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Relationship between serum markers and volume of liver metastases in castration-resistant prostate cancer

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ABSTRACT

Background: Prostate cancer patients with liver metastases have a poor prognosis. To date, no study exists investigating the relationship between liver tumor burden and clinical laboratory markers.

Materials and Methods: Metastatic castrate-resistant prostate cancer (mCRPC) patients with radiographic evidence of liver metastases were selected for this study. Volumetric measurements of liver metastases were ascertained for all available patients. Prostate specific antigen (PSA), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), total bilirubin and hemoglobin (HGB) levels were then assessed to coincide with the scan dates. Univariate and multivariate mixed-model regression analysis were performed to evaluate the relationship between laboratory markers and liver lesion volume. Data sets with non-normal distribution were logarithmically transformed. Akaike information criteria (AIC) was used to identify the most reliable multivariate model.

Results: In our heavily pretreated liver-metastatic patient population, univariate analysis demonstrated a statistically significant positive correlation between PSA ($p = 0.0002$), ALP ($p = 0.0305$), AST ($p < 0.0001$), ALT ($p = 0.0049$), and LDH ($p = 0.0019$) and liver lesion volume. Additionally, ALB ($p = 0.0006$) and HGB ($p = 0.0103$) had statistically significant negative correlation. Multivariate analysis identified AST and hemoglobin assessments as the best predictors of increasing liver lesion burden. Preliminary data on circulating tumor DNA (ctDNA) mutational and amplification findings are also reported.

Conclusions: Analysis identified AST and hemoglobin as optimal predictors of liver lesion volume. These patients have a heavy burden of ctDNA abnormalities. Further studies with a larger patient population are needed to verify these results.

Micro Abstract: This study investigates the association between liver lesion burden and clinical laboratory markers in castrate-resistant prostate cancer patients with hepatic metastases. Our univariate analysis identified multiple laboratory markers as significant indicators of worsening hepatic disease. Multivariate analysis demonstrated that AST and hemoglobin were the most effective predictors of change in liver lesion volume.

Introduction

Prostate cancer is one of the most commonly diagnosed malignancies among men and is known to have a broad range of disease courses. Even among patients with metastatic castrate resistant prostate cancer (mCRPC) such diversity is apparent from analyzing overall survival in large data sets. When considering the location of metastatic sites, hepatic metastases are known to have a particularly poor prognosis. Halabi et al. demonstrated in a dataset of 8820 men enrolled on phase III trials with mCRPC, that men with liver metastases had a median overall survival (OS) of 13.5 months compared to men with bone metastases of 21.3 months, compared to those with nodal only spread whose median survival was 31.6 months [1]. Although liver metastases (8.6% of total men in the pooled analysis) are less common

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than bone, lymph node spread, their response to a wide variety of therapies is diminished. Data from randomized trials using abiraterone [2], enzalutamide [3], and docetaxel [4] all indicate that these treatments are less effective in patients with measureable hepatic metastases.

Despite the importance of liver metastases in terms of prognosis, studies investigating the characteristics of liver metastases and laboratory correlates in mCRPC patients are limited. Recently, a study by Cotogno et al. demonstrated that aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and hemoglobin (HGB) were significant predictors for the presence of liver metastases on imaging [5], but no studies currently exist analyzing the relationship between liver lesion volume and laboratory markers. Our study aimed to investigate the association between liver lesion volume and clinical laboratory values in mCRPC patients with liver metastases. Preliminary data are presented on circulating tumor DNA (ctDNA) findings as well.

Methods

Subjects were selected for inclusion from patients treated at the Tulane Cancer Center in New Orleans, LA. Retrospective review of clinical documentation and imaging studies were performed and only subjects with documented mCRPC and liver metastases were included (regardless of the other sites of disease). Age, Gleason score at prostate cancer diagnosis, race, sites of metastatic disease, treatment history, and ctDNA genetic testing results were procured. Overall survival was calculated from the date of liver metastasis diagnosis to the date of death or censored at the last follow up appointment. Three dimensional measurements were obtained by a consultant radiologist using coronal and axial CT images to produce a liver lesion volume. For lesions with irregular contours or in confluence with other metastases, measurements were taken to approximate and incorporate as much of the lesion as possible. Total liver lesion burden was then calculated by summating the volumes of all lesions measured on a given scan date.

Prostate specific antigen (PSA), LDH, alkaline phosphatase (ALP), AST, alanine aminotransferase (ALT), albumin (ALB), Total bilirubin and HGB values were assessed at the time of each CT assessment to establish a set of clinical laboratory markers for each scan date. Mutations from ctDNA analysis, drawn at the time of documented liver metastases (Guardant 360 assays, Guardant Health, Redwood City, CA) were displayed through cBioPortal's Oncoprinter to produce a prevalence of specific mutations and genetic alteration type.

Laboratory variables and total liver lesion volume were evaluated with univariate and multivariate mixed-model regression analyses with the random intercept being utilized for inferences. Log transformations were performed on variables with a non-normal distribution. Only variables with a significant association with the outcome ($p < 0.05$) in the univariate analysis were selected for testing in multivariate setting. In addition, the number of days between the baseline and subsequent assessments were included in the model selection process to control for time. Akaike information criterion (AIC) is a relative indicator used to identify the best statistical model. A lower AIC indicates a better model and this metric was utilized to identify the optimal multivariate model.

Results

Twenty-three mCRPC patients with liver metastases were evaluated for this study. With serial measurements, 58 observations were available for the univariate and multivariate analysis. Median age at the time of diagnosis was 58 years, 86% were Caucasian and the remainder African American (Table 1). All patients had accompanying bone metastases at the time of evaluation and 77% had pathologic lymph nodes per RECIST 1.1 criteria. Median Gleason score at diagnosis was 8 (range 7–10). Overall survival from the date of liver metastases diagnosis to death was 6 months indicating that most patients developed liver lesions late in their disease course. Most patients had undergone treatment with either abiraterone acetate (91%) or docetaxel (61%) prior to the documentation of liver metastases; 74% of patients received two lines or more lines of treatment prior to demonstration of liver lesions.

Table 1
Descriptive statistics of mCRPC patients with hepatic metastases seen at Tulane Cancer Center.

Variable	*n*	%, Median (Range)
Age at Prostate Cancer Diagnosis	22	58 (39–73)
Gleason Score at Prostate Cancer Diagnosis	13	8 (7–10)
Race:		
Caucasian	18	85.7% Caucasian
African American	3	14.3% African American
Presence of:		
Bone Metastases	23	100%
Lymph Node Metastases	17	77.30%
Overall Survival from Liver Metastases Diagnosis (Days)	21	182 (18–1366)
Overall Survival from mCRPC Diagnosis (Days)	19	1000 (95% CI 758–1649)
Treatment History prior to Liver Metastases Diagnosis:		
Abiraterone	21	91.30%
Enzalutamide	6	26.10%
Radium-223	4	17.40%
Docetaxel	14	60.90%
Cabazitaxel	8	34.80%
Carboplatin	6	26.10%
Prior mCRPC Treatment Lines:		
0	1	4.35%
1	5	21.70%
2	7	30.40%
3	3	13%
4	5	21.70%
5	1	4.35%
6	1	4.35%
Laboratory Parameters at Liver Metastases Diagnosis		
Total Liver Lesion Volume (cm^3)	21	13.86 (0.378–6998.296)
PSA (ng/mL)	21	139 (0.1–1610)
ALP (U/L)	20	169.5 (60–2034)
LDH (U/L)	17	347 (160–3845)
AST (U/L)	20	29.5 (13–180)
ALT (U/L)	20	24 (12–82)
Albumin (g/dL)	20	3.4 (2.4–4.2)
Hemoglobin (g/dL)	15	10.5 (5.7–12.5)
Total Bilirubin (mg/dL)	20	0.5 (0.2–2)

Univariate analysis to assess the relationship between laboratory values and liver lesion volume demonstrated a statistically significant positive Pearson correlation between the logarithmically transformed data of PSA ($p = 0.0002$), ALP ($p = 0.0305$), AST ($p < 0.0001$), ALT ($p = 0.0049$), and LDH ($p = 0.0019$) and liver lesion volume (Table 2). Additionally, albumin ($p = 0.0006$) and hemoglobin ($p = 0.0103$) were found to have statistically significant negative Pearson correlations.

Multivariate modeling demonstrated that a mixed model including AST and hemoglobin were the most optimal predictors of change in total liver lesion volume based on Akaike Information Criteria (AIC)

Table 2
Pearson correlation of laboratory markers compared to liver lesion volume.

Univariate results Variable	*P*-value	Pearson R
Log PSA	**0.0002**	0.5653
Log ALP	**0.0305**	0.3189
Log AST	**<0.0001**	0.564
Log ALT	**0.0049**	0.3997
HGB	**0.0103**	−0.3232
Log LDH	**0.0019**	0.4283
Albumin	**0.0006**	−0.459
T. Bili.	0.2235	0.1727
Time	**0.0013**	0.4836

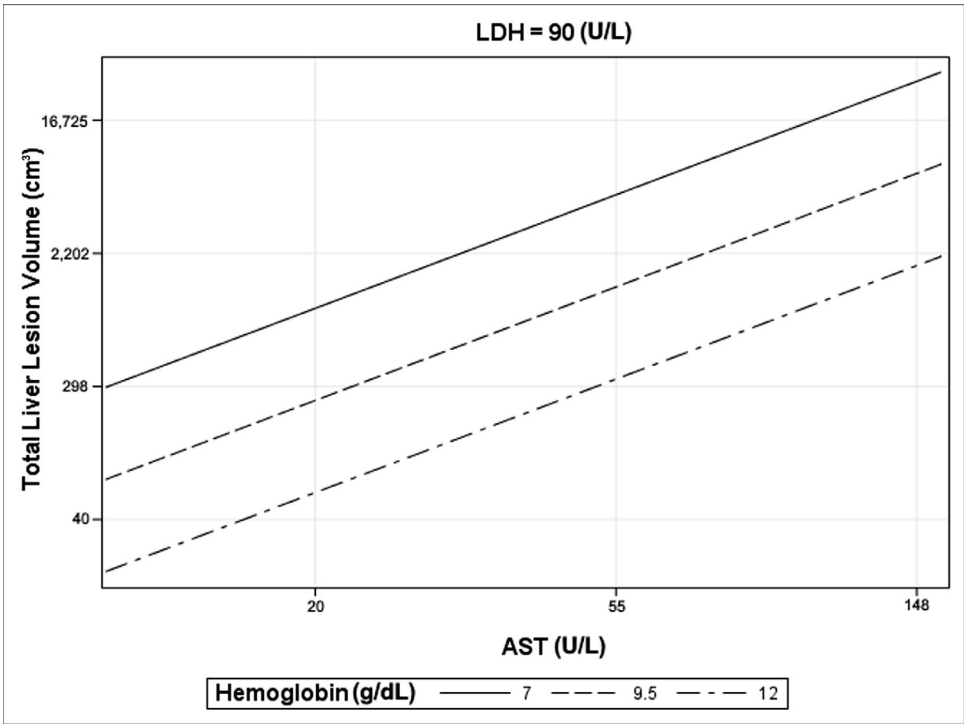

Fig. 1. Plot demonstrating changes in liver lesion volume with LDH fixed at 90 U/L and different hemoglobin level of 7, 9.5 and 12 g/dL (p = 0.0112).

(p = 0.0112). AST alone (AIC = 233.9), HGB alone (AIC = 212.2) and AST in combination with HGB (AIC = 206.37) were inferior to the model of AST, hemoglobin and LDH (AIC = 183.4). In the modeling, AST was directly proportional to total liver lesion volume and HGB was inversely proportional to total liver lesion volume. Additionally, inclusion of LDH resulted in a more stable model based on the standard errors (Fig. 1).

Multigene panel testing assessing somatic genetic alterations found that all patients had multiple ctDNA genetic abnormalities. Both TP53 and AR were genetically altered in 86% (6/7) samples using the Guardant 360 assay. A multiplicity of other genes was also either mutated or amplified (Table 3). Individual level data can be seen in Fig. 2.

Discussion

Understanding prognosis in mCRPC patients has many components but liver metastases appear in virtually all prognostic models. Herein we examine the variables that associate with total liver lesion volume. Prognosis is not directly assessed in this manuscript; the relationship between prognosis and the presence/absence of liver lesions has been addressed previously [1–4]. As noted above, median survival was only 6 months for the patients in this study, indicating that documentation of liver metastases was a late finding. Furthermore, most patients had multiple lines of therapy.

Table 3
Genetic mutations present in study population (N = 7) assessed by ctDNA.

Mutation	Patients with alteration	Patients with genetic alteration (%)		
	n	%	Amplification	Missense
TP53	6	86%	0%	100%
AR	6	86%	50%	66%
BRAF	5	71%	100%	40%
EGFR	5	71%	60%	40%
MYC	5	71%	100%	40%
PDGFRA	5	71%	60%	60%
PIK3CA	5	71%	100%	40%
KIT	4	57%	75%	50%
CDK6	4	57%	100%	0%
MET	4	57%	75%	25%

Analysis of the laboratory markers showed that the high AST and low hemoglobin may predict increasing liver lesion volume. As previously stated, Cotogno et al. demonstrated that AST, hemoglobin and LDH were significant predictors of radiographic evidence of liver metastases, but our analysis only identified AST and hemoglobin as significant predictors of change in liver lesion volume. Including LDH in the multivariate model provided stability in the standard errors and improved the predictive ability of the model, but it was not a significant predictor of change in liver lesion volume. This is possibly due to the high variability of LDH and the small sample size. While the sample size is limited, we hypothesize that further investigation of these markers is warranted as they could serve as a metric of worsening liver disease or response to treatment when monitoring mCRPC patients. More data are required to test this hypothesis.

AST and ALT are standard components of liver function tests and are used as crude assessments of liver health, but are not typically viewed as indicators of liver metastases. ALP values in prostate cancer patients are confounded by the often concomitant presence of osteoblastic bone disease. In these analyses, AST levels contribute to better modeling of liver lesion size than ALT levels. AST has also been shown to be of considerable prognostic importance in a separate larger analysis of mCRPC patients[6]. It is unknown if the relationship between AST and prognosis is related to an underlying relationship between AST and liver lesions. LDH is known to increase in patients with extensive neoplastic disease as cancer cells utilize anaerobic respiration for metabolic processes. LDH clearly associates with mCRPC prognosis in multiple studies [7–9] but relationships to liver lesion size are previously unreported in prostate cancer. Anemia of course is associated with poor prognosis in many cancers and prostate cancer in particular [10–11]. Relationships between anemia and liver lesion size are not previously reported. Given that our patient population is heavily treated, our results are possibly confounded by the total extent of disease and not necessarily the total liver lesion volume. We also recognize that the location of liver lesions could lead to worse laboratory values as obstruction of ducts or vasculature would accelerate damage to the

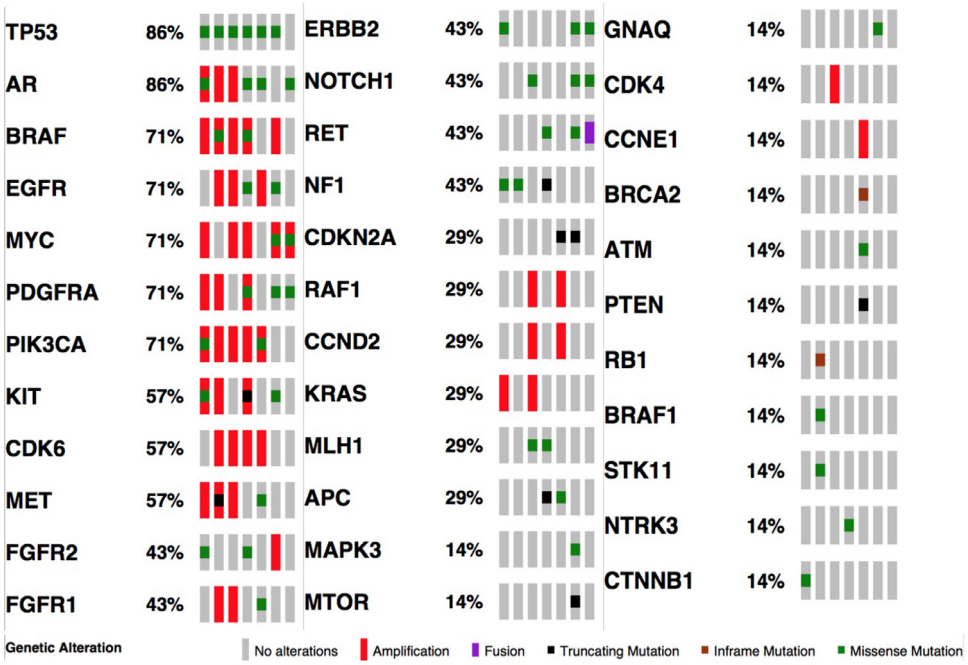

Fig. 2. Gene alterations from cBioPortal Oncoprinter analysis with each patient represented by one column.

parenchyma or cause larger changes in serum levels of biomarkers.

A study using Guardant assays for ctDNA analysis in mCRPC patients demonstrated that the most common recurrent somatic mutations were in TP53 (36% of patients), AR (22%), APC (10%), NF1 (9%), EGFR, CTNNB1 and ARID1A (6% each) and BRCA1, BRCA2 and PIK3CA (5% each). The most common genes with increased copy numbers were AR (30%), MYC (20%) and BRAF (18%) [12]. Guardant assays may not reflect the totality of ctDNA abnormalities, however, as RB and PTEN loss are not assessed by Guardant assays. Further, Guardant assays are not optimized for the assays of a number genes of known relevance in prostate cancer such as FANCA and FOXA1. Further studies with a larger sample size are needed to fully investigate the genetic profile of mCRPC patients with liver metastases as this could potentially inform future therapy for this group of patients.

Limitations of these analyses includes the single institution, retrospective nature of this study and that clinical variables were not included. Patients did not have similar therapeutic histories, were not CT scanned at consistent intervals, and at times there was incomplete clinical laboratory data. Additionally, the limited genomic samples restrict the conclusions that can be made from these studies.

These studies are the first to investigate relationships between blood biomarkers and metastatic liver lesion volume in mCRPC patients. We hypothesize that the AST and hemoglobin relationships identified herein may be useful for clinicians managing mCRPC patients with advanced disease. Further studies involving a larger population are needed to verify these findings.

Clinical practice points

- Patients with hepatic metastases have the poorest overall survival of mCRPC patients with visceral metastases.
- Clinical laboratory markers are associated with radiographic volume of liver metastases.
- Our data indicate that worsening liver lesion burden is associated with significant increases in PSA, LDH, ALP, AST and ALT and significant decreases in albumin and hemoglobin.
- Multivariate analyses support the concept that AST and hemoglobin are particularly valuable in assessing the volume of liver metastases in patients with advanced prostate cancer.

Conflict of interest

Authors of this manuscript declare no conflict of interest relevant to this material.

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