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Circulating Tumor Cell Number as a Prognostic Marker in Progressive Castration-Resistant Prostate Cancer: Use in Clinical Practice and Clinical Trials

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SUMMARY

Background—To assess the use of circulating tumor cell (CTC) number as a continuous variable as a prognostic factor for survival, and for the clinical management of patients with progressive metastatic castration-resistant prostate cancer receiving first-line chemotherapy.

Methods—The study included 164 men with progressive metastatic castration-resistant prostate cancer. CTCs were isolated by immunomagnetic capture from blood samples drawn at baseline and after the initiation of first-line chemotherapy. Baseline variables including CTC number, prostate-specific antigen (PSA), and lactate dehydrogenase (LDH), and posttreatment variables (fold change in CTCs and PSA) were tested for association with survival using the Cox proportional hazards models. The concordance probability estimate was used to gauge the discriminatory strength of the informative factors in separating low- and high-risk patients.

Findings—At baseline, variables associated with increased risk of death were a high LDH (hazard ratio [HR] 6.44), CTC number (HR 1.58), and PSA (HR 1.26), low albumin (HR 0.10), and low hemoglobin (HR 0.72) (all $p<0.001$). At 4, 8, and 12 weeks posttreatment, changes in CTC number were strongly associated with risk (all $p\leq0.001$), while changes in PSA were modestly associated ($p=0.04$ to 0.8). The combination of factors most predictive of survival were LDH and CTC number (concordance probability estimate 0.72–0.75). Time to CTC progression was modestly associated with time to death.

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Conflicts of Interest None.

Interpretation—CTC number, analyzed as a continuous variable, was more predictive of survival than PSA at baseline and during patient follow-up, and can be used to monitor disease status. A model including baseline and posttreatment CTC, independent of discrete cutoff values, and baseline LDH was most predictive. The prospective evaluation of CTC number as an intermediate endpoint of survival in randomized prospective clinical trials is warranted.

Funding—The Prostate Cancer Foundation.

Keywords

circulating tumor cells; prostate cancer; PSA; LDH; prognosis

INTRODUCTION

In both clinical trials and clinical practice, outcome measures are designed to assess disease activity so that the effects of an intervention can be assessed accurately. To monitor patients with metastatic castration-resistant prostate cancer (CRPC), bone scans are insensitive to changes in disease status,(1) and, although posttherapy PSA changes are used to guide treatment decisions, they are not surrogates of clinical benefit.(2) A series of trials for patients with metastatic breast, colorectal, and prostate cancer who were about to start a new line of chemotherapy showed that circulating tumor cell (CTC) number measured with the analytically valid CellSearch™ system (Veridex, LLC, Huntingdon Valley, PA) proved prognostic for survival before therapy and predictive of treatment outcome after therapy based on disease-specific cutoff values to define favorable and unfavorable groups.(3-5) The results led the US Food and Drug Administration (FDA) to clear the test to be used in conjunction with other clinical methods “as an aid in the monitoring of patients” with these diseases.(6)

In the IMMC38 trial on which the FDA clearance for prostate cancer was obtained, the favorable vs unfavorable groups were defined in the protocol by a CTC cutoff value of 4 cells or less vs 5 cells or more per 7.5 mL blood. The trial enrolled patients with CRPC who were about to begin a “new” first-, second-, or third-line chemotherapy regimen.(5) In a separate group of patients with CRPC treated at Memorial Sloan-Kettering Cancer Center, we also showed an association between baseline CTC number and survival, but the association did not have a threshold effect,(7) while a third study suggested that a 30% decline in CTC number was most predictive.(8) In all three series, the discriminatory power for patient risk was enhanced by accounting for known pretreatment prognostic factors.(2,7-13)

The use of *(or application of)* discrete cutoff values in a clinical practice setting assumes (or implies) that a patient with a 90% decline in CTC number from 100 to 10 is worse off than a patient with a 33% decline from 6 to 4, and that therapy should be discontinued in the patient with a post-treatment value that remains in the “unfavorable” range independent of a whether or not the value has declined from the pretreatment baseline. To address this, we reanalyzed the IMMC38 data by considering baseline and posttreatment CTC number as a continuous variable. The analysis considered the role of other pretreatment prognostic factors and outcome, and addressed the inherent survival difference between patients receiving first-, second-, and third-line chemotherapy,(14) by only evaluating patients about to receive first-line therapy, The median patient follow-up was 6 months longer than in the original report.(5) Last, we explored the association of different CTC and PSA progression definitions and survival based on either one or two rising values to further assess its application in both a clinical practice setting and as a potential intermediate endpoint for clinical trials.

METHODS

Study design

The study group consisted of patients with histologically confirmed progressive metastatic prostate cancer based on the PSA Working Group criteria(15) and castrate levels of testosterone (< 50 ng/dL) who were commencing first-line chemotherapy on IMMC38.(16) Eligibility requirements included an ECOG performance status of 0, 1, or 2, a pretreatment PSA ≥ 5 ng/mL, progression after a trial of anti-androgen withdrawal as appropriate, and no radiation therapy within 30 days of enrollment. Before treatment, all patients had a complete blood count and determination of PSA, alkaline phosphatase, and lactate dehydrogenase (LDH) levels, as well as a separate sample for CTC enumeration. Patients underwent a radionuclide bone scan, chest x-ray or computed tomography of the chest, and computed tomography of the abdomen and pelvis. After initiating treatment, PSA and CTC number were measured before each chemotherapy cycle until progression of disease was documented. Follow-up imaging was at the discretion of the treating physician. The protocol was approved by local institutional review boards and required written informed consent from each patient.

Isolation and enumeration of circulating tumor cells

CTC enumeration was performed using the CellSearch and CellTracks systems as described.(17,18) Blood samples were drawn into 10 mL evacuated blood-draw tubes (CellSave, Immunicon, Huntingdon Valley, PA), maintained at room temperature, and processed in a blinded fashion within 96 hours of collection in one of four laboratories (Immunicon, Huntingdon Valley, PA; Immunicon, Enschede, The Netherlands; IMPATH Predictive Oncology, Los Angeles, CA; and Cleveland Clinic, Cleveland, OH). CTCs were scored as DAPI-stained nucleated cells that express cytokeratin and not CD-45. Technical details of the assay, including accuracy, precision, linearity, and reproducibility, have been described elsewhere.(17,18)

Statistical design

The Kaplan-Meier method was used to estimate the probability of survival over time. The Kruskal-Wallis test was used to test for equality of CTC number between sites. The association between biomarkers and survival time was tested using the Cox proportional hazards models. The posttreatment markers were modeled using fold change (the ratio of the posttreatment value to the baseline value). The hazard ratio associated with each biomarker was derived from the Cox model, and represents an increase in the hazard for a unit increase in the biomarker. Because of their positively skewed distributions, the logarithms of LDH, albumin, CTCs, and PSA were used for the purpose of modelling. Tests for the association between biomarkers and survival time were based on the score statistic, derived from the Cox proportional hazards model. Subsequent to the individual tests, the Cox model was used to determine the factors associated with survival time. Factors which maintained a p-value less than 0.05 in the multiple variable Cox model, provided independent information for their association with survival time, and were included in the final regression models. Factors that were not found to have independent prognostic value were: albumin, hemoglobin, and Gleason score. In addition to adjusting for baseline markers, a landmark analysis was used to explore the prognostic significance of CTC and PSA values recorded 4, 8, and 12 weeks posttreatment. Landmark analyses were used to avoid the additional modeling assumptions needed to perform a continuously valued time-dependent covariate analysis.

To depict the relationship between survival time and CTC, LDH, and PSA, a smoothed Kaplan-Meier estimate of the median survival conditional on each covariate was generated.(19) The discriminatory power of these biomarkers for survival was assessed by entering the factors into a proportional hazards model and computing concordance probability estimate (CPE).(20) The

CPE represents the probability that for any pair of patients, the patient with the better predicted outcome from the Cox model had the longer survival time. Finally, to determine the association between survival time and time to PSA or CTC progression, a version of Kendall's tau was applied.(21) This measure of association varies between −1 and 1, with 1 representing perfect concordance between the two endpoints and −1 representing perfect discordance between them; a measure of zero represents no relationship between the two variables. For this analysis, either a single rise or two increases in the biomarker over time were defined as a progression.

Role of funding source

Complete study data was provided by the study sponsor (Immunicon Corporation) for the independent analysis reported herein. Funding for the analysis was provided by the Prostate Cancer Foundation. The sponsor had no role in the analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

RESULTS

A total of 276 patients were enrolled on IMMC38, of whom 164 were about to begin first-line chemotherapy. Of these 164 patients, 8 did not have evaluable baseline blood draws. The baseline characteristics of this first-line chemotherapy group are presented in Table 1. For 147 patients (90%), the ECOG performance status was 0 or 1. The first-line chemotherapy was docetaxel or a docetaxel-containing regimen (consistent with the established standard of care). At the time of analysis 103 (61%) of the 164 patients had died, with a median survival of 19 months (95% confidence interval [CI] 14 to 23 months). The median follow-up for the 51 patients still alive was 22 months (range, 0.03 to 33 months). The Kaplan-Meier estimate of survival is provided in Figure 1.

The distribution of CTC counts at baseline is detailed Table 2. The median and interquartile range of CTC number based on pattern of spread are shown in Figure 2. The median CTC number was higher for patients with bone disease than for patients with visceral spread, although this difference did not reach statistical significance (p=0.06).

Table 2 **also** shows the distribution of CTC counts at 4, 8, and 12 weeks posttherapy. The number of patients assessed at these time points was similar. At baseline, the proportion of patients with CTC counts in the range of 0 to 4 was 46%, (71/156) which increased to 63% (100/158), 69% (107/156), and 69% (107/154) at 4, 8, and 12 weeks respectively. Overall, the proportion of patients with CTC counts of 4 or less at baseline, 4, and 8 weeks showed no further change at 12 weeks.

Table 3a shows the association between each biomarker and survival. At baseline, high LDH, CTC number, and PSA were associated with increased risk of death. Low albumin and low hemoglobin were also associated with death, while the Gleason score at diagnosis was not. Relative to baseline, the fold change after treatment in CTC number remained a strong indicator for the risk of death, whereas the association between the fold change in PSA and survival was attenuated.

Figure 3 shows the estimated median survival time based on CTC number, PSA, and LDH before the start of therapy. Estimated median survival monotonically decreased with increasing baseline CTC number, although patients with low baseline CTC number had a range of survival times. The pattern for PSA was similar although the relationship was not as strong, while the pattern for LDH showed a sharper decline in median survival for LDH values above the normal range. The larger hazard ratio for LDH is indicative of this sharp decline.

Landmark analyses were performed for the postbaseline models (Table 3b). At each time point, only CTCs and the baseline LDH value were jointly informative for survival; after accounting for CTCs at the specific time point and LDH at baseline, PSA either at baseline or after treatment, baseline albumin, and baseline hemoglobin did not provide additional information on risk of death. Individually, the baseline values of CTC and LDH were superior in identifying patient risk (CPE=0.69) in comparison to the baseline PSA value (CPE=0.59) (Table 4). The combination of baseline CTC, baseline LDH, and CTC fold change at each follow-up interval (CPE=0.74, 0.75) produced the strongest discriminatory power. A CPE equal to 0.75 indicates that for a pair of patients, the odds that the patient with a lower risk of death as indicated by CTC and LDH will live longer, is three to one. The posttreatment CTC models also produced a CPE approximately equal to 0.75.

In addition to assessing the prognostic value of the biomarkers, we also examined their utility as intermediate endpoints for a clinical trial. To this end, we measured the association between the time to biomarker progression, defined as either a single rise or two increases in the biomarker over time. Because we had longitudinal data on only the CTCs and PSA, these were the markers analyzed. The association between biomarker progression and survival, both time-to-event variables, was measured by Kendall's tau and adjusted for possible censoring in both variables. This measure of association varies between −1 and 1, with 1 representing perfect concordance between the two endpoints and −1 representing perfect discordance between them; a measure of zero represents no relationship between the two variables. The results showed a lack of association between the time to a single rise in PSA and survival (τ =0.07; 95% CI −0.04, 0.19) and a modest association between the time to a second PSA increase and survival time (τ =0.21; 95% CI 0.07, 0.33). In contrast, a single rise in CTCs was moderately associated with survival time (τ =0.30; 95% CI 0.18, 0.42), and waiting for the second increase in CTCs gave little benefit (τ =0.33; 95% CI 0.19, 0.46). Thus, from these data, CTCs are a more robust measure of progression than PSA.

DISCUSSION

The study showed that CTC number as a continuous variable is prognostic for survival of patients with CRPC starting first-line chemotherapy. As univariate measures, both indicators of disease burden (high LDH, CTC number, and PSA) and the constitutional status of the patient (lower albumin and hemoglobin) were predictive of a shorter survival. Most predictive of survival were models incorporating only baseline LDH and CTCs and posttreatment fold change in CTCs at 4, 8, or 12 weeks; the addition of PSA or any other factor gave no increase in information. Whereas time to PSA progression was only marginally associated with survival time, time to CTC progression was moderately associated.

Generating the evidence to guide the use of biomarkers in clinical practice requires a series of prospective trials that are designed to study a specific intended use. In the trials that led to the FDA clearance of the CellSearch assay for CTC enumeration as an "aid in the monitoring of patients" with breast, colorectal and prostate cancer, CTC number was analyzed only as a dichotomous factor (i.e., CTC number above or below a disease-specific cut-point).(3-5) The current analysis, performed with an additional 6 months of patient follow-up, was restricted to a more homogeneous group of patients about to start a chemotherapy for the first time. The median survival time of 18.6 months, similar to that observed in two randomized trials of docetaxel plus prednisone, (22,23) shows that the cohort analyzed was indeed representative of CRPC patients about to receive first-line chemotherapy with a taxane-based regimen. The results showed the continuous nature of the association between baseline CTC number, PSA, and LDH and survival, arguing against the use of discrete cutoff values. The finding of higher CTC numbers in patients with bone vs soft-tissue only disease reaffirms a previous finding

(7) that suggests a distinct pattern of spread, for unique biologic subtypes as proposed in the recent Prostate Cancer Working Group guidelines.(24)

A unique aspect of the analysis was the graphical illustration of the relationship between each parameter and survival. As shown, CTC number and PSA level were inversely related to survival time, while survival was relatively constant for LDH values in the normal range, but inversely related to LDH values that were outside of the normal range. This transition from relatively constant survival times sharply decreasing survival occurred just above an LDH of 240 IU/mL, the cutoff between the normal and abnormal range. Prospective studies to validate the significance of these findings are warranted. The strength of the association between baseline CTC number and survival is limited by the range of survival times for patients with low CTC number at baseline. As such, a low CTC number at baseline alone does not ensure a favorable prognosis for an individual patient.

Posttherapy, the combination of baseline LDH and pre- and posttherapy CTC number were most predictive independent of a cutoff value. The finding supports continuing a patient on the same treatment as long as CTC counts are stable or decreasing and there are no other signs of worsening disease. Also of note is that the addition of PSA levels did not provide additional predictive power, which argues against basing treatment decisions on changes in PSA alone when CTC counts are being monitored. This finding is consistent with the recently published Prostate Cancer Working Group guidelines that recommend that posttreatment changes in PSA, up or down, should not be used alone when deciding whether to continue treatment.(24) The recommendation is reinforced by the finding in the current analysis that a single rise in PSA was minimally associated with survival and two PSA rises only slightly associated with survival. It is also consistent with a previous study showing a modest association between PSA progression defined by the first Prostate Cancer Working Group criteria(15) and survival. (25) For CTCs, the degree of information provided was similar for a single rise and a second rise, although the overall association was also modest. As such, in the event of a rise in CTC number, a confirmatory test should be performed.

Ultimately, biomarker qualification for an intended use requires multiple prospective randomized trials powered to show clinical benefit to patients. If the trial is successful, the question whether a biomarker such as CTC number as a measure of patient risk and as an intermediate endpoint can begin to be addressed. Use as an intermediate or surrogate endpoint for survival is one such benefit that if demonstrated, could shorten the time line for drug approvals. Our analysis demonstrated a strong level of concordance between CTC number and LDH with survival time (CPE=0.75), but much about survival time remains unexplained. The understanding of survival time for patients with CRPC will be enhanced through the discovery of additional biomarkers and by the effort to record all biomarkers throughout patient follow-up. A phase 3 randomized trial powered on survival in which specific CTC biomarker questions are embedded, is currently ongoing to begin to address these questions.

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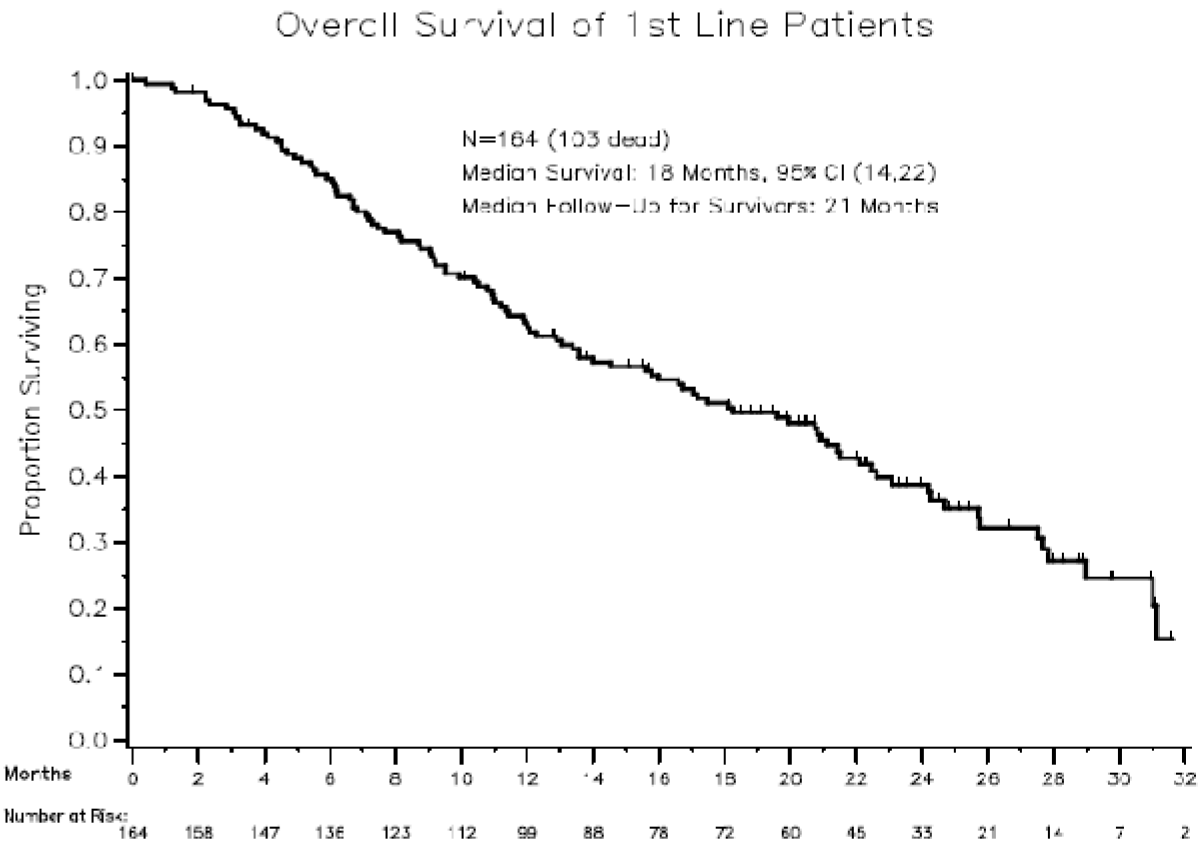

Figure 1. Overall survival of 1st line patients
Kaplan-Meier curve for overall survival.

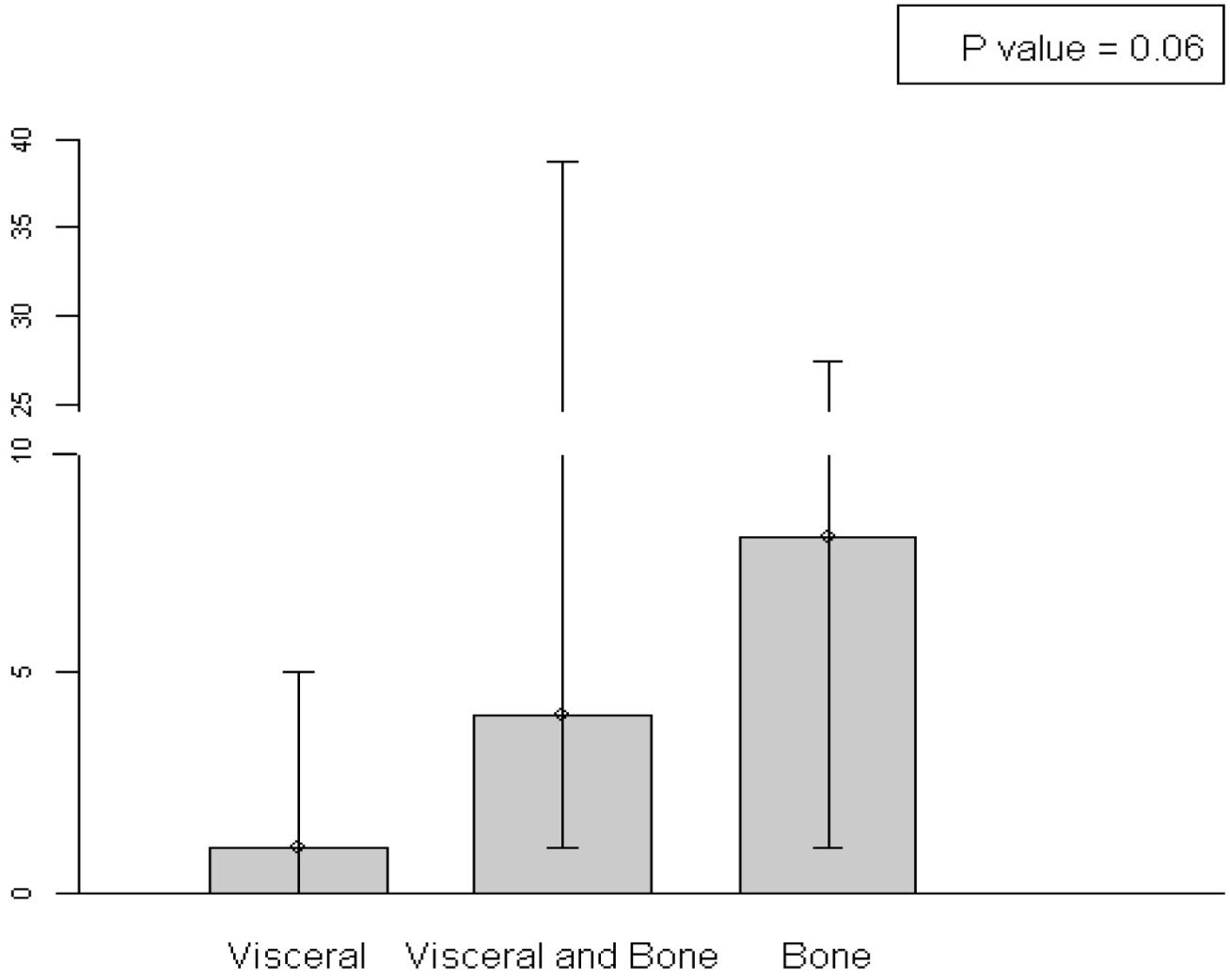

Figure 2. Baseline CTC number by metastatic site

Baseline CTC number by metastatic site. The p-value represents a Kruskal-Wallis test for equality of CTC number between sites.

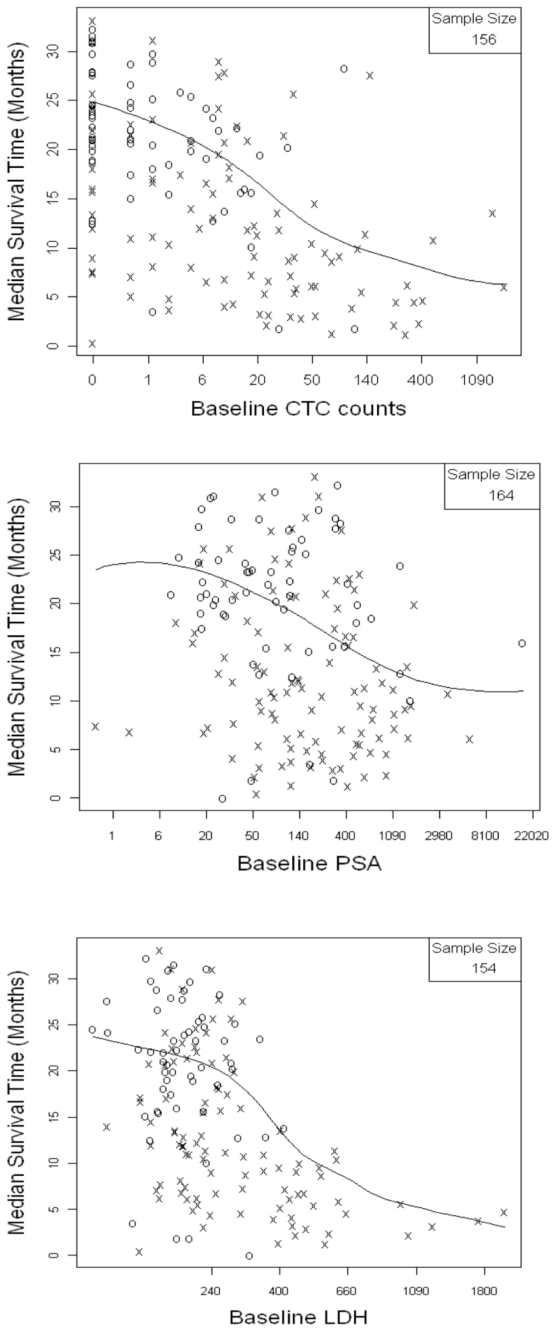

Figure 3. Estimated median survival time based on CTC number, PSA, and LDH

Solid line depicts the estimated median survival time according to baseline CTC number, PSA, and LDH. The symbols *x* represent time to death and *o* signify last follow up time.

Table 1

Characteristics of the 164 patients receiving first-line chemotherapy

Characteristic	N (%) or Median (Range)
Age, years	70 (49–87)
	7 (2–10)
Gleason score	
Primary therapy	
Radical prostatectomy	41 (25%)
Radiation therapy to the prostate	49 (30%)
No primary treatment	72 (44%)
Unknown (missing)	2 (1%)
Performance status (ECOG)	
0	75 (46%)
1	72 (44%)
2	11 (7%)
Unknown	6 (3%)
Chemotherapy	
Docetaxel	133 (81%)
Other	29 (18%)
Unknown	2 (1%)
Bone metastases	
Yes	143 (87%)
No	17 (10%)
Unknown	4 (3%)
Visceral metastases	
Yes	62 (38%)
No	101 (61%)
Unknown	1 (1%)
Biochemical markers	
PSA, ng/ml (n=164)	127 (1.9–17,800)
Lactate dehydrogenase, IU/ml (n=154)	223 (103 –1092)
Alkaline phosphatase, IU/ml (n=157)	144 (39 –2215)
Hemoglobin, g/dl (n=160)	12.6 (8.2–15.7)
Albumin, g/dl (n=158)	3.8 (2.1–4.1)
Circulating tumor cells (n=156)	6 (0-1816)

Table 2

Circulating tumor cell numbers at baseline and after initiation of first-line chemotherapy

	N (%)			
CTC Counts	**Baseline**	**4 weeks**	**8 weeks**	**12 weeks**
Total*	164	160	158	155
Evaluable†	156	158	156	154
0–4	71 (45)	100 (62)	107 (67)	107 (69)
5–9	20 (13)	18 (11)	11 (7)	9 (6)
10–50	39 (25)	29 (18)	27 (17)	27 (17)
>=51	26 (17)	13 (8)	13 (8)	11 (7)

At baseline, 8 patients had missing CTC values. Postbaseline, two or fewer patients had missing CTC values at each time point.

*Number of patients alive and on study.

†Number of patients with non-missing CTC data for that time point.

Table 3a

Association of individual biomarkers with the risk of death.

Factor	Baseline HR* (N)	P	4 Weeks HR† (N)	P	8 Weeks HR† (N)	P	12 Weeks HR† (N)	P
CTC	1.58 (155)	<0.0001	-		-		-	
PSA	1.26 (163)	0.0008	-		-		-	
LDH	6.44 (153)	<0.0001	-		-		-	
Albumin	0.10 (157)	0.0009	-		-		-	
hemoglobin	0.72(159)	<0.0001	-		-		-	
Gleason score	1.09(145)	0.2533	-		-		-	
CTC (FC)	-		1.57 (154)	0.0001	1.40 (152)	<0.0001	1.49 (147)	<0.0001
PSA (FC)	-		1.06 (161)	0.7622	1.24 (159)	0.0893	1.21 (154)	0.0424

All variables except hemoglobin and Gleason score were log-transformed.

FC represents fold change of the marker at k weeks relative to baseline. BL indicates baseline measure.

*Hazard ratios were generated using the score test, based on single-variable Cox models.

†Hazard ratio estimated from a two variable model that included the baseline value of the biomarker.

Table 3b

Cox models for prognostic factors associated with survival time.

Baseline (145)			4 Weeks (148)			8 Weeks (146)			12 Weeks (143)		
Factors	**HR**	**P**	**Factors**	**HR**	**P**	**Factors**	**HR**	**P**	**Factors**	**HR**	**P**
CTC	1.34	<0.0001	**CTC (FC)**	1.57	<0.0001	**CTC (FC)**	1.44	<0.0001	**CTC (FC)**	1.46	<0.0001
LDH	3.80	<0.0001	**CTC (BL)**	1.66	<0.0001	**CTC (BL)**	1.58	<0.0001	**CTC (BL)**	1.64	<0.0001
			LDH (BL)	4.20	<0.0001	**LDH (BL)**	4.25	<0.0001	**LDH (BL)**	3.96	<0.0001

Table 4

Concordance Probability Estimates (CPE) to assess the strength of prognostic factors to discriminate patient risk.

Factors	CPE (Std err)			
	Baseline	4 Weeks	8 Weeks	12 Weeks
CTC	0.69 (0.020)	-	-	-
PSA	0.59 (0.027)	-	-	-
LDH	0.69 (0.019)	-	-	-
CTC+LDH	0.72 (0.019)	-	-	-
CTC(BL)+ CTC(FC)	-	0.71 (0.018)	0.71 (0.019)	0.72 (0.019)
PSA(BL)+ PSA(FC)	-	0.60 (0.027)	0.61 (0.028)	0.61 (0.028)
CTC(BL)+ CTC(FC)+ LDH(BL)	-	0.75 (0.018)	0.74 (0.018)	0.74 (0.019)
CTC(BL)+CTC(FC)+PSA(BL)+PSA(FC)	-	0.72 (0.019)	0.72 (0.021)	0.72 (0.020)