Bone metastases from hepatocellular carcinoma: clinical features and prognostic factors

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BACKGROUND: Bone metastases (BMs) from hepatocellular carcinoma (HCC) is an increasingly common disease in Asia. We assessed the clinical features, prognostic factors, and differences in outcomes related to BMs among patients with different treatments for HCC.

METHODS: Forty-three consecutive patients who were diagnosed with BMs from HCC between January 2010 and December 2014 were retrospectively enrolled. The clinical features were identified, the impacts of prognostic factors on survival were statistically analyzed, and clinical data were compared.

RESULTS: The median patient age was 54 years; 38 patients were male and 5 female. The most common site for BMs was the trunk (69.3%). BMs with extension to the soft tissue were found in 14 patients (32.5%). Most (90.7%) of the lesions were mixed osteolytic and osteoblastic, and most (69.8%) patients presented with multiple BMs. The median survival after BMs diagnosis was 11 months. In multivariate analyses, survival after BM diagnosis was correlated with Karnofsky performance status (P=0.008) and the Child-Pugh classification (P<0.001); BM-free survival was correlated with progression beyond the University of California San Francisco criteria (P<0.001) and treatment of primary tumors (P<0.001). BMs with extension to soft tissue were less common in liver transplantation patients. During metastasis, the control of intrahepatic tumors was improved in liver transplantation and hepatectomy patients, compared to conservatively treated patients.

CONCLUSIONS: The independent prognostic factors of survival after diagnosis of BMs were the Karnofsky performance status and Child-Pugh classification. HCC patients developed BMs may also benefit from liver transplantation or hepatectomy.

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Introduction

epatocellular carcinoma (HCC) is the sixth most prevalent cancer worldwide and the third leading cause of cancer-related death. HCC has a heterogeneous geographical distribution, with most cases (>80%) occurring in eastern Asia and sub-Saharan Africa.^[1] Bone metastases (BMs) from HCC are highly vascularized lesions and cause severe deterioration of the patients' quality of life. The reported incidence of BM from HCC was relatively low before the 20th century. However, bone is now the second major site and accounts for approximately 25% of extrahepatic metastases from HCC.^[2-4] This increase is due to the advances of bone imaging technique and the prolonged survival of HCC patients.^[5-8] Hepatectomy, radiofrequency ablation, transhepatic arterial chemotherapy and embolization, and tyrosine kinase inhibitors such as sorafenib are effective treatment modalities for HCC.^[9] Liver transplantation (LT) has also been established as a promising treatment for malignant liver diseases.^[10-12] However, whether these treatments contribute towards the survival of patients with BMs from HCC, and whether they are related to the condition of patients during metastasis, remain unclear. In this study, the clinical features and prognostic factors were investigated in patients with BMs from HCC, and the clinical data were compared among patients with different treatments for intrahepatic tumors.

Methods

Study design

We reviewed the data of 43 consecutive patients diagnosed with BMs from HCC in the First Affiliated Hospital, Zhejiang University School of Medicine between

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January 2010 and December 2014. Sixteen patients underwent LT as treatment for HCC and subsequently developed BMs. The final follow-up date was June 30, 2015, and the median follow-up time was 11 months. None of the patients were enrolled in any clinical trials or experimental protocols. The Institutional Research Ethics Committee approved this retrospective observational study.

All patients diagnosed with BMs from HCC were provided with histological confirmation of the disease via bone biopsy or surgical pathology. ^{99m}Tc bone scintigraphy was used to locate all possible sites of BM. Magnetic resonance imaging (MRI) or computed tomography (CT) was performed to either confirm or provide detailed information on symptomatic sites.^[13] Additional pretreatment evaluation included assessment of the patient's medical history, as well as a physical examination, complete blood routine, serum chemistries, blood gas analysis, alpha-fetoprotein (AFP) level, γ -glutamyl transpeptidase (γ -GT) level, chest X-ray, and abdominal and cardiac ultrasonography.

The "first BM-related event" refers to the event that led to the diagnosis of BM from HCC. "Responsible sites" are metastatic sites that directly give rise to symptoms. Well-controlled primary tumors are defined as an absence of new lesions in the liver on enhanced CT or MRI at the completion of treatment for BMs. External beam radiotherapy (EBRT) was conducted as a palliative treatment for primary or recurrent BMs, either on its own or in combination with surgical treatment. EBRT was scheduled as 3 Grays (Gy)/fraction, five times a week, with a full dosage of 30 Grays, based on the status of the tumor and the patient's condition. Surgery was considered when the patient suffered from a pathological fracture, had a high risk for limb bone fractures, experienced an acute spinal cord injury caused by a compression fracture, or had a solitary metastasis with extended anticipated survival. Surgical modalities included curettage or wide resection, followed by cementing, internal fixation, or prosthesis replacement. A wide resection was first considered in solitary BMs without concurrent extraosseous recurrence.

The survival intervals investigated included BM-free survival (the interval from the diagnosis of HCC to the diagnosis of BMs) and survival after BM diagnosis. The factors assessed included age at time of diagnosis of HCC, number and size of intrahepatic lesions, criteria for LT,^[14-16] treatment of HCC, gender, age at diagnosis of BMs, Child-Pugh classification,^[17] median level of tumor markers, presence of extraosseous metastases, score systems for BMs,^[18-20] and features of and treatments for bone lesions.

Statistical analysis

Clinical features were assessed based on descriptive

statistics. The impact of prognostic factors on survival was analyzed by the Kaplan-Meier method and tested using the log-rank test. Median survivals were also calculated. Variables were entered using the Backward-Wald method in a Cox regression analysis (the level of statistical significance was set at a *P* value <0.05). The features of BMs in patients given different treatments were compared using Fisher's exact test (at *P*<0.017). All analyses and calculations were performed using the SPSS statistical software (version 17.0; SPSS Inc., Chicago, IL, USA).

Results

Clinical features

Of the 43 patients, 38 were male and 5 female, with a median age of 54 years (range 26-83). For the first BM-related event, 28 patients had pain (65.1%), 5 had dysneuria (11.6%), and 4 had a continuous rise in AFP levels (9.3%). Eight patients experienced no clinical symptoms, and their BMs were discovered by follow-up imaging studies of the HCC (18.6%). Five patients were diagnosed with BMs immediately after HCC diagnosis (11.6%), and 38 developed BMs later on (88.4%). Thirty patients had multiple BMs (69.8%), 39 presented with mixed osteolytic and osteoblastic lesions (90.7%), 4 presented with purely osteolytic lesions (9.3%), and no patient had a purely osteoblastic lesion. BMs with extension to the soft tissue were discovered in 14 patients (32.6%). Of the 101 BM sites, 69.3% were located on the trunk. The lumbar vertebrae (35.3%) were the most common responsible site, followed by the thoracic vertebrae (29.4%) (Table 1).

Table 1. BM sites in the 43 HCC patients (*n*, %)

	1	
Bone sites	Present sites	Responsible sites
	(<i>n</i> =101)	(<i>n</i> =34)
Skull	3 (3.0)	-
Trunk		
Cervical vertebrae	3 (3.0)	2 (5.9)
Thoracic vertebrae	23 (22.8)	10 (29.4)
Lumbar vertebrae	28 (27.7)	12 (35.3)
Sacrum	8 (7.9)	3 (8.8)
Sternum	3 (3.0)	-
Ribs	5 (5.0)	-
Upper limb		
Humerus	3 (3.0)	1 (2.9)
Scapula	5 (5.0)	2 (5.9)
Clavicle	1 (1.0)	-
Lower limb		
Ilium	5 (5.0)	1 (2.9)
Ischium	2 (2.0)	1 (2.9)
Acetabulum	4 (4.0)	2 (5.9)
Pubis	3 (3.0)	-
Femur	5 (5.0)	-
remur	5 (5.0)	-

BM: Bone metastase; HCC: hepatocellular carcinoma.

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