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Clinical characteristics and quality-of-life in patients surviving a decade of prostate cancer with bone metastases

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Objective

To describe characteristics and quality-of-life (QoL), and to define factors associated with long-term survival in a subgroup of patients with prostate cancer with M1b disease.

Patients and Methods

The study was based on 915 patients from a prospective randomised multicentre trial (No. 5) by the Scandinavian Prostate Cancer Group, comparing parenteral oestrogen with total androgen blockade. Long-term survival was defined as patients having an overall survival of ≥10 years, and logistic regression models were constructed to identity clinical predictors of survival. QoL during follow-up was assessed using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire – C30 version 1 (EORTC-C30) ratings.

Results

In all, 40 (4.4%) of the 915 men survived for >10 years. Factors significantly associated with increased likelihood of surviving for >10 years in the univariate analyses were: absence of cancer-related pain; Eastern Cooperative Oncology Group (ECOG) performance status of <2; negligible analgesic consumption; T-category of 1–2; prostate-specific antigen (PSA) level of <231 μg/L; and a Soloway score of 1. In the multivariate analyses, ECOG performance status of <2, PSA level of <231 μg/L, and Soloway score of 1, were all independent predictors of long-term survival. All subscales of the EORTC-C30 were higher in this group than for patients with short survival, but slowly declined over the decade.

Conclusion

A subgroup of patients with prostate cancer with M1b disease and certain characteristics showed a positive long-term response to androgen-deprivation therapy with an acceptable QoL over a decade or more. Independent predictors of long-term survival were identified as ECOG performance status of <2, limited extent of bone metastases (Soloway score of 1), and a PSA level of <231 μg/L at the time of enrolment.

Keywords

prostate cancer, bone metastases, long-term survival, quality-of-life

Introduction

Prostate cancer is a major health concern in all Western countries. The most important reason for the marked increase in incidence of dominantly localised disease has been the growing use of PSA as a diagnostic tool. However, until now, prostate cancer mortality has remained relatively stable. Only a small annual decrease in survival has been seen over the last decade, despite the fact that the proportion of cases with distant metastases at diagnosis has decreased from 25% in the 1990s to currently <11% [1]. In contrast to Sweden, prostate cancer mortality in the USA fell markedly during the 'PSA era' [2]. However, an improvement in survival for patients with distant metastases was not seen [3]. Nevertheless, the survival curve for men with metastasising prostate cancer is skewed, with a relatively large minority surviving more than a decade.

The outcome of prostate cancer is mainly determined by the presence of distant metastases (M1). These metastases most frequently (90%) involve the skeleton [4]. For most malignant diseases, distant metastases are associated with a very poor prognosis and a substantial deterioration in health-related quality-of-life (QoL). However, prostate cancer differs in

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many aspects from most other malignant diseases. Generalisation does not inevitably imply the same rapid decline in health-related QoL, at least not if the tumour responds to androgen-deprivation therapy (ADT). When deciding on treatment for men with skeletal metastases, the chance of a relatively unaffected prognosis and life situation should be kept in mind.

ADT has been the 'gold standard' for treating prostate cancer with distant metastases for more than half a century. Originally this was achieved by surgical orchidectomy and oestrogen therapy [5], but since the 1980s medical castration by means of LHRH agonists has been standard. Total androgen blockade (TAB), orchidectomy or medical castration in combinations with anti-androgen, have been evaluated in clinical trials [6–8].

According to one meta-analysis, TAB with non-steroidal anti-androgens provides a small survival advantage compared with orchidectomy or medical castration [6]. Median survival times ranged from 30 to 49 months [9]. However, because of the rather short survival time in many high-risk patients, long-term data on survival and health-related QoL in M1 patients are limited. Follow-up is seldom for >5 years after diagnosis.

The natural course of untreated prostate cancer with skeletal metastases may be derived from the pre- ADT era. In a study from the Mayo Clinic in 1925, the presence of bone metastases at diagnosis was associated with a 9-month mortality of 66% [10]. The extremes in a series of 260 patients with bone metastases were 1 month and 176 months. The longest survival was seen in an untreated man who had metastases in the spine and pelvis at the time of diagnosis, who survived nearly 15 years [11].

The aim of the present study was to analyse long-term survival and to define factors associated with long-term survival in patients with prostate cancer and skeletal metastases treated with TAB or high-dose parenteral oestrogen. The 915 patients in the present study were taken from a prospective non-inferiority clinical trial (No. 5) conducted by the Scandinavian Prostate Cancer Group.

Patients and Methods

The present phase III study recruited 915 patients with hormone-naïve metastatic prostate cancer from 61 centres in Denmark, Finland, Iceland, Norway, and Sweden between December 1992 and June 1997 [12,13]. To be eligible, patients had skeletal metastases (M1) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 (0 = denotes fully active; 1 = restricted in strenuous activity but ambulatory; 2 = ambulatory and capable of self-care but unable to work). The primary objective of the trial was to determine whether or not overall survival (OS) and cause-specific survival (CSS) with high-dose parenteral oestrogen therapy was inferior to that with TAB. The secondary objective was to provide information on cardiovascular side-effects and about health-related QoL before and during ADT. The extent of the primary tumour was determined by means of DRE according to the TNM classification from 1987 [14] and cytological or histological specimens graded according to the WHO system [15]. PSA, alkaline phosphatase (ALP), and haemoglobin levels were determined by routine laboratory testing before the start of treatment.

Skeletal involvement was assessed using bone scans supplemented by X-ray when needed. The extent of skeletal metastases was calculated according to a modified Soloway score: 1 = the total area of 'hot spots' <3 bodies of a lumbar vertebra; 2 = the total area of hot spots larger than of score 1, but <75% of the total scan; and 3 = >75% of the total scan or super scan [16]. The European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire –C30 version 1 (EORTC-30) was used to evaluate QoL. The questionnaire is appropriate for self-administration and consists of 30 items, including nine multi-item scales, five functional scales, three symptom scales and a global health-status scale and single items, making a total of 15 ratings [17].

Patients were asked specific questions about symptoms the previous week using a mixture of dichotomous 'yes/no' response categories and a 4-point response scale ranging from 'not at all' to 'very much'. Global health status was calculated from answers to two questions asking patients to rate their overall health and QoL on a 7-point scale ranging from 1 (very poor) to 7 (excellent). The raw scores from the questionnaire were linearly transformed into a standardised 0–100 scale score.

Treatment

The patients were randomised to TAB or treatment with polyoestradiol phosphate (240 mg) given by i.m. injection every 2 weeks for 8 weeks, and monthly thereafter. TAB consisted of orchidectomy or medical castration, according to clinician and patient preference, combined with 250 mg flutamide orally three-times daily. Orchidectomy was chosen by 298 patients, and 159 men received medical castration by monthly injection of the LHRH agonist, triptorelin. There were no significant differences in survival between the two treatment groups.

Follow-up

The patients were followed up at 1, 3 and 6 months after the start of the study, and thereafter every 6 months. When

clinical progression of prostate cancer was confirmed, further therapy was at the discretion of the clinician. All 915 patients were to be followed until death and the clinician obliged to register the cause of death (Fig. 1).

Ethics

The study was performed in accordance with the recommendations of the Helsinki Declaration and approved by the ethics committees of all centres participating in the study. Patients were given verbal and written information, and gave their informed consent to be included in the study.

Statistical Methods

In the present study, short-, medium- and long-term survival were defined as patients having survived <5, 5–10 and >10 years, respectively. Differences in OS groups were tested using the chi-square test based on: age at enrolment (in 3-year intervals); cancer-related pain; ECOG performance status; analgesic consumption; grade of malignancy; T category; PSA level (median); metastatic involvement of the skeleton (Soloway score); cardiovascular comorbidity; haemoglobin (> vs <100 g/L); and initial treatment (orchidectomy or not). To estimate the likelihood of long-term survival we used univariate logistic regression models, with odds ratio (OR) and corresponding 95% CI for each variable. To identify independent predictors of long-term survival, a multivariate logistic regression model was then constructed using all variables that were statistically significant in the univariate analyses. In addition Kaplan–Meier curves and median CSS and OS in relation to presence of at least one, at least two, or all three independent prognostics factors, identified the multivariate logistic regression model with corresponding 95% CIs calculated. Next we calculated the 15 baseline EORTC-30 ratings of the survival groups, expressed as mean values, which were then compared using ANOVA. In a subsequent step, we identified the repeated responses for eight EORTC-30 ratings among the long-term survivors. For each rating, a smoothing-splines mixed-effects model was used related to duration of follow-up. The fitted mean values with corresponding 95% CIs for the EORTC-30 ratings were then plotted against follow-up time. All P values were two-sided and statistical significance was considered at $P < 0.05$, and analyses were performed using the R version 3.1.1 [18].

Results

Baseline demographic and clinical characteristics for each survival group from the 915 patients enrolled in the study are presented in Table 1. Most of the patients were aged

Fig. 1 Flow chart showing study group assembly and long-term follow-up of the SPCG5 trial. The study was aimed at studying ADT with parenteral oestrogen or TAB in men with prostate cancer and bone metastases.

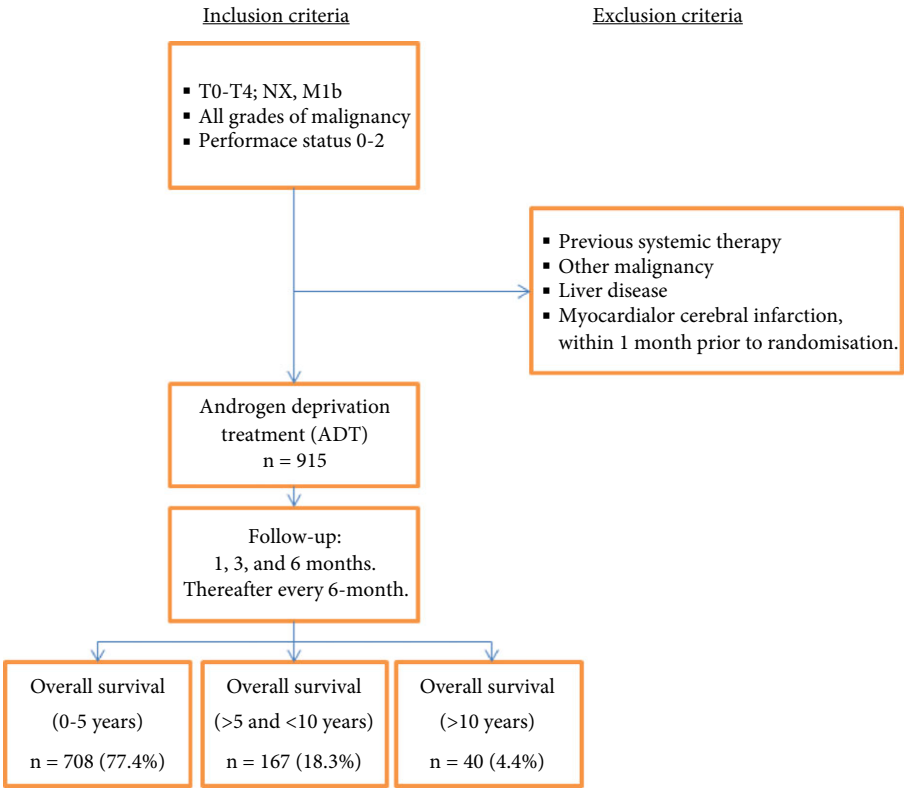

Table 1 Demographic and clinical characteristics of the 915 patients with metastatic prostate cancer (M1b) at the time of diagnosis by three survival groups.

	Survival, *n* (%)			*P*	Total cases, *n* (%)
	Short-term <5 years	Medium-term 5–10 years	Long-term >10 years		
All cases	708 (100.0)	167 (100.0)	40 (100.0)		915 (100.0)
Age, years					
<65	107 (15.1)	19 (11.4)	7 (17.5)		133 (14.5)
65–74	334 (47.2)	81 (48.5)	19 (47.5)		434 (47.4)
≥75	267 (37.7)	67 (40.1)	14 (35.0)	0.753	348 (38.0)
Cancer-related pain					
No pain	258 (36.7)	93 (55.7)	26 (65.0)		377 (41.4)
Pain	445 (63.3)	74 (44.3)	14 (35.0)	<0.001	533 (58.6)
Missing	5	–	–		5
ECOG performance status					
0	268 (38.1)	109 (65.3)	28 (70.0)		405 (44.5)
1	302 (43.0)	42 (25.1)	11 (27.5)		355 (39.0)
2	133 (18.9)	16 (9.6)	1 (2.5)	<0.001	150 (16.5)
Missing	5	–	–		5
Analgesic consumption					
Negligible	299 (42.5)	105 (62.9)	31 (77.5)		435 (47.8)
≥1	404 (57.5)	62 (37.1)	9 (22.5)	<0.001	475 (52.2)
Missing	5	–	–		5
Grade of malignancy					
WHO 1	90 (13.1)	38 (23.2)	8 (21.1)		136 (15.3)
WHO 2	301 (43.8)	93 (56.7)	20 (52.6)		414 (46.5)
WHO 3	297 (43.2)	33 (20.1)	10 (26.3)	<0.001	340 (38.2)
Missing	20	3			23
T-category					
T0–T2	138 (19.8)	37 (22.4)	14 (35.0)		189 (21.0)
T3–T4	559 (80.2)	128 (77.6)	26 (65.0)	0.062	713 (79.0)
Missing	11	2			13
PSA level (median 231 μg/L)					
Low	326 (46.4)	97 (58.1)	33 (82.5)		456 (50.1)
High	377 (53.6)	70 (41.9)	7 (17.5)	<0.001	454 (49.9)
Missing	5				5
Soloway score					
1	201 (28.9)	88 (53.3)	30 (75.0)		319 (35.4)
2–3	494 (71.1)	77 (46.7)	10 (25.0)	<0.001	581 (64.6)
Missing	13	2	–		15
Cardiovascular comorbidity					
None	623 (89.1)	153 (92.2)	35 (87.5)		811 (89.6)
Present	76 (10.9)	13 (7.8)	5 (12.5)	0.464	94 (10.4)
Missing	9	1	–		10
Haemoglobin, g/L					
<100	285 (40.8)	45 (27.1)	10 (25.6)		340 (37.7)
>100	413 (59.2)	121 (72.9)	29 (74.4)	0.001	563 (62.3)
Missing	10	1	–		11
Initial treatment					
Orchidectomy and flutamide	121 (17.1)	32 (19.2)	6 (15.0)		159 (17.4)
Other treatments	587 (82.9)	135 (80.8)	34 (85.0)	0.753	756 (82.6)

>65 years at enrolment, had cancer-related pain, and a ECOG performance status of ≥1. Four out of five patients had a locally advanced tumour (T3–T4), 85% had a WHO grade of 2–3, and 65% of the cases had a Soloway score of 2 or 3 (a total area of hot spots larger than three lumbar vertebra bodies or super scan). The median PSA level was 231 μg/L.

In all, 40 of the original 915 patients (4.4%) survived for >10 years (long-term survival), 167 of the men died between 5 and 10 years, and 708 at <5 years after enrolment into the study (Table 1). There were no differences in age between the three survival groups ($P = 0.753$). There were observed differences in the proportion of patients with cancer-related pain, ECOG performance status, and analgesic consumption between the three survival groups ($P < 0.001$), where most of the long-term survivors had no sign of cancer-related pain, a good ECOG performance status, and did not require analgesics. There were differences for WHO grade ($P < 0.001$), PSA level ($P < 0.001$), Soloway score ($P < 0.001$), and haemoglobin level ($P < 0.001$) between the survival groups. One in four of the long-term survivors had a Soloway score of 1, but there were no differences in distribution between T category ($P = 0.062$), absence of cardiovascular

events ($P = 0.464$), and men undergoing orchidectomy or not ($P = 0.753$) between the three survival groups.

Prognostic factors associated with long-term survival were defined using univariate and multivariate logistic regression analyses (Table 2). Factors significantly associated with long-term survival in the univariate analyses were: no sign of cancer-related pain; ECOG performance status of <2; negligible analgesic consumption; localised tumour (T0–T2); PSA level of <231 μg/L; and Soloway score of 1. In the multivariate logistic regression analyses, ECOG performance status of <2, PSA level of 231 μg/L, and Soloway score of 1 were all independent predictors of long-term survival. Patients with a Soloway score of 1 or a PSA level of <231 μg/L had a three-fold likelihood of long-term survival compared with men with a Soloway score of 2–3 or PSA level of >231 μg/L (Table 2).

Of the men surviving for 10 years, 98% had at last one, 85% at last two and 45% all three favourable prognostics factors (Table 3). The OS and CSS in relation to the number of favourable prognostics factors are shown in Fig. 2a,b and Table 4.

Table 2 Univariate and multivariate logistic regression for long-term survival (>10 years).

	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Age, years				
<65	1.00	Ref.	–	–
65–74	1.09	0.54–2.25	–	–
≥75	1.33	0.49–3.26	–	–
Cancer-related pain				
Pain	1.00	Ref.	1.00	Ref.
No pain	2.75	1.44–5.47	0.77	0.31–2.13
ECOG performance status				
2	1.00	Ref.	1.00	Ref.
1	4.76	0.91–87.5	4.38	0.81–81.47
0	11.07	2.33–198.19	5.83	1.11–107.67
Analgesic consumption				
≥1	1.00	Ref.	1.00	Ref.
Negligible	3.97	1.95–8.96	2.22	0.74–6.51
Grade of malignancy				
WHO 3	1.00	Ref.	–	–
WHO 2	1.68	0.79–3.78	–	–
WHO 1	2.06	0.77–5.34	–	–
T-category				
T3–T4	1.00	Ref.	1.00	Ref.
T0–T2	2.11	1.05–4.07	1.95	0.95–3.87
PSA level, (median 231 μg/L)				
High	1.00	Ref.	1.00	Ref.
Low	4.98	2.31–12.38	3.24	1.47–8.19
Soloway score				
2–3	1.00	Ref.	1.00	Ref.
1	5.93	2.96–12.92	3.58	1.71–8.06
Cardiovascular comorbidity				
Present	1.00	Ref.	–	–
None	0.80	0.33–2.39	–	–
Haemoglobin, g/L				
<100	1.00	Ref.	–	–
>100	1.79	0.89–3.91	–	–
Initial treatment				
Orchidectomy and flutamide	1.00	Ref.	–	–
Other treatments	1.20	0.53–3.22	–	–

The multivariate model is adjusted for all the statistically significant variables in the univariate analyses.

The EORTC-30 ratings expressed as observed mean values are presented for each survival group in Table 5. A wide range of mean values were obtained, and seven out of 15 EORTC-30 ratings were significantly different between the survival groups ($P < 0.001$). The mean value of the global health status was 62.8, 69.7 and 72.6 for the short-, medium- and long-term survivors, respectively. Figure 3 shows eight EORTC-30 ratings, expressed as fitted mean values as a function of follow-up time among the long-term survivors. There was a small decrease in the global health rating and functional ratings with time, a change that was most pronounced for physical functioning ratings. Among the long-term survivors, problems with fatigue and dyspnoea were reported to increase during follow-up, from baseline mean values of 22 and 17–32 and 29, respectively at the 10-year follow-up.

Discussion

The present study showed some differences in the clinical characteristics of men diagnosed with M1b disease between the three different survival groups (low-, medium-, and long-term survivors) treated with ADT. Independent predictors of long-term survival were ECOG performance status of <2; limited extent of bone metastases (Soloway score of 1); and a PSA level of <231 μg/L at the time of enrolment. Patients who survived a decade had an acceptable health-related QoL for several years, with a relatively slow decline.

All patients received primary ADT. Subsequent therapy for disease progression was according to the preference of the clinician. In most cases, estramustine phosphate was given, and most men were not put on chemotherapy. New agents, such as abiraterone and enzalutamide, were not available at the time of the study. Intermittent ADT is sometimes given to men with slowly progressing tumours, although data are insufficient to determine whether intermittent treatment is able to prevent long-term complications of ADT [19]. However in our present study intermittent ADT was not practised.

The present study focuses on 40 men with prostate cancer and bone metastases, who survived a decade or more after starting ADT. Likely prognostic factors were recorded before the start of treatment and QoL was evaluated before and during treatment.

Site of Distant Metastases

Metastases to the bone may contribute significantly to disease-specific morbidity in men with prostate cancer. Pain,

Table 3 The number and the proportion of patients having at least one, two, or all three independent prognostic factors (PSA level of <231 μg/L, Soloway score of 1, and ECOG performance status of <2) in relation to short-, medium- and long-term (>10 years) OS.

OS	At least one prognostic factor, *n* (%)	At least two prognostic factors, *n* (%)	All three prognostic factors, *n* (%)	Total, *n*
Short-term	492 (69)	241 (34)	62 (9)	708
Medium-term	143 (86)	102 (61)	49 (29)	167
Long-term	39 (98)	34 (85)	18 (45)	40
Total	674 (74)	377 (41)	129 (14)	915

Fig. 2 CSS (**a**) and OS (**b**) of 915 patients with at least one, at least two, all three, or none of the favourable prognostics factors.

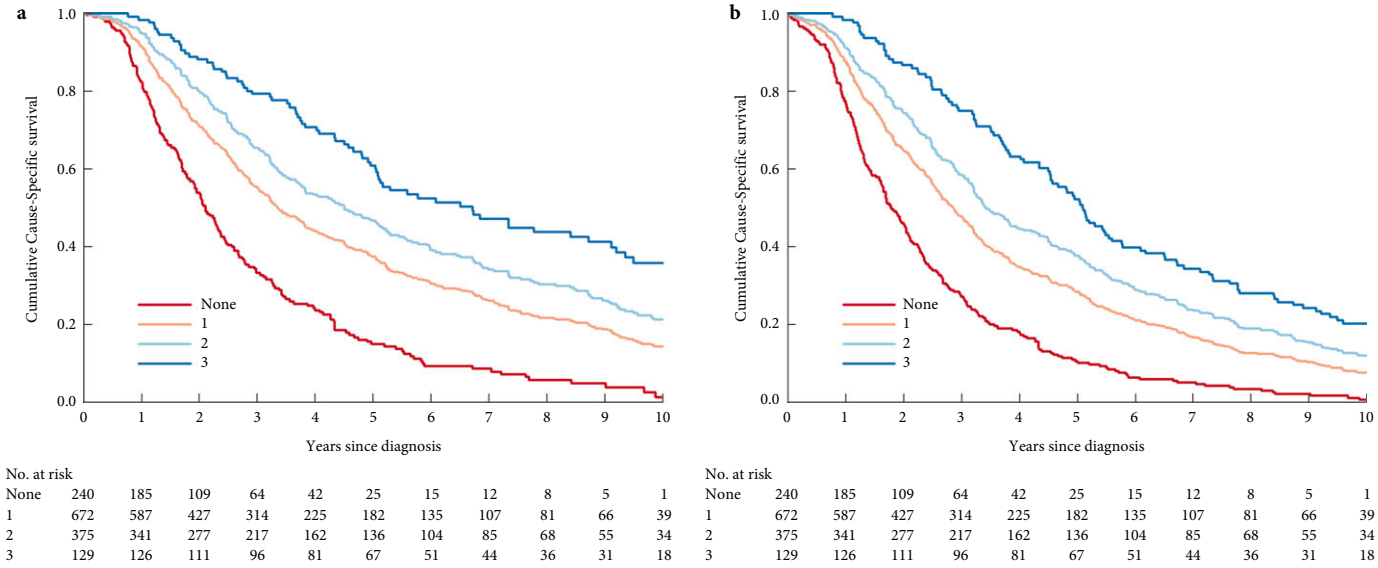

Table 4 Median CSS and OS with corresponding 95% CIs of 915 patients having none, at least one, two, or three independent prognostics factors.

	None of the prognostic factors	At least one prognostic factor	At least two prognostic factors	All three prognostic factors
Median (95% CI)				
CSS	2.11 (1.90–2.38)	3.35 (3.11–3.82)	4.50 (3.82–5.22)	6.71 (5.09–9.21)
OS	1.79 (1.61–2.07)	2.86 (2.63–3.11)	3.43 (3.21–4.02)	5.10 (4.54–5.78)

pathological fractures, nerve compression, and hypocalcaemia are common symptoms and signs of bone metastases. However, despite the dismal prognosis once the tumour has spread to a distant location, generalised prostate cancer differs from other malignant diseases. A small, but not negligible, minority of men with metastasising cancer may live for several years without substantial reduction in QoL.

The TNM classification system according to the Union Internationale Contre le Cancer (UICC) is used for stage classification of malignant diseases, including prostate cancer. The classification correlates prognoses and is used as a basis for treatment decisions. In the 1992 edition, a prognostic grouping was advocated by dividing metastatic spread (M1) into three different site groups: M1a non-regional lymph nodes; M1b bone; and M1c other sites i.e. soft tissue. The site of distant metastases (M1a, b, or, c) is sometimes recorded in the literature, but the prognostic value of this classification is not clear. In a recent validation of the prognostic grouping of M1 disease, a considerable variation in 5-year OS was found [20]. There is some evidence from clinical trials that treatment results are not related to the site of distant metastases [21]. However, in one study, the presence of soft tissue and bone metastases worsened the 2-year survival rate, while patients with soft tissue metastases only had a more favourable outcome [22]. In another study, patients with axial or appendicular bone metastasis location had different survival profiles [23].

The present study explored a homogeneous group of patients with bone metastases quantified according to a modification of the Soloway score. The prevalence of non-regional lymph

Table 5 Baseline EORTC-30 ratings expressed as mean values by the three survival groups of patients with prostate cancer during ADT.

	Survival			*P*
	Short-term <5 years	Medium-term 5–10 years	Long-term >10 years	
Mean (SD) EORTC-30 ratings				
Global health status	62.8 (21.9)	69.7 (18.5)	72.6 (19.8)	<0.001
Physical functioning	74.1 (26.6)	85.1 (20.9)	91.7 (15.1)	<0.001
Role functioning	91.5 (11.9)	94.4 (9.9)	97.0 (7.5)	<0.001
Emotional functioning	81.5 (20.0)	84.7 (16.5)	87.1 (13.9)	0.06
Cognitive functioning	85.1 (19.8)	88.5 (15.1)	84.2 (16.0)	0.124
Social functioning	87.3 (21.1)	89.4 (18.0)	90.8 (14.9)	0.336
Fatigue	33.0 (25.4)	23.4 (20.5)	20.2 (17.3)	<0.001
Dyspnoea	20.7 (26.1)	16.8 (21.6)	15.8 (21.6)	0.139
Nausea/vomiting	6.0 (15.4)	2.9 (7.9)	0.9 (3.8)	0.007
Pain	24.0 (25.2)	18.2 (21.9)	13.2 (15.1)	0.002
Insomnia	19.5 (28.4)	18.0 (25.7)	21.1 (25.0)	0.766
Appetite loss	15.5 (27.8)	6.7 (19.1)	1.8 (7.5)	<0.001
Constipation	17.3 (26.5)	13.4 (24.3)	9.9 (17.3)	0.082
Diarrhoea	7.8 (18.2)	4.8 (13.5)	4.4 (13.8)	0.092
Financial problems	5.0 (15.8)	5.2 (15.8)	0.9 (5.4)	0.267

nodes (M1a) and soft tissue (M1b) metastases was not investigated with CT or MRI.

Long-Term Survival

The long-term response to ADT is not well documented in the literature. In a large randomised trial from the end the 1990s, evaluating the efficacy of different forms of ADT 64 of 1 387 (4.6%) were alive 6 years after start of treatment [24]. A separate analysis disclosed three groups with 46%, 25% and 14% survival after 5-years ADT [23]. Other studies evaluating risk factors related to outcome have had short or medium follow-ups (Table 6) [16,22,23,25–29]. Several individual prognostic factors that affect survival after initiation of hormonal treatment in M1 disease have been identified. These have included performance status, pain before start of treatment, extent of metastases by bone scan, ALP, PSA and testosterone levels, and grade of malignancy (Table 6). Examination of histochemical stains from bone metastases has provided additional prognostic information in 68 patients that underwent surgery for pathological fractures. Positive for chromogranin A and poor differentiation of the specimen were significantly associated with prostate cancer death [30]. After 4 years of follow-up there were only seven patients left at risk but they were not evaluated further. There is no validated decision guidelines i.e. monograms in the setting of hormone-sensitive metastasising prostate cancer. The Halabi monogram [31], for example, is based on castration-resistant prostate cancer, but has not been adapted for men with skeletal metastases before starting ADT.

Strengths of the Study

The data in our present study would appear to be more mature than others, as only 4.4% of the patients were alive at the time the analysis was conducted 10 years after enrolment. Our present study confirms the results of previous studies about the favourable survival prognosis of good performance status, low PSA level, and limited extent of bone metastases.

Limitations of the Study

The present study has some limitations. It is based on men included in a randomised controlled trial, which limits the external validity, as only men who fulfilled all inclusion criteria and were in a mental state to give consent to the trial were eligible for inclusion. Furthermore, the treatment of prostate cancer has progressed since the time of the start of the study. Today, ADT is no longer the only treatment alternative for men with metastasising prostate cancer [32]. The high PSA levels at treatment start indicate large tumour burdens. However, PSA does not always correlate with tumour burden, especially not in men with PSA levels of <50 μg/L. In another study of men with prostate cancer and distant metastases, the median PSA level was only 132 μg/L. A PSA level of <65 μg/L was associated with favourable effect on outcome [23]. In the present study, the median PSA level was 231 μg/L, i.e. almost twice as high as in the study of Glass et al. [23].

Prognostic Factors

We investigated several potential prognostic factors using univariate and multivariate regression models. Seven of these factors were significantly favourably related to survival in the 40 patients who survived a decade or more. In the multivariate analyses only three factors at enrolment were significant predictors of long-term survival after starting ADT. OS and CSS were significantly related to the number of these favourable prognostic factors. However, none of the

Fig. 3 A smoothing-splines mixed-effects model as a function of the EORTC-30 ratings for the 40 patients during 10 years follow-up and plotted the fitted mean values of QoL against follow-up time.

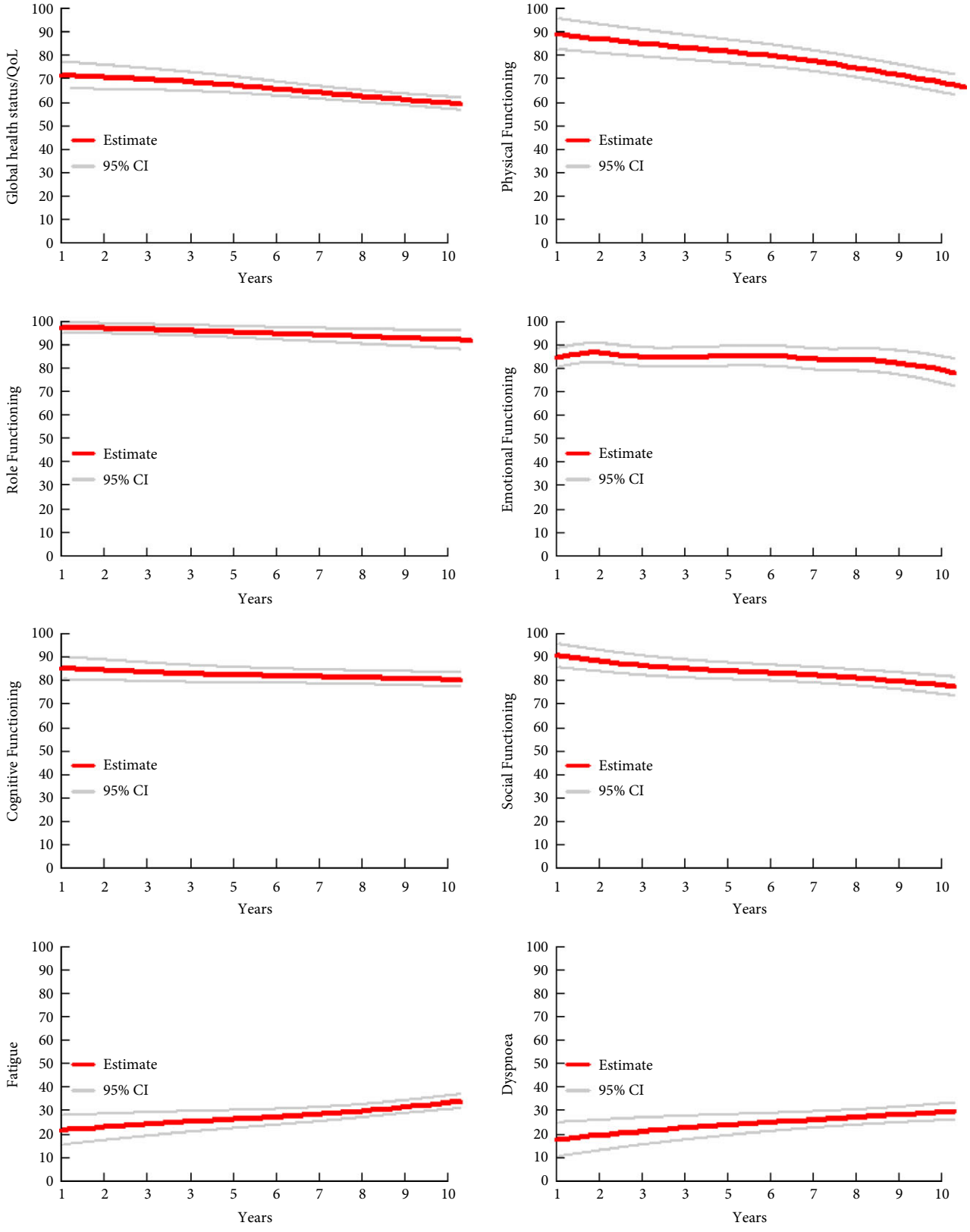

Table 6 Prognostic factors at start of ADT in patients with prostate cancer with distant metastasis: summary of evaluation of survival from selected series.

Reference	No. of patients with distant metastasis	Longest follow-up, years	Significantly related to survival	Statistically methods
Soloway et al. [16]	166	2	Extent of bone disease	Semi-quantitative grading system
Mulders et al. [24]	175	4	Performance status, Hb, ALP	Multivariate
Chodak et al. [25]	240	2	Performance status, ALP, bone pain, testosterone	Multivariate
Reynard et al. [26]	134	4	ALP, testosterone	Multivariate
Sylvester et al. [27]	695	3.5	Performance status, Hb, ALP, pain score, T-category, grade	Univariate
Glass et al. [22]	1 076	5	Performance status, PSA, Gleason score, Appendicular vs axial disease	Recursive partitioning
Noguchi et al. [28]	56	4.2	Extent of bone disease	Multivariate, visual and computer analysis
James et al. [21]	917	4	Performance status, Gleason score, age, lymph node and bone metastasis	Multivariate
Present study Klaff et al. 2015	915	>10	Performance, PSA, extent of bone disease	Multivariate

Hb, haemoglobin.

predictors was strong enough to reliably identify those men likely to survive for >10 years. The way in which advanced prostate cancer affects survival and QoL is probably too complex to be predicted at the start of treatment. Factors involved include tumour growth rate, response to ADT, and the condition and comorbidity of the host. Whenever initiating therapy for men with metastasising prostate cancer, the possibility of long survival with QoL not substantially reduced by widespread tumour should be kept in mind.

QoL

Data on QoL at the time of enrolment of the patient in the present study have been published elsewhere [33]. The overall mean QoL was found to be 56.7, which was much lower than that in a reference population of normal Swedish and Norwegian men, underlining the general clinical importance of prostate cancer with bone metastases as a serious disease. Data regarding QoL during long-term follow-up of continuous ADT are still limited. However, several recent studies have shown a growing interest in QoL during intermittent ADT [34].

Conclusion

In conclusion, this supplementary analysis of a prospective clinical trial made it clear that a subgroup of M1b patients with certain characteristics have a long-term positive response to ADT. A small group of men survived for more than a decade with an acceptable QoL. Independent predictors of long-term survival were identified as good ECOG performance status, limited extent of bone metastases, and a low PSA level at the time of enrolment [35]. The outcome from our present study should be taken into consideration when deciding on treatment for men with metastasising prostate cancer.

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Conflict of Interest

The authors declare no conflict of interest.

References

1 **Ohmann EL, Loeb S, Robinson D, Bill-Axelson A, Berglund A, Stattin P.** Nationwide, population-based study of prostate cancer stage migration between and within clinical risk categories. *Scand J Urol* 2014; 48: 426–35

2 **Siegel R, Ward E, Brawley O, Jemal A.** Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011; 61: 212–36

3 **Wu JN, Fish KM, Evans CP, Devere White RW, Dall'Era MA.** No improvement noted in overall or cause-specific survival for men presenting with metastatic prostate cancer over a 20-year period. *Cancer* 2014; 120: 818–23

4 **Bubendorf L, Schöpfer A, Wagner U et al.** Metastatic patterns of prostate cancer: an autopsy study of 1,589 patients. *Hum Pathol* 2000; 31: 578–83

5 **Huggins C, Hodges CV.** Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *CA Cancer J Clin* 1972; 22: 232–40

6 **Prostate Cancer Trialists' Collaborative Group.** Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. *Lancet* 2000; 355: 1491–8

7 **McLeod DG.** Hormonal therapy: historical perspective to future directions. *Urology* 2003; 61(Suppl): 1

8 **Pagliarulo V, Bracarda S, Eisenberger MA et al.** Contemporary role of androgen deprivation therapy for prostate cancer. *Eur Urol* 2012; 61: 11–25

9 **Tangen CM, Hussain MH, Higano CS et al.** Improved overall survival trends of men with newly diagnosed M1 prostate cancer: a SWOG phase III trial experience (S8494, S8894 and S9346). *J Urol* 2012; 188: 1164–9

10 **Bumpus HC.** Carcinoma of the prostate: a clinical study of one thousand cases. *Surg Gynecol Obstet* 1926; 43: 150–5

11 **Nesbit RM, Plumb RT**. Prostatic carcinoma; a follow-up on 795 patients treated prior to the endocrine era and a comparison of survival rates between these and patients treated by endocrine therapy. *Surgery* 1946; 20: 263–72

12 **Hedlund PO, Damber JE, Hagerman I et al.** Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. *Scand J Urol Nephrol* 2008; 42: 220–9

13 **Hedlund PO, Ala-Opas M, Brekkan E et al.** Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer – Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. *Scand J Urol Nephrol* 2002; 36: 405–13

14 **Hermanek P, Scheibe O, Spiessl B, Wagner G**. [TNM classification of malignant tumors: new edition 1987]. *Rofo* 1987; 146: 732–3

15 **Mostofi FK**. *Histologic Typing of Prostate Cancer Tumors*, Geneva: World Health Organisation, 1980: 17–21

16 **Soloway MS, Hardeman SW, Hickey D et al.** Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. *Cancer* 1988; 61: 195–202

17 **Fayers PM**. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. *Eur J Cancer* 2001; 37: 1331–4

18 **R Core Team. R**. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2014. http://www.R-project.org/. Accessed 1 April 2013.

19 **Sciarra A, Abrahamsson PA, Brausi M et al.** Intermittent androgen-deprivation therapy in prostate cancer: a critical review focused on phase 3 trials. *Eur Urol* 2013; 64: 722–30

20 **Kimura T, Onozawa M, Miyazaki J et al.** Validation of the prognostic grouping of the seventh edition of the tumor-nodes-metastasis classification using a large-scale prospective cohort study database of prostate cancer treated with primary androgen deprivation therapy. *Int J Urol* 2013; 20: 880–8

21 **Saeter G, Fossa SD, Ous S, Blom GP, Kaalhus O**. Carcinoma of the prostate with soft tissue or non-regional lymphatic metastases at the time of diagnosis: a review of 47 cases. *Br J Urol* 1984; 56: 385–90

22 **James ND, Spears MR, Clarke NW et al.** Survival with newly diagnosed metastatic prostate cancer in the "Docetaxel Era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). *Eur Urol* 2015; 67: 1028–38

23 **Glass TR, Tangen CM, Crawford ED, Thompson I**. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. *J Urol* 2003; 169: 164–9

24 **Eisenberger MA, Blumenstein BA, Crawford ED et al.** Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 1998; 339: 1036–42

25 **Mulders PF, Dijkman GA, Fernandez del Moral P, Theeuwes AG, Debruyne FM**. Analysis of prognostic factors in disseminated prostatic cancer. An update. Dutch Southeastern Urological Cooperative Group. *Cancer* 1990; 65: 2758–61

26 **Chodak GW, Vogelzang NJ, Caplan RJ, Soloway M, Smith JA**. Independent prognostic factors in patients with metastatic (stage D2) prostate cancer. The Zoladex Study Group. *JAMA* 1991; 265: 618–21

27 **Reynard JM, Peters TJ, Gillatt D**. Prostate-specific antigen and prognosis in patients with metastatic prostate cancer – a multivariable analysis of prostate cancer mortality. *Br J Urol* 1995; 75: 507–15

28 **Sylvester RJ, Denis L, de Voogt H**. The importance of prognostic factors in the interpretation of two EORTC metastatic prostate cancer trials. European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Cooperative Group. *Eur Urol* 1998; 33: 134–43

29 **Noguchi M, Kikuchi H, Ishibashi M, Noda S**. Percentage of the positive area of bone metastasis is an independent predictor of disease death in advanced prostate cancer. *Br J Cancer* 2003; 88: 195–201

30 **Cheville JC, Tindall D, Boelter C et al.** Metastatic prostate carcinoma to bone: clinical and pathologic features associated with cancer-specific survival. *Cancer* 2002; 95: 1028–36

31 **Halabi S, Small EJ, Kantoff PW et al.** Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. *J Clin Oncol* 2003; 21: 1232–7

32 **Labrie F**. GnRH agonists and the rapidly increasing use of combined androgen blockade in prostate cancer. *Endocr Relat Cancer* 2014; 21: R301–17

33 **Jonler M, Nielsen OS, Groenvold M et al.** Quality of life in patients with skeletal metastases of prostate cancer and status prior to start of endocrine therapy: results from the Scandinavian Prostate Cancer Group Study 5. *Scand J Urol Nephrol* 2005; 39: 42–8

34 **Salonen AJ, Taari K, Ala-Opas M et al.** Comparison of intermittent and continuous androgen deprivation and quality of life between patients with locally advanced and patients with metastatic prostate cancer: a post hoc analysis of the randomized FinnProstate Study VII. *Scand J Urol* 2014; 48: 513–22

35 **Bellardita L, Valdagni R, van den Bergh R et al.** How does active surveillance for prostate cancer affect quality of life? A systematic review. *Eur Urol* 2015; 67: 637–45

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Abbreviations: ADT, androgen-deprivation therapy; ALP, alkaline phosphatase; CSS, cause-specific survival; ECOG, Eastern Cooperative Oncology Group; EORTC-30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire –C30 version 1; OR, odds ratio; OS, overall survival; QoL, quality-of-life; TAB, total androgen blockade.