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ARTICLE

Clinical Research

Incidence and survival of castration-resistant prostate cancer patients with visceral metastases: results from the Dutch CAPRI-registry

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BACKGROUND: The objective of this real-world population study is to investigate incidence and treatment of visceral metastases (VMs) in castration resistant prostate cancer (CRPC) patients and their survival.

METHODS: CRPC-patients in the CAPRI-registry between 2010 and 2016 were included in the analyses and followed till 2017. Outcomes were proportion of patients radiologically screened for VMs and proportion of patients with VMs at CRPC-diagnosis and at the start of every treatment line. Groups have been created based on location of VMs (lung, liver, or both) at date of first VM diagnosis. The outcome for these groups was overall survival (OS). Statistics included descriptive analyses, Kaplan-Meier method, and Cox proportional hazard regression analysis for survival analyses.

RESULTS: Of 3602 patients from the CAPRI registry, 457 patients (12.7%) were diagnosed with VMs during follow-up: 230 patients with liver, 161 with lung, and 66 with both liver and lung metastases. The proportion of patients radiologically screened for VMs increased per treatment line as did the occurrence rate of VMs. However, 80% of patients at CRPC diagnosis to 40% in the 6th line were not screened for VMs at the start of a systemic treatment. Median OS was 8.6 months for patients with liver, 18.3 with lung and 10.9 with both liver and lung metastases ($p < 0.001$) from date of first VM diagnosis. After correction for prognostic factors patients with lung metastases had significantly better OS than patients with liver metastases (HR 0.650, $p = 0.001$).

CONCLUSION: This real-world analysis showed that despite the increased rate of radiological staging during follow-up, still 80% to 40% of the patients (CRPC diagnosis to 6th treatment line respectively) were not screened for VMs at the start of a systemic treatment. VMs and location of VMs are key prognostic patient characteristics, impacts survival and have implications for treatment decisions, so routine staging of CRPC-patients is warranted.

CLINICAL TRIAL IDENTIFICATION: The CAPRI study is registered in the Dutch Trial Registry as NL3440 (NTR3591).

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INTRODUCTION

Androgen deprivation therapy (ADT) is the cornerstone of treatment in patients with distant metastatic hormone-sensitive prostate cancer (mHSPC), either alone or combined with chemotherapy or androgen receptor targeting drugs (ART) [1]. Although mHSPC patients initially respond well to treatment, progression to metastatic castration resistant prostate cancer (mCRPC) is inevitable [2]. Prostate cancer mostly disseminates to the lymph nodes and bone, but visceral metastases (VMs) are increasingly detected during the course of disease, mostly during the mCRPC phase [3]. In a retrospective analysis of clinical trial participants with CRPC who were systematically screened for VMs every twelve weeks, 32% of 359 patients had VMs, mostly liver (20%) or lung (13%) metastases [3]. The prevalence of VMs increased during the course of the disease from 14% in nine to twelve months prior to death to 49% within 3 months before death [3]. We previously reported a 4% incidence of VMs at CRPC diagnosis in a real-world population (albeit 77% of patients lacked

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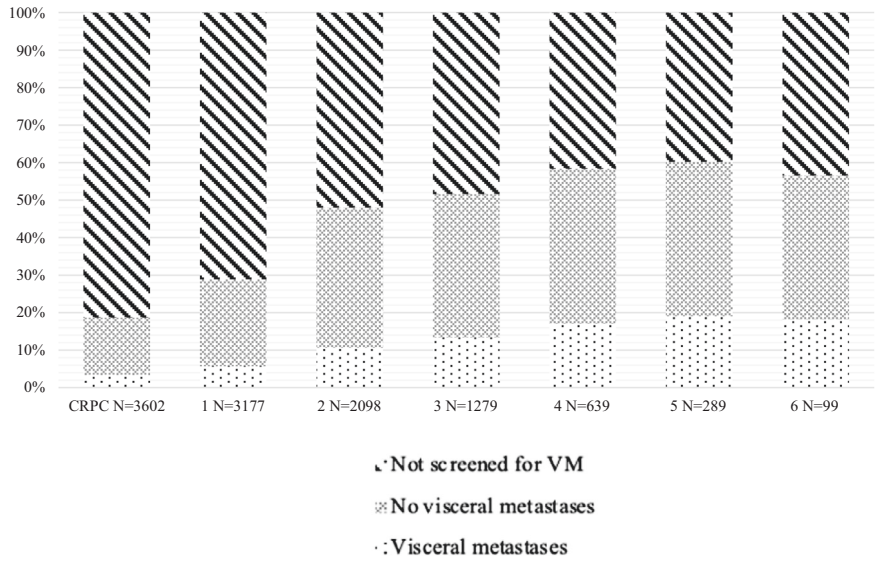

Fig. 1 Screening rate of visceral metastases from CRPC-diagnosis to treatment line 6.

imaging for VMs at diagnosis) [4]. VMs at CRPC diagnosis have a negative impact on overall survival [4, 5]. Moreover, the location of VMs influences survival: patients with lung metastases have a better survival than patients with liver metastases (19.4 vs 13.5 months respectively) [6].

Although CRPC is incurable, several therapies have been registered based on a survival benefit for treatment of CRPC since 2004: the chemotherapies docetaxel (DOC) and cabazitaxel (CAB), the ART abiraterone acetate plus prednisone (ABI + P) and enzalutamide (ENZ), and the radioisotope radium-223 (Ra-223) [7]. In 2020, olaparib was also registered as new treatment for CRPC in patients previously treated with ART [8]. Selecting the optimal treatment for an individual patient remains challenging. Prognostic factors, for example the presence of liver metastases, can guide treatment decisions. To illustrate, treatment with chemotherapy is advised over ART in chemo fit patients with poor prognostic diseases especially in the first treatment line [1, 9, 10]. Off-label platinum containing regimens are also considered in patients with visceral metastases as part of a broader definition of aggressive variant prostate cancer, where the addition of platinum to cabazitaxel has showed a clinical meaningful progression-free survival benefit in a randomized phase 2 trial [11]. Moreover, Ra-223 is contraindicated in patients with visceral disease [7].

Little is known about the presence of VMs and outcomes in a contemporary real-world population. Therefore, we studied the proportion of patients radiologically screened for VMs (i.e. screening rate) and the occurrence of VMs in a real-world CRPC population. We also assessed the impact of the presence of VMs and their location on overall survival.

PATIENTS AND METHODS

Study design and setting

Data from the observational, retrospective and Dutch 'castration-resistant prostate cancer registry' (CAPRI) were used for this study. The study design has been described before [4]. Radiologic assessment of disease state was recorded at the date of CRPC-diagnosis and the start of every subsequent systemic treatment. Radiologic assessment was not protocol mandated. CAPRI is registered in the Dutch Trial Registry as NL3440.

Participants

Patients with CRPC between 2010 and 2016 were included and followed up to December 2017. CRPC was defined by the European Urology Association (EAU) CRPC definition [1] or as progression according to treating physician. Antiandrogen therapy following progression on ADT was considered as first-line treatment for CRPC. Patients with prior docetaxel treatment for metastatic hormone-sensitive prostate cancer were excluded. Groups were created based on the presence of VMs at CRPC diagnosis and every subsequent treatment line: visceral metastases (subgroup 1) vs no visceral metastases (subgroup 2) vs not screened for visceral metastases (subgroup 3).

Patients diagnosed with VMs were included in further analysis by location (liver, lung or both liver and lung metastases) based on the first presentation of VMs. VMs at pancreatic, adrenal, and other sites were excluded due to a very limited number of these events.

Outcome

The screening rate was defined as the proportion of patients with radiologic imaging for VMs of the total number of patients. Overall survival (OS) was measured as time in months from CRPC-diagnosis and every subsequent systemic treatment line to date of death. Patients alive or lost-to-follow-up at the end of follow-up were censored at last visit date in all survival analyses. For patients with VMs, OS was estimated from the date of first diagnosis of VMs based on groups by location of VMs.

Statistical analysis

Descriptive analyses were performed. Differences between groups were tested using a one-way ANOVA test and a Kruskal Wallis for continuous variables and a chi-square test for categorical variables. Survival analyses were performed using Kaplan–Meier analysis with log-rank test and Cox proportional hazard regression analysis, the latter after multiple imputations of missing baseline characteristics at first diagnosis of visceral metastases by the Monte Carlo Markov Chain method. The missing data were approximated in ten independent sets by using the distributions of the gathered data [12]. Before the multiple imputations LOG transformation of LDH, ALP, PSA, and time from castration to CRPC were performed to improve the normality. The imputed data were approximated within the range of the gathered data and differed over the 10 sets. After the performance of the multiple imputations each set was analysed individually and finally combined. As a result, this generated new overall approximations [12]. The outcomes, end of follow-up and OS, were entered as indicators only. IBM SPSS Statistics version 24.0 (IBM, Armonk, NY, USA) has been chosen and a p-value lower than 0.05 is considered statistically significant for all statistical analyses.

RESULTS

In total, 3602 patients with CRPC were included in the analyses.

Screening rate per treatment line

During the course of the disease, the percentage of patients radiologically screened for VMs increased per treatment line, from 18.7% at the initial diagnosis of CRPC to 56.6% at the start of

Table 1. Baseline characteristics at first diagnosis of visceral metastases.

	Location of visceral metastases ($N = 457$)			*p*-value
	Liver $N = 230$	Lung $N = 161$	Liver and Lung $N = 66$	
Age (years)				
Median (IQR)	71 (65–76)	72 (68–78)	70 (64–76)	0.004*
<75, *n* (%)	151 (66)	100 (62)	45 (68)	
≥75, *n* (%)	79 (34)	61 (38)	21 (32)	
ECOG PS, *n* (%)				
0	15 (7)	13 (8)	5 (8)	0.098
1	18 (8)	18 (11)	3 (5)	
≥2	142 (62)	70 (44)	45 (68)	
Missing	55 (24)	60 (37)	13 (20)	
CCI, *n* (%)				
6	169 (74)	108 (67)	49 (74)	0.330
≥6	61 (27)	53 (33)	17 (26)	
LN metastases, *n* (%)				
No	33 (14)	34 (21)	11 (17)	0.213
Yes	158 (69)	102 (63)	49 (74)	
Missing	39 (17)	25 (16)	6 (9)	
Bone metastases, *n* (%)				
No	15 (7)	13 (8)	8 (12)	0.386
Yes	190 (83)	141 (88)	54 (82)	
Missing	25 (11)	7 (4)	4 (6)	
Gleason Score**, *n* (%)				
≤7	83 (36)	43 (27)	26 (39)	0.089
8–10	122 (53)	100 (62)	35 (53)	
Missing	25 (11)	18 (11)	5 (8)	
Time to CRPC (mo)				
Median (IQR)	12.0 (6–22)	13.6 (8–27)	11.0 (7–20)	0.203
Time CRPC to VM (mo)				
Median (IQR)	10.0 (1–22)	6.0 (0–16)	6.5 (0–23.5)	0.029*
Opioid use, *n* (%)				
No	58 (25)	43 (27)	20 (30)	0.119
Yes	70 (30)	28 (17)	20 (30)	
Missing	102 (44)	90 (56)	26 (39)	
Hb (mmol/L)				
Median (IQR)	7.3 (6.4–8.1)	7.9 (7.1–8.4)	7.4 (6.7–8.3)	0.001*
Missing, *n* (%)	25 (11)	30 (19)	10 (15)	
LDH (U/L)				
Median (IQR)	307 (226–526)	236 (193–302)	291 (223–537)	<0.001*
Missing, *n* (%)	50 (22)	67 (42)	15 (23)	
ALP (U/L)				
Median (IQR)	155 (108–344)	125 (82–238)	187 (104–337)	0.005*
Missing, *n* (%)	29 (13)	33 (21)	8 (12)	
PSA (μg/L)				
Median (IQR)	99.8 (26–274)	44.2 (16–159)	54.3 (22–199)	0.019*
Missing, *n* (%)	18 (8)	14 (8)	5 (8)	
Prior treatments, *n* (%)				
0	131 (57)	122 (76)	49 (74)	0.001*
1	53 (23)	24 (15)	7 (11)	
>1	46 (20)	15 (9)	10 (15)	

IQR interquartile range, *ECOG PS* Eastern Cooperative Oncology Group Performance Score, *CCI* Charlson comorbidity index, *LN* lymph nodes, *CRPC* castration resistant prostate cancer, *mo* months, *Hb* haemoglobin, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *PSA* prostate specific antigen.
*Significant at $p < 0.05$.
**Gleason score is measured at CRPC diagnosis.

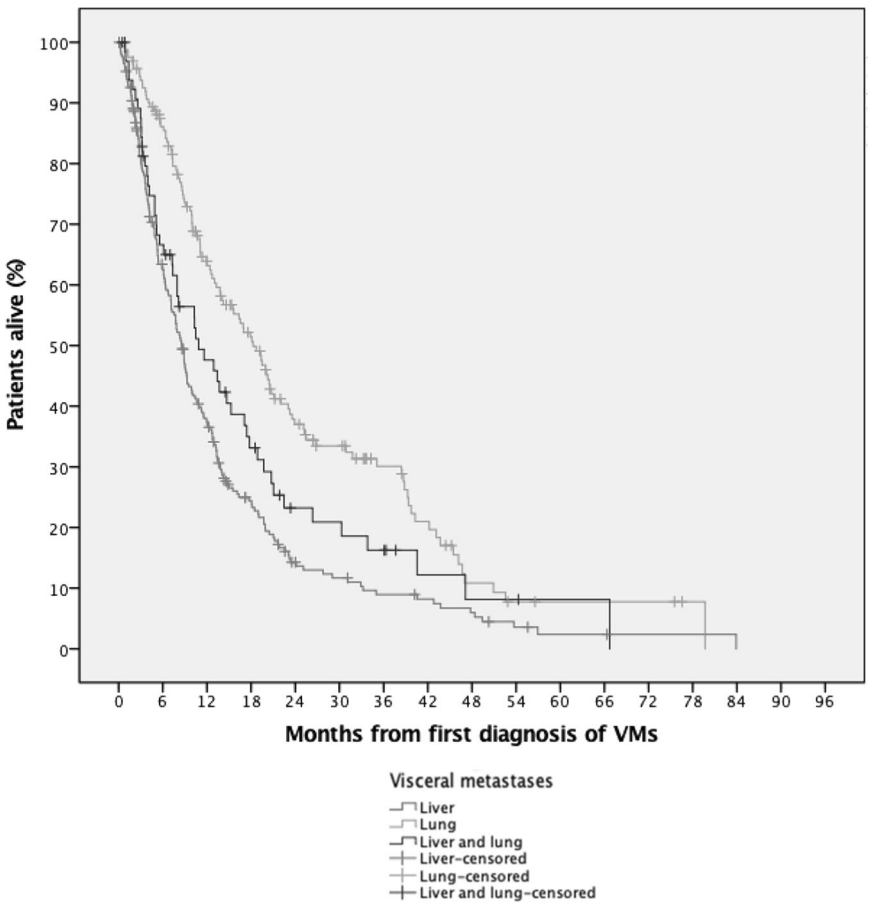

Fig. 2 Kaplan Meier survival curves of the location of visceral metastases.

systemic treatment line 6 (Fig. 1). In turn, over 80% of the patients were not screened for VMs at CRPC diagnosis and about 40% did not have a screening at start of systemic treatment, i.e. lines 4 to 6.

The proportion of patients diagnosed with VMs over the total number of patients screened increased per treatment line: from 18.6% at CRPC-diagnosis to 32.1% at the start of line 6. However, in later lines the absolute number of screened patients decreased due to a lower total number of patients (Fig. 1).

In total 457 of 3602 patients (12.7%) were diagnosed with VMs at CRPC diagnosis or during follow-up. VMs included liver metastases in 230 patients (6.4%), lung metastases in 161 patients (4.5%) and both liver and lung metastases in 66 patients (1.8%).

Treatment decisions

As a first treatment line, first generation hormonal agents as bicalutamide (defined as 'non-LPD') were commonly prescribed to all CRPC patients. In the first and second treatment line, the percentage of patients with VMS receiving docetaxel or cabazitaxel was 44.8% and 55.8% respectively in comparison with 31.4% and 39.6% respectively in patients without VMs (Supplementary Material Table 1).

Baseline characteristics of patients with VMs

At first diagnosis of VMs, patients with liver metastases had generally worse prognostic characteristics compared to patients with lung metastases and comparable with both liver and lung metastases, namely higher lactate dehydrogenase (307 vs 236 and 291 U/L respectively, $p < 0.001$), higher prostate specific antigen (100 vs 44 and 54 µg/L respectively $p = 0.019$), higher alkaline phosphatase (155 vs 125 and 187 U/L respectively, $p = 0.005$) (Table 1). liver metastases as sole site of VMs presented at a later point in time from CRPC diagnosis compared to patients with only lung metastases, however not compared to both liver and lung metastases (10.0 vs 6.0 and 6.5 months respectively, $p = 0.029$). Patients with liver metastases were more heavily pre-treated (20% vs 9% and 15% respectively with >1 prior treatment, $p = 0.001$). The number of lymph node (69% vs 63% and 74% respectively, $p = 0.213$) and bone metastases (83% vs 88% and 82% respectively, $p = 0.386$) were similar in all groups.

Overall survival

The median follow-up of all CRPC patients was 25.1 months (IQR 12.6–39.8 months) from CRPC diagnosis. At the end of follow up 2432 patients (67.5%) had died, 415 patients (11.5%) were alive, and 755 patients (21.0%) were lost to follow-up. Survival of patients with VMs remained at least 4 months worse compared to patients without VMs, at any point in time from CRPC diagnosis to the 6th treatment line (Supplementary Material Table 2).

The median follow-up of the 457 patients with VMs was 9.9 months (IQR 4.3–19.9) from first diagnosis of VMs. At the end of follow-up 362 patients (79.2%) had died, 34 patients (7.4%) were alive, and 61 patients (13.3%) were lost-to-follow-up. Median OS from VM diagnosis was 8.6 months (IQR 3.8–16.3) in patients with liver metastases, 18.3 months (IQR 8.7–39.3) in patients with lung metastases and 10.9 months (IQR 4.2–22.5) in patients with both liver and lung metastases ($p < 0.001$) (Fig. 2).

In univariable Cox-regression, lung metastases were associated with better OS than liver metastases (HR 0.519 CI 95% 0.411–0.655). However, both liver and long metastases were not associated with better OS than liver metastases (HR 0.769 CI 95% 0.565–1.047) (Table 2). Also, after correction of prognostic

Table 2. Univariable and multivariable Cox-regression analysis.

	n/N[a]***	Univariable analysis			Multivariable analysis		
		HR	CI 95%	*p*-value	HR	CI 95%	*p*-value
Visceral metastases							
Liver	197/229	REF	-	-	REF	-	-
Lung	114/161	0.519	0.41–0.66	<0.001*	0.650	0.50–0.84	0.001*
Liver+lung	51/66	0.769	0.57–1.05	0.095	0.970	0.69–1.36	0.858
Age (years)	362/456	1.003	0.99–1.02	0.696	1.021	1.01–1.04	0.005*
ECOG PS							
0	23/33	REF	-	-	REF	-	-
1	24/39	0.664	0.37–1.19	0.169	1.049	0.55–2.00	0.884
≥2	210/256	1.853	1.20–2.85	0.005*	1.694	1.03–2.78	0.038*
CCI							
6	258/325	REF	-	-	REF	-	-
≥6	104/131	1.107	0.88–1.39	0.383	1.125	0.87–1.45	0.360
LN metastases							
No	56/78	REF	-	-	REF	-	-
Yes	252/308	1.378	1.03–1.84	0.031*	1.280	0.92–1.79	0.145
Bone metastases							
No	23/36	REF	-	-	REF	-	-
Yes	311/385	2.135	1.39–3.27	<0.001*	1.454	0.91–2.33	0.119
Gleason Score**							
≤7	119/152	REF	-	-	REF	-	-
8–10	205/256	1.022	0.82–1.28	0.853	0.837	0.66–1.06	0.143
Time to CRPC (mo)	362/456	0.987	0.98–0.99	<0.001*	0.987	0.98–0.99	<0.001*
Time CRPC to VM (mo)	362/456	1.006	1.00–1.01	0.128	NA	NA	NA
Opioid use							
No	97/121	REF	-	-	REF	-	-
Yes	106/118	2.094	1.57–2.79	<0.001*	1.663	1.19–2.33	0.004*
Hb (mmol/L)	315/391	0.668	0.60–0.74	<0.001*	0.820	0.73–0.93	0.001*
LDH (U/L)	254/324	1.001	1.00–1.00	<0.001*	1.001	1.00–1.00	<0.001*
ALP (U/L)	308/386	1.001	1.00–1.00	<0.001*	1.000	1.00–1.00	0.379
PSA (ug/L)	331/419	1.000	1.00–1.00	0.007*	1.000	1.00–1.00	0.574
Prior treatments							
0	243/302	REF	-	-	REF	-	-
1	68/84	2.045	1.55–2.70	<0.001*	2.359	1.72–3.23	<0.001*
>1	51/70	2.756	2.01–3.78	<0.001*	2.222	1.58–3.13	<0.001*

HR hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group Performance Score, *REF* reference category, *CCI* Charlson comorbidity index, *LN* lymph nodes, *NA* not applicable, *CRPC* castration resistant prostate cancer, *mo* months, *Hb* haemoglobin, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *PSA* prostate specific antigen.

[a]number of events of total number of patients.

*Significant at *p*-value <0.05.

**Gleason score is measured at CRPC diagnosis.

***1 case censored before the earliest event in a stratum.

factors, differences in survival were seen between lung and liver metastases (HR 0.650, CI 95% 0.502–0.843) and not in both liver and lung metastases compared to those with liver metastases (HR 0.970 CI 95% 0.693–1.357) (Table 2 and Fig. 3). Higher haemoglobin (HR 0.820, CI 95% 0.727–0.925) and a longer time from castration to CRPC diagnosis (HR 0.987, CI 95% 0.981–0.993) were also related to longer OS. In contrary, higher LDH (HR 1.001, CI 95% 1.001–1.001), higher age (HR 1.021, CI 95% 1.006–1.036), opioid use (HR 1.663, CI 95% 1.185–2.334) and one or more prior treatment (HR 2.359 CI 95% 1.724–3.228 and HR 2.222, CI 95% 1.576–3.134 respectively) were associated with shorter OS. Moreover, an ECOG score of 2 or higher was associated with worse OS than an ECOG of 0 (HR 1.694, CI 95% 1.031–2.782).

DISCUSSION

We performed retrospective analyses using real-world data to determine the incidence and treatment of VMs in CRPC patients and the corresponding survival. The results reflect daily practice without mandatory use of research protocols in the period between 2010 and 2017. During and after this period new treatments for CRPC patients were registered and screening protocols could have been changed.

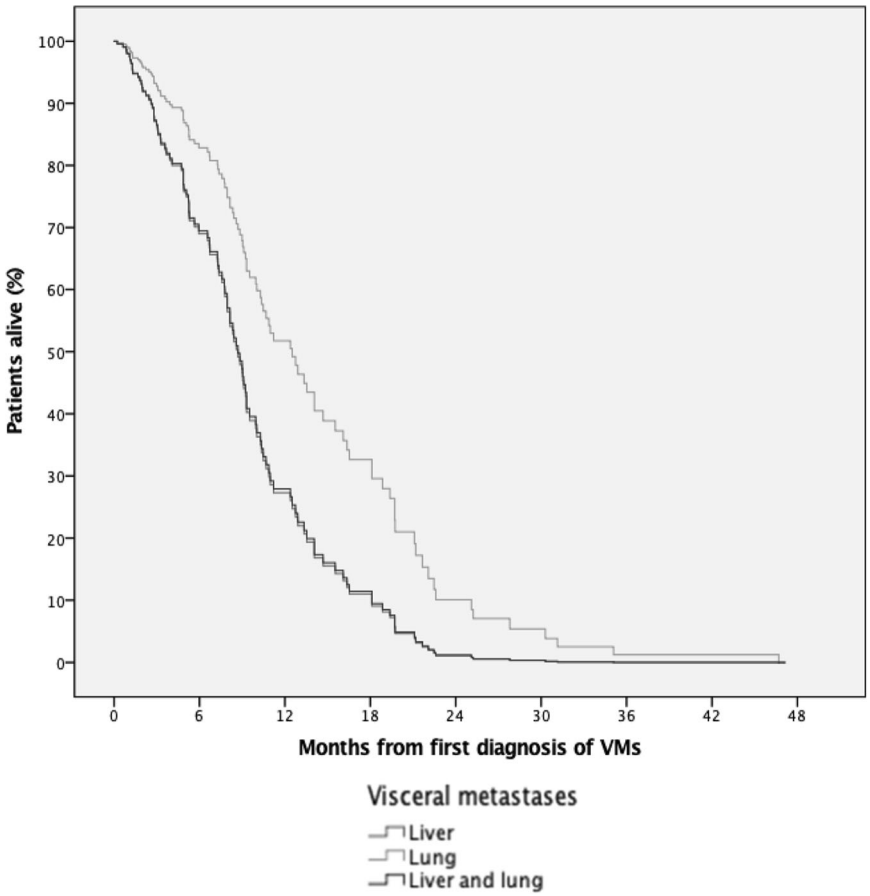

Fig. 3 Cox-regression survival curve of the locations of visceral metastases.

We observed an increase in the proportion of patients screened for VMs during the course of disease. However, over 80% of the patients at CRPC diagnosis to 40% at the start of systemic treatment lines 4 to 6 were not radiologically screened for VMs. This might reflect a limited assessment of known prognostic factors, however in the early years of our study guidelines not specifically recommended radiological screening for VMs. Nowadays it is clear that patients with VMs have worse OS than patients without VMs, making it important to screen for VMs in order to adequately estimate life span and prevent inappropriate care [5, 13]. Identification of visceral disease is necessary to initiate the appropriate treatment or best supportive care [1, 9, 10]. Overuse of treatments and hospitals resources should be prevented when life expectancy is short. In order to guide treatment decisions, better screening of CRPC patients for VMs is thus warranted.

In this study VMs were qualified of CRPC origin, solely by radiological examination, without necessitating histologic confirmation, since biopsies are not common practice in advanced stage CRPC. We could therefore not discriminate between VMs of prostate cancer or VMs of a second primary malignancies (SPM), as a result, possibly overestimated the incidence of VMs.

In this study we show the importance of the location of VMs. Patients with lung metastases had a significantly better OS than patients with liver metastases, which is in line with a previously published meta-analysis of randomised controlled trials [6]. The difference in survival between patients with lung and liver metastases could be explained by a difference in genomic makeup of patients with prostate cancer and lung-only and liver-only metastases. ADT-naïve patients with lung-only metastatic prostate cancer show higher proportions of actionable DNA-repair gene alterations (50%), including DNA mismatch-repair gene alterations, and homologous recombination defects, when compared to the TCGA dataset [14]. Also, fewer TP53 mutations were found compared to the SU2C dataset, with similar proportions in PTEN inactivation. These data in limited patients with lung-only VMs support differences in prognostic genomic molecular driver mutations [14]. Liver metastases appear more genomically unstable compared to lung or other sites of metastases and are enriched in poor prognostic alterations such as MYC amplification, PTEN deletion and PIK3CB amplification [15]. A difference in survival between patients with lung-only and liver metastases may also be due to higher rates of poor prognostic characteristics in the latter group. In this study there was no difference in survival between CRPC-patients with liver metastases and CRPC-patients with both liver and lung metastases, although we would have expected worse survival in the latter group. This might be explained by a small population with both liver and lung metastases.

In general, median OS of patients with liver metastases in our study was shorter (8.6 months) than in a meta-analysis from data of multiple randomised controlled trials (13.5 months) [6]. One explanation might be relatively worse prognostic factors at the diagnosis of VMs (i.e., low haemoglobin, high age) in our real-world patient populations compared to the clinical patient population in the meta-analysis [6]. Moreover, only 70% of patients in our cohort was treated with a life-prolonging treatment, while in the clinical trial populations included in the analysis, everyone had prior treatment with docetaxel [6]. Furthermore, radiologic assessment in our study was based on clinicians' opinion while in the randomized controlled trials this was protocol mandated [6]. This suggests lead-time bias due to earlier detection and longer survival in clinical trial populations include in the meta-analysis [6].

In addition to the location of VMs, haemoglobin, lactate dehydrogenase, age, time from castration to CRPC, opioid use, ECOG performance score, and prior treatment also had a significant impact on survival. These are known factors related to more aggressive disease states with poorer survival [16, 17].

The first limitation of this study is the low VM screening ratio by lack of routine use of CT-imaging of the lungs and abdomen. Real world radiologic assessment was not protocol mandated. CRPC patients were screened on clinicians' opinion, which might be the suspicion of metastases. Therefore, the proportion of patients diagnosed with VMs over the total patients screened could have been overestimated. Moreover, clinical signs of VMs are often present at later disease phases. If radiologic screening was performed based on the suspicion of VMs, this could have led to a selection bias and effect survival outcomes in our study. We do not know who were responsible for and which criteria were used for the decision whether or not to screen CRPC patients and therefore the extent of selection bias is hard to determine.

The second limitation of this study is that we had substantial missing data. We lacked information on prognostic characteristics, as for example albumin and liver transaminases, which could have influenced the survival outcomes [6]. Also values of included characteristics (e.g., lactate dehydrogenase) were missing. Missing data results in smaller study populations in multivariable analyses and indicates the importance of thorough documentation of patient characteristics. Multiple imputation of missing baseline values prior to multivariable cox-regression analysis offers a valid solution for this limitation [12].

In conclusion, this real-world analysis showed that the radiologic screening rate of VMs improved during follow-up, but over 80% of the CRPC patients at CRPC diagnosis to 40% at the start of systemic treatment lines 4 to 6 were not screened for VMs in CRPC. Nowadays it is known that VMs impact survival and treatment decisions, as do the location of the metastases (i.e., worse survival in patients with liver metastases). Therefore, better screening of CRPC-patients for VMs is warranted.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Study concept and design: GPAvdB and MCPK. Data analysis and/or interpretation: GPAvdB, MCPK, HMW, NM, WRG, KKHA, IMvO, RJAvM, DMS, AJMvdE, AMB, ACMvdB, CAUdG. Drafting of the manuscript: GPAvdB, MCPK, HMW, NM, WRG, ACMvdB, CAUdG. Critical revision and final approval of the manuscript: GPAvdB, MCPK, HMW, NM, WRG, KKHA, IMvO, RJAvM, DMS, AJMvdE, AMB, ACMvdB, CAUdG.

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COMPETING INTERESTS

GPAvdB and MCPK report no conflict of interest. HMW reports travel expenses from Astellas and Ipsen; honoraria from Astellas and Roche. NM reports advisory role for Astellas, AstraZeneca, Janssen, JNJ, MSD, Pfizer, and Roche; funding (institutional and/or personal) from Astellas, Janssen and Pfizer; research grants (institutional) from AstraZeneca and BMS; coordinating PI (institutional) for BMS and Jansen; and non-financial interests (leadership-role or PI) in Castration-resistant Prostate Cancer Registry, Dutch Uro-Oncology Study Group and Prospective Bladder Cancer Infrastructure (Netherlands). WRG reports speaker fees (institutional and/or personal) from MSD; advisory role (institutional) for Bristol-Myers Squibb and Bayer; research grants (institutional) from Astellas, Bayer, Janssen-Cilag and MSD. KKHA reports no conflict of interest. IMvO reports conflicts of interest for Astellas, Bayer, Jansen, MSD/Astra and AAA Novartis. RJAvM reports conflicts of interest for Astellas, AstraZeneca, Bayer, Janssen, Pantarhei Oncology and Sanofi-Genzyme. DMS reports research grants/funding (institution) from Astellas, Besins and Dutch Cancer Society; Advisory/consultancy role for Astellas, Janssen, Bayer and MSD; contracted research (institution) for Janssen, Eli Lilly, Astellas, Blue Earth Diagnostics, Bayer, SPL medical and QED therapeutics. AJMvdE reports study grants from Sanofi, Roche, Bristol-Myers Squibb, TEVA and Idera; travel expenses from MSD Oncology, Roche, Pfizer and Sanofi; speaker honoraria from Bristol-Myers Squibb and Novartis; advisory role for Bristol-Myers Squibb, MSD Oncology, Amgen, Roche, Novartis, Sanofi, Pfizer, Ipsen, Merck and Pierre Fabre. AMB reports conflicts of interest for Astellas, Sanofi, Bayer and Janssen. ACMvdB and CAUdG report no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

ADDITIONAL INFORMATION

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