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Advanced Hepatocellular Carcinoma with Bone Metastases: Prevalence, Associated Factors, and Survival Estimation

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Background: The objective of the present research was to explore the prevalence, risk, and prognostic factors associated with bone metastases (BM) in newly diagnosed hepatocellular carcinoma (HCC) patients.


Material/Methods: From 36 507 HCC patients who were registered in Surveillance, Epidemiology, and End Results (SEER) database, we enrolled 1263 with BM at the initial diagnosis of HCC from 2010 to 2014. Kaplan-Meier curves and log-rank tests were used to estimate overall survival for different subgroups. Univariate and multivariate logistic and Cox regression analyses were performed to identify risk factors and independent prognostic factors for BM.

Results: A total of 1567 (4.29%) HCC patients were detected with BM at initial diagnosis. Male sex, unmarried status, higher T stage, lymph node involvement, intrahepatic metastases, and extrahepatic metastases (lung or brain) were positively associated with BM. The median survival of the patients was 3.00 months (95% CI: 2.77–3.24 months). Marital status and primary tumor surgery were independently associated with the better survival.

Conclusions: A list of factors associated with BM occurrence and the prognosis of the advanced HCC patients with BM were found. These associated factors may provide a reference for BM screening in HCC and guide prophylactic treatment in clinical settings.

MeSH Keywords: **Carcinoma, Hepatocellular • Neoplasm Metastasis • Risk Factors • SEER Program**

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Background

Hepatocellular carcinoma (HCC), a leading cause of cancer-related deaths worldwide, represents more than 90% of all liver cancer cases [1]. Despite advances in HCC treatment, it remains one of the deadliest cancers.

With the development of a series of treatments, such as novel surgical techniques, ablation treatment, transcatheter arterial chemoembolization (TACE), and liver transplantation, HCC patients' survival have been improved in recent years [2–4]. It is widely accepted that HCC treatment should be multidisciplinary. Personalized treatment options should be based on various factors, including tumor stage, liver function, and patient's general health condition [5,6]. Since HCC treatment plans vary widely, different guidelines are proposed by National Comprehensive Cancer Network (NCCN), European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASLEORTC), and the Asian Oncology Summit 2009 (AOS). To preserve liver function and improve long-term survival, surgical resection is thought to be the only curative treatment [7]. Patients undergoing surgery are evaluated by clinical and biochemical measures, including hepatic volumetry, surgically feasibility at tumor location, adequate liver reserve, and sufficient liver remnant [8,9].

HCC is often diagnosed when it becomes an advanced disease. HCC frequently metastasizes to bone, including the spine, pelvis, and ribs [10]. Bone metastases (BM) occur in 2–25% of metastatic HCC, and BM frequently leads to poor HCC prognosis [1,11,12]. Among all patients with BM, 40% are spinal, which leads to skeletal-related events (SREs), including pathological fractures, need for surgery or radiotherapy, spinal cord compression, and malignant hypercalcemia [13]. Previously, none of the guidelines suggested performing routine assessment for BM screening in HCC patients. With the development of medical and nursing technology, the survival of HCC has been prolonged, resulting in increased risk of BM development [14–17]. Thus, to promote early diagnosis of BM in HCC and to further improve the survival of HCC patients with BM, the characteristics of HCC patients with BM should be summarized.

In the present study, using the Surveillance, Epidemiology, and End Results (SEER) database, we evaluated the prevalence and the risk factors of bone metastases in hepatocellular carcinoma. Furthermore, we performed survival analyses and identified prognostic factors among the HCC patients with BM.

Material and Methods

Study population

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database using SEER*Stat 8.3.5 software. Since the details of metastases were not recorded before 2010, primary HCC patients who were aged ≥ 18 years at diagnosis between 2010 and 2015 were collected. The primary site was labeled as "Liver and Intrahepatic Bile Duct", and histological types for HCC were limited to 8170/3, 8171/3, 8172/3, 8173/3, 8174/3, and 8175/3 according to the International Classification of Diseases for Oncology-3 (ICD-O-3). The exclusion criteria were as follows: diagnosed with carcinoma *in situ* and benign, diagnosed at autopsy or via death certificate, unknown bone metastases, or follow-up.

A total of 36 507 patients identified as having HCC from 1 January 2010 to 31 December 2015 were enrolled to analyze BM prevalence and risk factors. Among those, 1263 initially diagnosed HCC patients with BM between 2010 and 2014 were retrieved for conducting survival analysis. Furthermore, to compare the characteristics between different treatment groups (with or without surgery of primary site), 3 of 1263 patients were excluded because surgical status was not provided.

Statistical analysis

Patient demographic and clinical characteristics were: age (≤ 40 , 41–60, 61–80, and ≥ 81 years); sex (female and male); race [white, black, AI (American Indian/Alaska Native), and API (Asian or Pacific Islander)]; marital status (married and unmarried); insurance status (insured and uninsured); primary tumor (T) stage (T1, T2, T3, and T4); regional lymph node stage (N0 and N1); tumor differentiation grade (grade I, grade II, grade III, and grade IV), presence or absence of lung metastases, intrahepatic metastases, or brain metastases; AFP (alpha fetoprotein, normal and elevated); and fibrosis score (0 and 1). The risk factors for HCC patients with initial BM were determined primarily by univariate logistic regression. If the characteristic was significant (with $P < 0.05$) by univariate logistic regression, then the risk factors were further analyzed using a multivariate logistic regression model. The primary outcome of the survival analysis was the overall survival, which was defined as from the time of diagnosis of HCC to all causes of death. Kaplan-Meier curves and log-rank tests were employed to analyze survival differences. We also performed multivariable Cox proportional hazards regression based on the aforementioned factors with p -value < 0.05 and the surgical treatments of primary site (None or Yes). Furthermore, the difference in the demographic and clinical characteristics between HCC patients receiving surgical treatments and the ones without surgery were determined by univariate and multivariate logistic

regression. All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY) and all charts on survival were prepared by MedCalc 15.2.2. Two-sided $p < 0.05$ was considered as statistically significant.

Results

Prevalence of bone metastases

Based on the inclusion criteria, a total of 36 507 eligible patients were collected. The prevalence of BM was 4.29% (1567/36 507)

in the entire cohort with the initial diagnosis (Table 1). Among those, 1263 HCC patients with initial BM were followed up to more than 1 year (Table 2).

Risk factors for developing bone metastasis

Univariate analysis showed multiple factors were significantly associated with BM occurrence. These factors were: male sex (OR=1.80, 95% CI: 1.56–2.08, $P < 0.001$); race (OR=0.92, 95% CI: 0.88–0.97, $P = 0.001$); marital status (OR=1.13, 95% CI: 1.02–1.25, $P = 0.02$); insurance status (OR=1.45, 95% CI: 1.16–1.81, $P = 0.001$); primary tumor (T) stage (OR=1.70, 95% CI:

Table 1. Multivariable logistic regression analysis of characteristics of hepatocellular carcinoma patients diagnosed with bone metastases.

Subject characteristics	No. of patients with HCC (2010–2015)		OR (95% CI)	P
	With BM (N=1567, %=4.29)	Without BM (N=34940)		
Sex				
Female	228 (2.71)	8198	1 (Reference)	1.00
Male	1339 (4.77)	26742	1.77 (1.17–2.69)	0.01
Race				
White	1091 (4.32)	24186	1 (Reference)	1.00
Black	278 (5.48)	4794	1.37 (0.93–2.00)	0.11
AI	25 (5.21)	455	1.73 (0.54–5.61)	0.36
API	168 (3.07)	5312	0.83 (0.52–1.31)	0.42
Unknown	5 (2.53)	193	NA	NA
Marital Status				
Married	721 (4.05)	17083	1 (Reference)	1.00
Unmarried	760 (4.55)	15936	1.61 (1.20–2.20)	0.002
Unknown	86 (4.29)	1921	NA	NA
Insurance status				
Insured	1454 (4.24)	32863	1 (Reference)	1.00
Uninsured	88 (6.03)	1372	1.37 (0.73–2.59)	0.33
Unknown	25 (3.42)	705	NA	NA
T stage				
T1	332 (2.13)	15286	1 (Reference)	1.00
T2	186 (2.41)	7521	1.12 (0.73–1.73)	0.61
T3	525 (6.16)	7999	1.66 (1.14–2.41)	0.01
T4	96 (7.50)	1184	1.20 (0.61–2.35)	0.60
Unknown	428 (12.67)	2950	NA	NA

Table 1 continued. Multivariable logistic regression analysis of characteristics of hepatocellular carcinoma patients diagnosed with bone metastases.

Subject characteristics	No. of patients with HCC (2010–2015)		OR (95% CI)	P
	With BM (N=1567, %=4.29)	Without BM (N=34940)		
Lymph node met.				
N0	988 (3.15)	30412	1 (Reference)	1.00
N1	288 (11.29)	2264	2.74 (1.87–4.04)	<0.001
Unknown	291 (11.39)	2264	NA	NA
Grade			1.04 (0.85–1.27)	0.73
I	101 (2.62)	3747	1 (Reference)	1.00
II	149 (2.53)	5749	0.70 (0.48–1.03)	0.07
III	144 (5.43)	2509	1.15 (0.77–1.73)	0.49
IV	9 (4.23)	204	0.46 (0.10–2.08)	0.31
Unknown	1164 (4.87)	22731	NA	NA
Lung met.				
None	1143 (3.34)	33063	1 (Reference)	1.00
Yes	356 (17.19)	1715	4.45 (2.93–6.74)	<0.001
Unknown	68 (29.57)	162	NA	NA
Intrahepatic met.				
None	1386 (3.86)	34531	1 (Reference)	1.00
Yes	114 (27.47)	301	5.39 (2.77–10.48)	<0.001
Unknown	67 (38.29)	108	NA	NA
Brain met.				
None	1456 (4.01)	34828	1 (Reference)	1.00
Yes	45 (39.47)	69	60.90(25.00–48.33)	<0.001
Unknown	66 (60.55)	43	NA	NA
AFP				
Normal	185 (2.38)	7580	1 (Reference)	1.00
Elevated	974 (4.57)	20349	1.24 (0.86–1.78)	0.25
Unknown	408 (5.50)	7011	NA	NA

HCC – hepatocellular carcinoma; AI – American Indian/Alaska Native; API – Asian or Pacific Islander; Met – metastases; NA – not available; AFP – alpha fetoprotein. All factors with unknown data were removed from the multivariable logistic regression model.

1.60–1.80, $P<0.001$); regional lymph node (N) stage (OR=3.92, 95% CI: 3.41–4.50, $P<0.001$); tumor differentiated grade (OR=1.44, 95% CI: 1.27–1.64, $P<0.001$); presence of lung metastases (OR=6.01, 95% CI: 5.28–6.83, $P<0.001$), intrahepatic metastases (OR=9.44, 95% CI: 7.56–11.78, $P<0.001$), and brain metastases (OR=15.60, 95% CI: 10.68–22.79, $P<0.001$); and AFP (OR=1.96, 95% CI: 1.67–2.30, $P<0.001$).

Multivariate logistic regression analyses indicated male sex, unmarried status, higher T stage, higher N stage, and presence of lung metastases, intrahepatic metastases, and brain metastases were positively associated with BM at initial diagnosis (Table 1).

Table 2. Multivariable Cox regression analysis of mortality among hepatocellular carcinoma patients with bone metastases.

Subject characteristics	No. of HCC patients with BM		Survival, median (95%CI), mo.	HR (95% CI)	P
	Overall	Dead (N,%)			
Marital status					
Married	572	542 (94.76)	3 (2.51–3.49)	1 (Reference)	1.00
Unmarried	619	597 (96.45)	2 (1.68–2.32)	1.56 (1.12–2.18)	0.01
Unknown	72	70 (97.22)	NA	NA	NA
Insurance status					
Insured	1167	1118 (95.80)	3 (2.76–3.24)	1 (Reference)	1.00
Uninsured	75	70 (93.33)	2 (1.36–2.64)	1.15 (0.63–2.10)	0.65
Unknown	21	21 (100.00)	NA	NA	NA
T Stage					
T1	264	253 (95.83)	3 (2.31–3.69)	1 (Reference)	1.00
T2	147	139 (94.56)	3 (2.28–3.72)	1.40 (0.83–2.38)	0.21
T3	423	405 (95.74)	3 (2.60–3.40)	1.05 (0.70–1.57)	0.82
T4	73	72 (98.63)	2 (1.31–2.69)	1.40 (0.65–3.02)	0.39
Unknown	356	340 (95.51)	NA	NA	NA
Lymph node met.					
N0	780	742 (95.13)	3 (2.61–3.39)	1 (Reference)	1.00
N1	238	233 (97.90)	2 (1.66–2.34)	1.09 (0.72–1.64)	0.69
Unknown	245	234 (95.51)	NA	NA	NA
Grade					
I	82	73 (89.02)	5 (3.45–6.55)	1 (Reference)	1.00
II	123	115 (93.50)	5 (3.75–6.25)	1.05 (0.67–1.65)	0.83
III	119	115 (96.64)	2 (1.55–2.45)	1.59 (1.01–2.50)	0.047
IV	7	7 (100.00)	2 (0.00–4.57)	1.29 (0.30–5.60)	0.73
Unknown	932	899 (96.46)	NA	NA	NA
Lung met.					
None	908	862 (94.93)	3 (2.60–3.40)	1 (Reference)	1.00
Yes	294	290 (98.64)	2 (1.69–2.31)	1.41 (0.95–2.10)	0.09
Unknown	61	57 (93.44)	NA	NA	NA
AFP					
Normal	146	134 (91.78)	4 (2.73–5.27)	1 (Reference)	1.00
Elevated	783	754 (96.30)	3 (2.72–3.28)	1.12 (0.76–1.65)	0.57
Unknown	334	321 (96.11)	NA	NA	NA
Surg (pri)					
None	1224	1176 (96.08)	3 (2.77–3.23)	1 (Reference)	1.00
Yes	36	30 (83.33)	9 (6.07–11.94)	0.29 (0.14–0.60)	0.001
Unknown	3	3 (100.00)	NA	NA	NA

HCC – hepatocellular carcinoma; BM – bone metastases; Met – metastases; Surg (pri) – surgical treatments of primary site; NA – not available; AFP – alpha fetoprotein. All factors with unknown data removed from the Cox and Kaplan-Meier model.

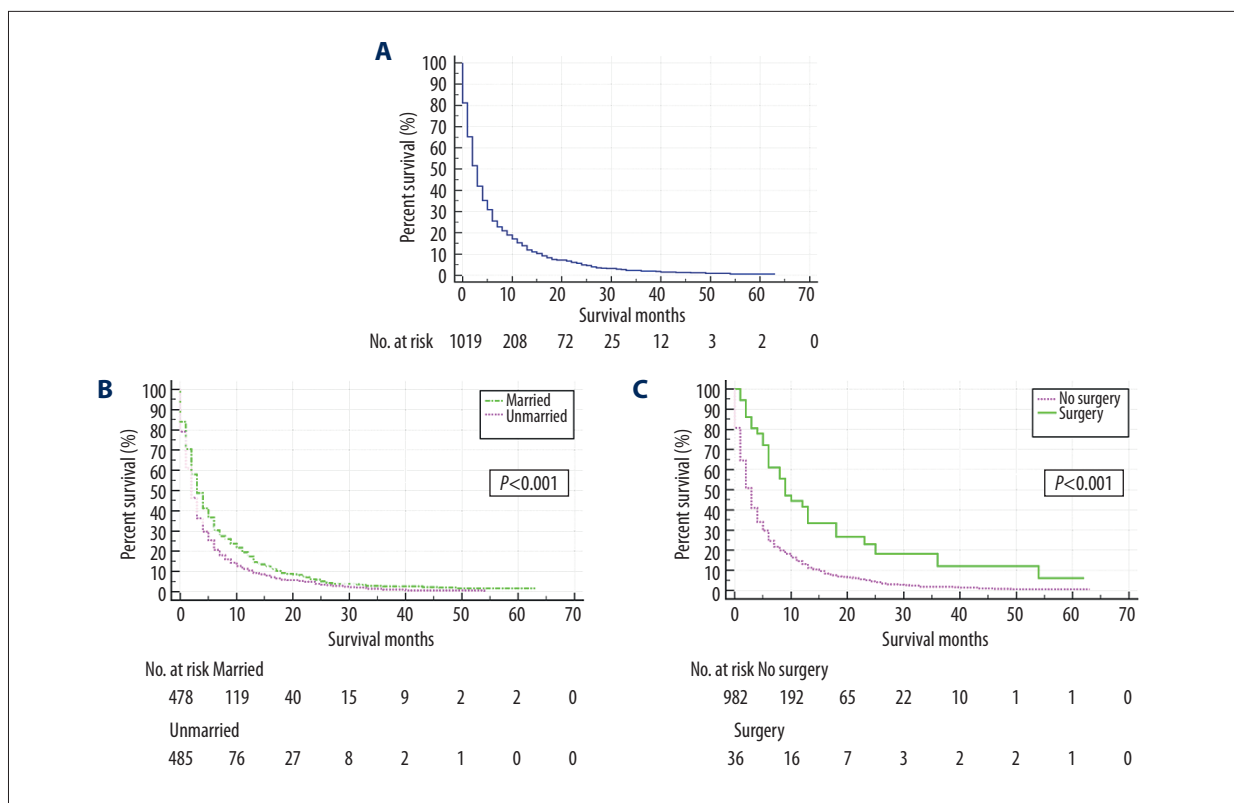


Figure 1. Kaplan-Meier analysis of overall survival among patients diagnosed with hepatocellular carcinoma with initial bone metastases (A, overall), stratified by marital status (B) and surgical treatments of primary site (C).

Survival time and prognostic factors for BM

At the end of follow-up, 95.72% (N=1209) of HCC patients with initial BM had died. The median overall survival for these HCC patients was 3.00 months (95% CI: 2.77–3.24 months, Figure 1A), while the median survival of the cohort was 12.00 months (95% CI: 11.66–12.34). The overall survivals of patients with unmarried ($P < 0.001$, Figure 1B), uninsured ($P = 0.02$), higher primary tumor (T) stage ($P = 0.03$), higher regional lymph node (N1) ($P < 0.001$), lung metastases ($P < 0.001$), poor tumor differentiated grade ($P < 0.001$), and elevated AFP ($P = 0.001$) were worse than their counterparts. The overall survival of patients with a history of surgical treatment at the primary site was significantly better than in those without surgery ($P < 0.001$, Figure 1C). The median survival of patients with surgery at primary site was 9.00 months compared to 3.00 months without surgery (Table 2).

Both unmarried status ($P = 0.01$) and surgical treatment of primary site ($P = 0.001$) were significantly associated with overall survival by multivariate Cox regression analyses (Table 2).

Discussion

To the best of our knowledge, this is the largest population-based study to investigate the prevalence, risk, and prognostic factors for BM in HCC. With the deleterious effect on survival and quality of life caused by BM among HCC patients, a screening approach to determine whether HCC patients have BM should be delineated. The results presented in our study suggest HCC patients have significantly greater odds of BM at diagnosis if they are male, unmarried, have higher T stage, and have lymph node involvement, intrahepatic metastases, and extrahepatic metastases (lung or brain). Accordingly, we propose that skeletal radiographic scanning be considered at diagnosis for HCC patients with the aforementioned factors. The latest relevant study suggested patients with metastatic disease at other locations instead of bone have lower risk of developing BM later; thus, radiographic screening for those patients is not necessary [1]. Undoubtedly, more research is needed to verify this proposition.

Various prognostic factors were reported in previous studies, including SREs [1], alpha fetoprotein [18], Tomita score [10], and body mass index [19]. In the present study, based on the SEER database, we found 2 prognostic factors of BM among HCC patients at initial diagnosis. The HCC patients were associated

with significantly higher risk of mortality if they were unmarried or did not have a history of surgical treatment of the primary liver lesion.

The association of marital status with mortality may be due to various reasons. First, compared with unmarried patients, married patients may have more financial support, which can prompt early diagnosis and timely medical intervention [20,21]. Second, depression and stress were reported to be associated with tumor metastasis [22,23]. Compared with unmarried patients, married patients were likely to be less depressed and stressed after being informed of their cancer diagnoses. Undoubtedly, the mechanism underlying this phenomenon needs to be explored.

Extrahepatic metastasis of HCC was long thought to be a terminal event, so neither surgical resection nor ablation were considered [14,15]. The latest case report indicated that primary liver tumor surgery can improve the survival of HCC patients with BM [16]. Although some recent studies reported a series of molecular markers for predicting prognosis of HCC [24–26], few studies have reported on surgical treatment of the primary liver tumor among HCC patients with BM. In our study, significantly improved survival was observed among the BM patients who underwent primary liver tumor surgery. However, we attribute this result to biased selection of the patients. In future, randomized comparison clinical trial is warranted.

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Conclusions

This study demonstrates that the prevalence of initial BM was 4.29%. Risk of bone metastasis was significantly associated with the following risk factors: male sex, unmarried status, higher T stage, higher N stage, and the presence of lung metastases, intrahepatic metastases, and brain metastases. Unmarried HCC patients with BM tended to have a worse prognosis.

Conflict of interest

None.

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