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RESEARCH ARTICLE

Clinical characteristics and prognostic factors of prostate cancer with liver metastases

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Abstract Liver metastasis from prostate cancer is uncommon and remains poorly understood. We computer searched the clinical records of all our patients registered into a database to identify patients that presented or developed liver metastases. A total of 27 prostate cancer patients with ultrasound or CT/MR imaging evidence of liver metastases were included in our analysis. The liver metastasis rate from metastatic prostate cancer was 4.29 %. Eight (29.63 %) patients had previously untreated, hormone-naive prostate cancer (synchronous liver metastases at diagnosis of prostate cancer), whereas 19 (70.37 %) patients had already been diagnosed as having hormone-refractory prostate cancer. In the hormone-naive group, the median overall survival after liver metastases diagnosis was 38 months and half of the patients were still alive at the latest follow-up, whereas only 6 months in the hormone-refractory group ($p=0.003$). High concentration of serum neuron-specific enolase and previous chemotherapy were associated with a significantly poor overall survival after liver metastases in the hormone-refractory group using Kaplan–Meier curves and logrank tests for univariate analysis.

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Introduction

Prostate cancer (PCa) is the most common malignancy in Western countries and the second leading cause of cancer-related deaths in males [1–3].

In China, the incidence of prostate cancer has increased dramatically over the past two decades, most likely due to economic development and lifestyle changes [4]. According to the recent statistics in China, PCa is the seventh most common cancer in males, and its incidence rose to 11 per 10^5 in the year 2008 [5]. Despite improvements in diagnosis, surgical techniques, and chemotherapies, most deaths of PCa patients occur due to disease progression and metastasis.

Metastatic disease to the bones and lymph nodes has long been recognized as the most typical pattern of extraprostatic tumor spread [6]. Liver metastasis (LM) originating from prostate cancer has only rarely been reported and remains poorly understood [7–9]. With earlier detection and more advanced treatment options, prostate cancer patients are living longer and may therefore be developing liver metastases at greater rates than in years past [10].

In this study, we did a retrospective study that described the patient characteristics, clinical manifestations, and diagnosis in patients diagnosed with prostate cancer with liver metastases and investigated patient outcomes, including survival, to provide prognostic data in these rare tumors.

Materials and methods

We computer searched the clinical records of all our patients registered into a Tianjin prostate cancer database from 2005 to 2012, to identify patients that presented or developed LM. The

computer-searched terms in the database included "prostate cancer" or "prostatic neoplasms" combined with "liver metastases" or "liver metastasis" in the "Materials and methods" section. Clinical and pathological data were obtained from the electronic database. The following parameters were registered: demographics, histological characteristics of primary prostate cancer, serum profile including prostate-specific antigen (PSA), neuron-specific enolase (NSE), alanine aminotransferase (ALT), time interval between diagnosis of primary PCa and LM, the presence or absence of symptoms, localization of other metastases, type of treatment applied for LM, date of death, and/or last follow-up. NSE was measured by electrogenerated chemiluminescence (Roche, Germany). The manufacturer's instructions were followed. The cutoff upper limit of normal serum NSE was 12.5 ng/mL as per manufacturer's manual.

The staging work-up for the newly diagnosed prostate cancer in our center included a chest X-ray, radionuclide bone scan, and MR/CT scan of the pelvis. The diagnosis of LM was based on clinical examination with the integration of US, CT, and/or MRI. If possible, histological examination was obtained. LM diagnosed within 30 days of diagnosis of the primary PCa was considered synchronous. All patients with a second primary malignancy in addition to prostate were excluded from the study. We followed up all patients from the date of the first visit to the date of death or last follow-up. The abdominal ultrasound scan or CT or MRI was performed only when there was suspicion of liver metastatic disease based on the specific symptoms (such as upper abdominal pain, jaundice, distention of abdomen) or nonspecific symptoms (such as extreme fatigue, lack of appetite, weight loss, etc.) while with abnormal liver function tests or physical examination (hepatomegaly or ascites).

Statistical analysis

The liver metastasis rate was calculated as the ratio between the observed patients with LM and metastatic prostate cancer patients present in our electronic database.

The time interval between the diagnosis of primary PCa and LM was defined as the number of months between the initial diagnoses of prostate cancer to initial detection of liver metastases by imaging. Overall survival (OS) was calculated from the date of diagnosis of LM on US or CT, MRI to the date of death or last follow-up for survivors. To establish risk factors, we analyzed the following parameters: age at diagnosis of prostate cancer (≥60 or <60 years), age at diagnosis of LM (≥60 or <60 years), ALT at diagnosis of LM (>2× normal or <2× normal), previous chemotherapy (yes or no), specific symptoms (presence or absence), PSA at diagnosis of prostate cancer (≥120 or <120 ng/mL), PSA at diagnosis of LM (≥100 or <100 ng/mL), serum NSE level (≥12.5 or <12.5 ng/mL), stage at diagnosis of prostate cancer (IV or I–III), Gleason score of prostate cancer (≥8 or <8), and interval between prostate cancer diagnosis and LM (≥15 or <15 months). The above continuous variables were dichotomized using the median values, normal values, and the established reference values as the cutoff, respectively.

Response to androgen deprivation treatment for LM was assessed by WHO criteria and refers to response in the liver only [11]. Correlation between NSE levels and other clinical evaluated parameters was performed by the Pearson's correlations. Univariate analyses were performed via the logrank test to compare Kaplan–Meier survival distribution curves among various patient groups. Multivariable modeling was not performed due to an insufficient number of events (deaths). A "rule of ten" events as the minimum per risk factor considered in the model has been advocated for Cox regression which was not achieved in our sample. Patients who were lost to follow-up or who were alive at the time of last follow-up were censored at the date of their last follow-up. A p value <0.05 was considered statistically significant.

Results

We identified a total of 29 eligible prostate cancer patients with liver metastases. Two patients with a second primary malignancy (rectal cancer and lung cancer, respectively) in addition to prostate cancer were excluded from the study. A total of 27 patients with LM were included in our analysis. The liver metastasis rate was 4.29 % (27/629) in our electronic database.

Nineteen patients had already been diagnosed as having hormone-refractory prostate cancer (HRPC), whereas eight patients had previously untreated, hormone-naive prostate cancer (synchronous LM at diagnosis of prostate cancer; Table 1).

Patient characteristics

Patient characteristics are shown in Table 1.

Clinical manifestations

Eleven patients (40.74 %) had symptoms specific to the liver during the onset of LM, while 16 (59.26 %) did not have symptoms specific to the liver. The most common specific symptoms were as follows: upper abdominal pain, jaundice, and distention of abdomen.

Liver function tests are deranged in 13 patients (48 %) at presentation with ALP and AST being the most commonly elevated enzymes.

Diagnosis

In ten patients (37.04 %), the diagnosis of LM was based only on a positive ultrasound scan of the liver. In 17 patients

Table 1 Clinical characteristics of 27 patients with liver metastases

Clinical characteristics	Hormone status	
	Hormone-naive group ($n=8$)	Hormone-refractory group ($n=19$)
Age at diagnosis of primary tumor	75 (54–84)	65 (47–82)
Age at liver metastasis	75 (54–84)	66 (48–86)
PSA at diagnosis of primary tumor (ng/mL)	55.6 (10.66–1,152)	180 (24–1,520)
PSA at liver metastasis (ng/mL)	55.6 (10.66–1,152)	100 (1.26–1,249)
Interval between primary tumor diagnosis and liver metastasis (months)	0	14 (4–53)
NSE at diagnosis of LM	ND	28 (6.94–370)[a]
Gleason score of primary tumor		
6	1	2
7	3	5
8	2	8
9	1	4
10	1	0
Other sides of metastasis at the time of LM		
Liver alone	1	1
Bone	6	15
Lymph nodes	3	8
Lung	2	2
Stage at diagnosis		
I–III	0	3
IV	8	16
Prior therapy		
Hormonal therapy alone	0	14
Hormonal + chemotherapy	0	5
None	8	0
Histology of prostate cancer		
Prostate adenocarcinoma	8	19

Values are given as median (min–max) or absolute numbers (number of patients)

ND not documented, *NSE* neuron-specific enolase

[a] NSE level at liver metastasis was not available in five patients

(62.96 %), the diagnosis of hepatic metastases was based on a CT or MRI.

Invasive techniques were rarely used for the diagnosis of liver metastases. Only two of these patients had pathologically proven prostate metastasis to the liver via needle liver biopsy. All patients had pathologically proven prostate adenocarcinoma via prostate needle biopsy. Five patients had pathologic sampling from other sites in the body that demonstrated widely disseminated prostate metastases. Twenty patients treated for LM only had biopsies of the primary site, but they demonstrated imaging evidence of widespread systemic metastases in a pattern typical of advanced prostate cancer and had no additional known cancers to explain their liver disease.

Treatment and outcome

After LM diagnosis, the eight patients with hormone-naive prostate cancer were treated with androgen ablation (luteinizing hormone-releasing hormone agonists (six patients) or orchiectomy (two patients)). In addition, seven patients also received anti-androgens. After failure of hormone treatment, one patient was given docetaxel-based chemotherapy. The response of LM to androgen deprivation for hormone-naive group is shown in Table 2.

After LM diagnosis, 11 patients (57.89 %) in the hormone-refractory group were treated with docetaxel-based chemotherapy, while 3 patients (15.79 %) refused chemotherapy. For another five patients (26.32 %) who had received previous chemotherapy before LM (docetaxel in three cases, mitoxantrone in two), one patient received further chemotherapy (paclitaxel, estramustine, and carboplatin combination), and the remaining four patients only received palliative therapy because of the poor performance status.

Bone metastases were treated with palliative radiotherapy (17 patients). Fifteen patients received bisphosphonates (zolendronic acid) and four were given radioisotopes.

Survival curves comparing hormone-naive and hormone-refractory patients are shown in Fig. 1. In the hormone-naive group, median survival was 38 months and half of the patients were still alive at the latest follow-up, whereas there was a median survival of only 6 months in the hormone-refractory group ($p=0.003$; Fig. 1).

Patients in the hormone-refractory group were analyzed separately. Table 3 lists the median survival of patient subgroups and their corresponding logrank tests. High concentration of serum NSE and previous chemotherapy were associated with a significantly poor survival in this univariate analysis (Table 1 and Figs. 2 and 3). The concentrations of NSE were available after the diagnosis of liver metastases in 14 patients. Eight of 14 patients received chemotherapy. During the course of chemotherapy, of the seven patients followed up serially, NSE was raised in all two patients who had normal NSE prior to chemotherapy. Out of five patients with elevated NSE levels, four showed a fall in NSE. In two of the latter, it became normal. It is interesting to note that all the four patients with a decrease of NSE during the course of chemotherapy showed radiologically assessed partial response ($n=3$) or stable disease ($n=1$). There were no correlation between NSE levels and other clinical parameters ($p>0.05$).

Discussion

While metastatic prostate cancer to the liver is not an uncommon finding at autopsy, being the third most common site after bone and lung, with the incidence of liver metastases to be as high as 25 %, prostate cancer with clinical liver

Table 2 Clinical response to androgen deprivation and survival in eight hormone-naive prostate cancer patients

No.	PSA	Metastases status	Gleason scores	Age	Therapy	Response	Survival time
1	10.66	Liver, bone, lymph node	7	74	LHRH agonists	PR	18[a]
2	89.09	Liver (solitary),bone	8	79	LHRH agonists	PR	30[a]
3	1,152	Liver, lung	10	54	LHRH agonists	SD	11
4	16.1	Liver, lung, bone	8	84	LHRH agonists, chemotherapy	PD	11
5	785.68	Liver, bone, lymph node	9	80	LHRH agonists	PR	10
6	105	Liver, bone	6	74	LHRH agonists	CR	68[a]
7	22	Liver only	7	68	Orchiectomy	CR	38[a]
8	14.62	Liver, bone, lymph node	7	76	Orchiectomy	PR	38

LHRH luteinizing hormone-releasing hormone

[a] Alive

metastases is uncommon and has not been well reported. After a review of PubMed literature (1966–present), we identified only two retrospective studies dealing with prostate cancer patients with liver metastases alone [7, 8]. The first series of over 345 metastatic prostate cancer patients at the Montpellier Cancer Center between 1995 and 2005 yielded an incidence of 8 % [7]. Another recent study retrospectively reviewed 1,050 metastatic castration-resistant prostate cancer patients; 59 cases of LM were identified with an incidence of 5.62 % [8]. The liver metastasis rate of LM in the current study was 4.29 %, which is lower than the previous reports. All these results showed that the prevalence of LM was quite lower than the autopsy result. The disparity in the incidence of prostate liver metastases between autopsy and clinical studies is due in part to the limitations of current liver imaging techniques. Additionally, in patients who have severe systemic disease, the possible diagnosis of LM may not have been pursued due to the overall poor prognosis of the patients. Therefore, the frequency we report must underestimate the true frequency of LM.

LM has been reported to be usually a late manifestation of systemic disease and most often occurs in patients after extensive therapy with hormone and/or chemotherapy [7]. This holds true for the patients in our study. Nineteen patients (70.4 %) are present with more aggressive hormone refractory disease. Most of them had disseminated systemic disease and had received many previous treatments. However, the results of our study differ slightly from the previous report, which reported only one hormone-naive prostate cancer with synchronous liver metastasis at prostate cancer diagnosis, while in this report, we found eight patients with synchronous liver

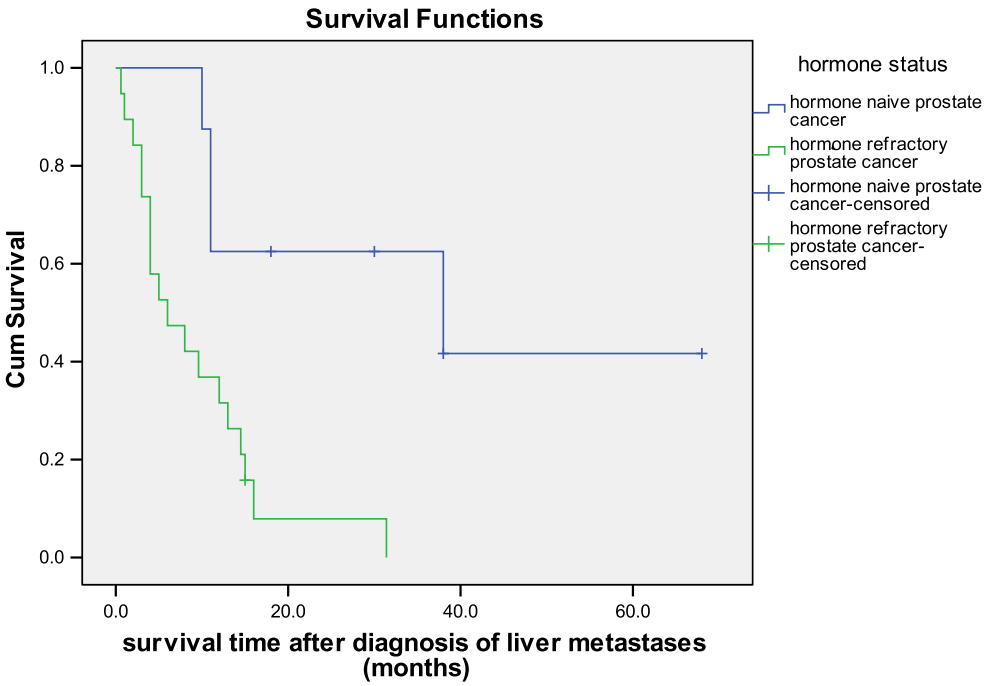

Fig. 1 Kaplan–Meir analysis of survival after diagnosis of liver metastases according to hormone status

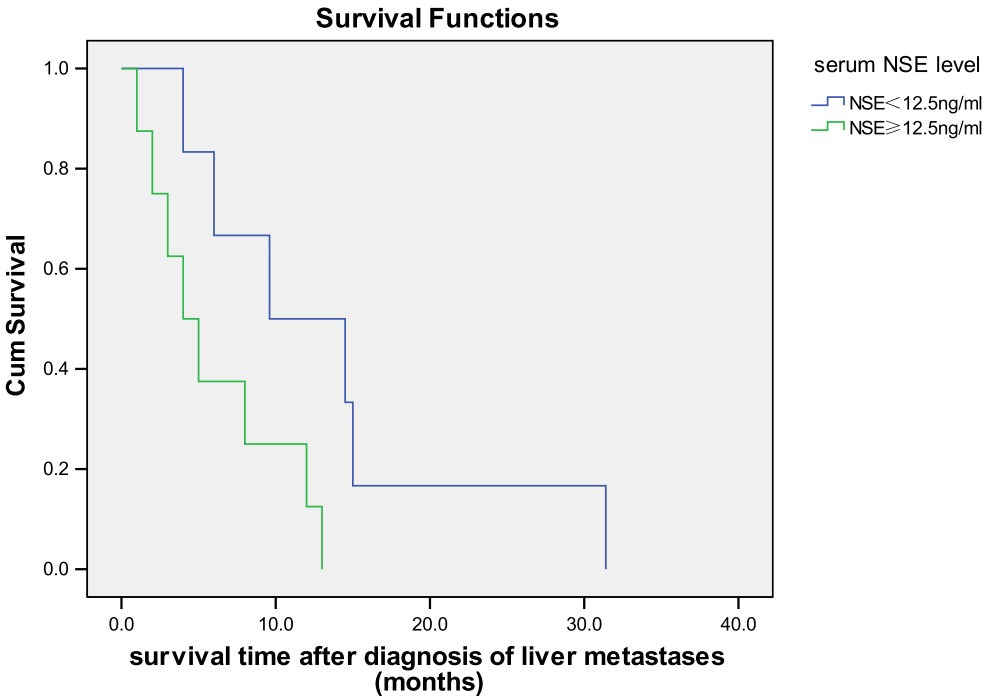

Fig. 2 Kaplan–Meir analysis of survival after diagnosis of liver metastases according to serum NSE level

metastases at prostate cancer diagnosis (hormone naive). This is higher obviously than the previous report. Furthermore, there was one patient that at time of diagnosis of LM had no evidence of systemic disease. What is the underlying reason for this? One possible explanation is that most newly diagnosed prostate cancer patients in China already have metastatic disease because prostate cancer screening using PSA and digital rectal examination is not a routine practice in China [12].

LM may present asymptomatically during a metastatic screen or may present with specific symptoms. About 41 % of our patients had specific symptoms and signs, most commonly upper abdominal pain, jaundice, and distention of abdomen. Careful clinical assessment of prostate cancer patients suspected of liver metastases is thus important. Furthermore, all except four of our patients (78.95 %) had evidence of bone metastases, and 42.11 % had nodal disease. This suggests that prostate cancer patients

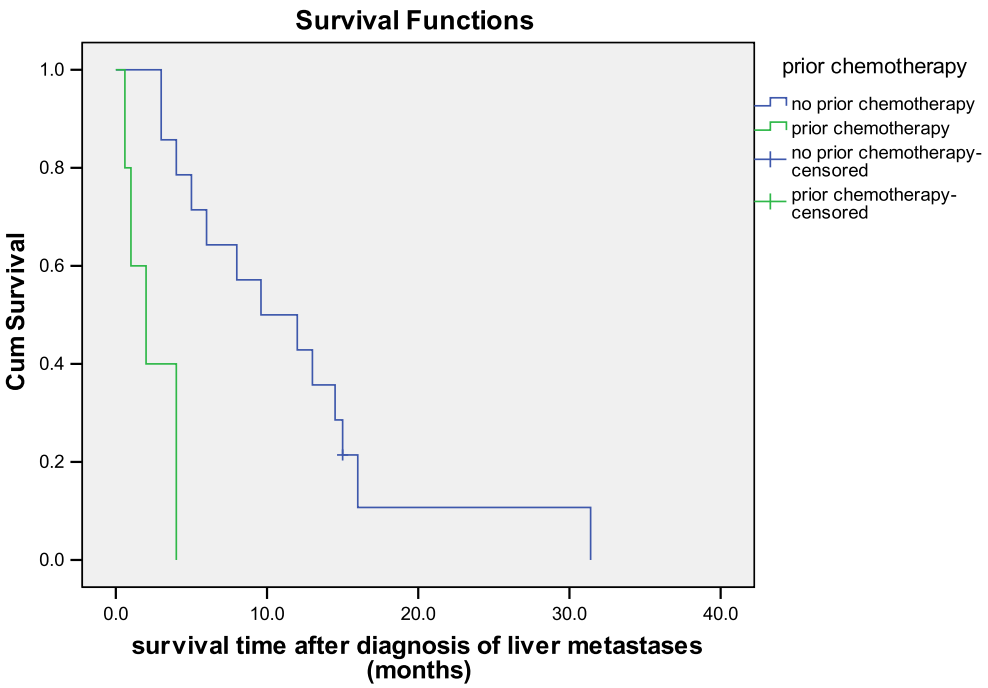

Fig. 3 Kaplan–Meir analysis of survival after diagnosis of liver metastases according to with or without prior chemotherapy

Table 3 Median survival after the diagnosis of liver metastases in patient subgroups according to the prognosticators and univariate comparison using logrank test

Prognosticators	Factor	No.	Median survival (95 %CI) (month)	Logrank *p* value
Age at diagnosis of prostate cancer	>60	12	6 (0.908, 11.092)	0.309
	≤60	7	4 (1.434, 6.566)	
Age at diagnosis of LM	>60	13	8 (NE, 16.220)	0.162
	≤60	6	3 (0.60, 5.40)	
NSE level at LM[a]	≥12.5 ng/mL	8	4 (1.228, 6.772)	0.042
	<12.5 ng/mL	6	9.6 (NE, 19.802)	
ALT at LM[b]	>2× normal	8	4 (3.026, 4.974)	0.347
	<2× normal	9	12 (4.988, 19.012)	
Prior chemotherapy at diagnosis of LM	Yes	5	2 (NE, 4.147)	<0.001
	No	14	9.6 (2.266, 16.934)	
Specific symptoms	Presence	7	6 (0.868, 11.132)	0.556
	Absence	12	5 (NE, 11.790)	
PSA at diagnosis of prostate cancer	≥120 ng/m	9	6 (3.078, 8.922)	0.814
	<120 ng/m	10	4 (NE, 9.165)	
PSA at liver metastasis	≥100 ng/m	10	4 (1.676, 6.324)	0.548
	<100 ng/m	9	8 (NE, 16.765)	
Stage at diagnosis of prostate cancer	I–III	3	13 (1.79, 24.20)	0.212
	IV	16	4 (2.04, 5.96)	
Gleason score of prostate cancer	≥8	12	5 (NE, 11.790)	0.717
	<8	7	6 (0.868, 11.132)	
Interval between prostate cancer diagnosis and LM	≥15 months	9	6 (0.156, 11.844)	0.426
	<15 months	10	5 (NE, 13.677)	

LM liver metastases, *NE* not evaluable

[a] NSE level at liver metastasis was not available in five patients

[b] ALT value was not available in two patients

without bone and/or lymph node metastases are highly unlikely to have LM. These findings are potentially important diagnostic insights and deserve further research.

Survival analysis showed that hormone status (hormone refractory or hormone naive) is a statistically significant and clinically relevant predictor of poor overall survival in prostate cancer with liver metastases after diagnosis of LM (Fig. 1). In the present study, median survival of hormone-naive patients with LM treated with androgen deprivation was 38 months and half of them were still alive at the latest follow-up. This compares with published median survivals between 28 and 52 months for large series employing androgen deprivation for treatment of patients with minimal or extensive metastatic prostate cancer [13]. Therefore, LM does not necessarily predict a worse outcome when seen as synchronous LM at the diagnosis of prostate cancer; when seen as a site of progressive HRPC, prognosis was worse. The median survival in hormone-refractory group was 6 months, thus confirming previous report [7]. Taking this into consideration, we evaluated HRPC patients suffering LM separately to determine which pretreatment variables may predict for OS. To our knowledge, this is the first report to investigate predictive factors of survival in HRPC with liver metastases. The results of our study are thus important for physicians to guide in treatment selection and to counsel patients about their long-term outlook in HRPC with liver metastases. On univariable analysis, factors that predict poor survival after LM include high concentration of serum NSE and previous chemotherapy.

An important finding from our study is that a high concentration of serum NSE at LM diagnosis appeared to predict poor prognosis. The results support previous report that LM are frequently associated with the neuroendocrine differentiation (NED) [7]. Recently, increasing attention has been given to NED in prostate cancer, and its prognostic and therapeutic usefulness is recognized more widely. NED in PCa appears to be a poor prognostic factor, possibly related to the increasing degree of dedifferentiation, resistance to hormonal therapy, and growth stimulation of the tumor by neurosecretory products [14]. In contrast to detecting NED at tissue level, measurement of neuroendocrine markers such as CgA and NSE in the serum of PCa patients constitutes a more representative and more objective assessment of the NED of tumors, as it may correspond to the entire primary tumor cell population and its associated metastasis [14]. Previous studies have reported that high serum NE marker constitutes an independent factor predictive of poor prognosis in metastatic HRPC, including visceral metastases [15]. However, no papers have reported that neuroendocrine marker can predict prognosis in HRPC with liver metastases. In our study, the number of patients with high concentration of serum NSE was too small to enable meaningful conclusions. Our results indicate that high concentration of serum NSE may be an important predictive and prognostic factor for HRPC with liver metastases and merit further research.

Another important prognostic factor for survival is the presence or absence of previous chemotherapy as part of their

management. The finding that previous chemotherapy is a significant prognostic factor does not mean that chemotherapy itself makes survival worse. The possible reason is that those with previous chemotherapy have no or few effective options for chemotherapy left after LM occurred. In the context of an increasing pipeline of novel approved agents (abiraterone acetate, sipuleucel-T) and emerging agents (radium-223, MDV-3100), optimal survival will probably be realized by the sequential utilization of several different classes of agents. Actually, studies have suggested that abiraterone may be effective in castration-resistant prostate cancer (CRPC) patients pretreated with docetaxel chemotherapy [16, 17]. In a most recent case report, a partial response of LM was observed in a CRPC patient treated with abiraterone after docetaxel chemotherapy [9].

A potential limitation of this investigation is that only two of the patients we studied had LM that was confirmed to be of prostatic origin by direct histopathologic examination. Although histopathology is the gold standard, liver biopsy may be impractical, unnecessary, or unethical in some patients, especially those with poor overall health associated with widely disseminated disease. The patients without direct histopathologic examination had tissue confirmation of other metastatic sites ($n=5$) or imaging ($n=20$) that confirmed advanced PCa with widespread metastases, which enabled the confident clinical diagnosis of LM. All patients with a second primary malignancy in addition to prostate were excluded from the study, thereby minimizing the possibility that the liver lesions not biopsied were from another source. Another potential limitation of this investigation is the retrospective nature of data collection and small number of patients. Therefore, the statistical results should be interpreted cautiously. The absence of association of some factors with survival could be attributed to the small patient numbers and resulting insufficient statistical power. Nevertheless, the findings of this study are still valuable for better understanding the incidence, clinical manifestations, diagnosis, and the factors affecting the survival of patients with this rare disease.

Conclusions

LM originating from prostate cancer is uncommon and is usually a late manifestation of systemic disease and most often occurs in patients after extensive therapy with hormone and/or chemotherapy. Our findings suggest that liver metastases do not necessarily predict a worse outcome when seen as synchronous LM at diagnosis of prostate cancer and that the prognosis was worse when seen as a site of progressive HRPC. Although limited by the small number of patients, our study indicates that high concentration of serum NSE and previous chemotherapy were associated with a significantly poor overall survival after LM in the hormone-refractory group. Additional work is also necessary to identify specific molecular features of the disease or treatment that may be associated with liver metastases.

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Conflicts of interest None

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