistical power is limited. There are even fewer patients in post-hoc analysis. The data collected may not accurately reflect the condition of patients because the follow-up protocol was not standardised.

Furthermore, the data abstraction process was not blinded. For better presentation of data, several factors such as PSA nadir, initial PSA, and age at diagnosis were analysed as categorical data. This could lead to information bias. The definition of CRPC was less stringent than that suggested from international guidelines[12] because testosterone level and follow-up imaging such as bone scans were not routinely performed due to limited resources. Potential confounding factors for survival such as smoking and co-morbidity were also not included in the study and may have affected the validity of the results. The small number of patients prescribed novel treatments or bone-modulating agents did not allow a comprehensive understanding of their influence on SRE occurrence. Further prospective trials with a large cohort size are necessary.

Conclusions

Skeletal-related events were common in men with metastatic prostate cancer and were first shown by this study to be an independent prognostic factor of OS and CSS in patients with metastatic prostate cancer prescribed ADT. A PSA nadir of >4 ng/mL is an independent poor prognostic factor for OS and CSS following development of SREs.

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