Hepatocellular carcinoma with skeletal metastasis: Prognostic analysis

Alaa Maria and Rabab Mahmoud.

Clinical Oncology Department, Faculty of Medicine, Tanta University, Egypt alaamarial@hotmail.com

Abstract: *Purpose:* Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver worldwide. HCC most commonly metastasizes hematogenously or through lymphatics with carrying a poor prognosis. The aim of this study is to perform a survival analysis of consecutive HCC patients with extrahepatic skeletal metastasis. Material and Methods: Between January 2007 and December 2011, 351 consecutive patients with HCC were admitted to Clinical Oncology Department, Tanta University. Among those patients, extrahepatic metastases were detected in 123 patients (35%). Extrahepatic skeletal metastases were detected in 63 patients and were enrolled in the present study. The median age was 58 (range 37-80) years with Male: Female ratio 6: 1. Extrahepatic metastases were diagnosed by X-ray, CT scan, MRI and/or bone scintigraphy. Patients were presented either with skeletal metastases at the initial diagnosis of HCC, 40 (63.5%) patients or developed skeletal metastases during the followup period, 23 (36.5%) patients. **Results:** Palliative irradiation was given to a total of 84 (87.5%) metastatic sites. Spine was the most common site (54 lesions). The main indications for palliative irradiation were pain (100%); associated soft tissue formation (67.9%); neurological complications due to cord compression (64.3%) and instable lesions with increased risk of pathological fracture (13%). Response to radiation therapy varied with pain reduction in 59 lesions (70.2%). The median survival period for all patients from the time of initial diagnosis of metastatic HCC was 7 (range 2-18) months with 1-year survival rate 20.1%. Identified factors influencing survival for extrahepatic skeletal metastatic patients were: performance status (PS), (p<0.0001); Child-Pugh score, (p<0.0001); size of the primary intra-hepatic tumor (p=0.029); portal venous thrombosis, (p=0.0008); CLIP score (p=0.022); intra-hepatic T stage (p=0.004); number of metastatic systems (p=0.0002) and number of metastatic lesions. (p=0.043). When multivariate analysis was performed, the following variables were independent determinants of survival: PS (p=0.001) and Child-Pugh score (p=0.0006). *Conclusion:* HCC should be considered in the differential diagnosis in patients presenting with bone metastasis especially in areas with a high incidence of HCC. Considering the possibility of extrahepatic metastases, HCC patients with early intra-hepatic tumor stage should be followed up carefully, particularly those who have been treated for intra-hepatic HCC. Selected HCC patients with skeletal metastases could undergo treatment for intra-hepatic lesion. However, these selected patients must have good hepatic reserve and have good performance status. Further studies are needed to improve the prognosis of HCC patients with skeletal metastases.

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Key words: Hepatocellular carcinoma, skeletal metastasis, prognostic factors.

1. Introduction

Hepatocellular carcinoma (HCC) constitutes the 6th most common cancer and the 3rd most common cause of cancer death worldwide ⁽¹⁻³⁾. The incidence of HCC demonstrates a striking geographic variability, with the highest rates in South-East Asia and Sub-Saharan Africa with rising incidence of in North America. The most common etiologic factor is related to viral hepatitis B and C, particularly in the presence of cirrhosis ⁽⁴⁻⁶⁾.

According to Gharbiah population-based cancer registry, the incidence of liver cancer is ranked as the second in men and the seventh in women during 2000–2002 ⁽⁷⁾. Moreover, there has been an alarming increase in incidence of liver cancer in Egypt, which is now three times higher than that in the USA ⁽⁸⁾. Several reports showed an overall estimate of

seroposeitivity for HCV as an etiological factor of approximately $22\%^{(9-13)}$.

In the west, the disease is diagnosed in 30-40% of all patients at early stages and is amenable to potentially curative treatments. Unfortunately, most cases of HCC in developing countries present late and curative treatment via resection or liver transplantation is not possible and carrying a dismal prognosis. Palliative therapy alone is recommended for end stage HCC due to the very poor life expectancy (14-18).

Regardless of primary site control with the improvement in surgical techniques and effective local therapeutic modalities, there is a higher chance for an extrahepatic metastasis. HCC most commonly metastasizes via lymphatics or blood vessels to the regional lymph nodes, lungs and bone. Other less common sites of spread that have been reported include the adrenal gland, stomach, peritoneum, small

bowel, kidney, spleen, heart, and brain ^(19, 20). Rarely the establishment of the diagnosis of metastatic HCC can occasionally be problematic, particularly when the primary tumor has not been identified ⁽²¹⁻²³⁾.

The prognosis of patients with metastatic HCC is poor with no consensus on the treatment strategy. For example, what treatment strategy should be used to? and which patients should be treated? (24-26).

The aim of this study is to perform a survival analysis of consecutive HCC patients with extrahepatic skeletal metastasis.

2. Material and Methods

Between January 2007 and December 2011, 351 consecutive patients with HCC were admitted at Clinical Oncology Department, Tanta University. Among those patients, extrahepatic metastases were detected in 123 patients (35%), Table 1. Extrahepatic skeletal metastases were detected in 63 patients (51.2%) and were enrolled in the present study. The median age was 58 (range 37-80) years with Male: Female ratio 6: 1. Table 2 summarizes the clinical profile of skeletal metastatic patients.

Table (1): Sites of extra-hepatic metastasis

Sites of extra-hepatic	Number of Metastatic patients	All HCC (351 pts)	Metastatic HCC (123 pts)	
metastasis	patients	%	%	
LNs	65	18.5	52.8	
Bone	63	17.9	51.2	
Lung	19	5.4	15.4	
Adrenal	4	1.1	3.3	
Brain	2	0.6	1.6	

Of all skeletal metastatic patients, 69.8% were presented with poor performance status (PS) \geq 2 according to criteria of the Eastern Cooperative Oncology Group (ECOG)⁽²⁶⁾. The hepatic reserve was calculated using the Child-Pugh score ⁽²⁸⁾ (Table 3) and grade A was presented in 73.0% of patients.

On evaluation the primary tumor stage according to the Cancer of the Liver Italian Program Score (CLIP score) (29, 30), that incorporates measures of tumor size, vascular invasion, Alpha-fetoprotein (AFP) level, and hepatic function as measured by Child–Turcotte–Pugh (CTP) class. Nine (14.3%) patients were presented with score 4 or more that represent advanced disease.

Concerning the American Joint Committee on Cancer (AJCC) TNM staging (2010) ⁽³¹⁾, the primary HCC T-stage at the first diagnosis of extrahepatic metastases was T1 in 32 (50.8%) patients, LN metastasis was detected in 13 (20.6%) patients with 74.6% of all patients had multiple metastatic sites.

Table (2): Characteristics of 63 patients with extrahepatic, skeletal metastatic HCC

hepatic, skeletal met				
Characters	No.	%		
Age~				
<60	38	60.3		
≥60	25	39.7		
Sex				
Male	54	85.7		
	9			
Female	9	14.3		
Performance status				
<2	19	30.2		
≥2	44	69.8		
Primary tumor location				
One lobe	43	68.3		
Both lobes	20	31.7		
Number of primary tumor		.		
Solitary	39	61.9		
Multiple	24	38.1		
		36.1		
Bilirubin mg/dL: Median 1.0 (range				
Albumin g/dL: Median 3.1 (range 2	2.2-4.2)			
Child-Pugh score				
A	46	73.0		
В	16	25.4		
C	1	1.6		
Size of primary tumor	•	•		
≤2 cm	5	7.9		
>2-5 cm	30	47.6		
>5 cm	28	44.4		
Alpha-fetoprotein	20	77.7		
	1 20	47.6		
<400	30	47.6		
≥400	33	52.4		
Portal vein thrombosis				
+ve	18	28.6		
-ve	45	71.4		
Cancer of the Liver Italian Program score				
<4	54	85.7		
≥4	9	14.3		
Intra-hepatic T stage		1 - 1.0		
T1	32	50.8		
T2	13	20.6		
	7			
T3a	-	11.1		
T3b	11	17.5		
Other sites of extra-hepatic metasta		1		
LN	13	20.6		
Lung	7	11.1		
Adrenal	3	4.8		
Brain	1	1.6		
Number of metastatic systems		•		
Skeletal	46	73		
Skeletal + others	17	27		
Number of metastatic lesions	1/	121		
	16	25.4		
Solitary	16	25.4		
Multiple 47 74.6				
Time for development of metastasis				
Synchronous	40	63.5		
Metachronous	23	36.5		
~Mean 59.1±8.6 years, Median 58	years, Rang	ge 37-80 years		
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All the metastatic patients were presented either with extra-hepatic metastases at the initial diagnosis of

HCC, 40 (63.5%) patients or developed extra-hepatic metastases during the follow-up period, 23 (36.5%) patients. The median interval between initial HCC diagnosis and that of the metachronous metastasis was 13.7 months, ranging from 6 months to 72 months. Among them, 17 (73.9%) patients were treated previously for primary HCC in other hospitals; liver transplantation (1 patient), lobectomy (2 patients), trans-arterial chemo-embolization TACE (9 patients) and radiofrequency (5 patients) and the remaining 6 patients received supportive therapy.

Table (3): Child-Pugh scoring system (28)

Measure	1	2	3	
Total bilirubin (mg/dl)	≤2	2-3	>3	
Serum albumin, g/L	>35	28-35	<28	
INR	<1.7	1.71-2.30	> 2.30	
Ascites	None	Mild	Moderate to Severe	
Hepatic encephalopathy	None	Grade I-II	Grade III-IV	
A: 5-6 B: 7-9	C: 10-15			

HCC was assessed by abdominal ultrasound and/or triphasic abdominal CT scan and measuring α -fetoprotein (AFP). A definitive diagnosis of HCC was based on the finding of typical hypervascular radiological features or histopathological examination of needle biopsy specimen. Extrahepatic metastases were diagnosed by bone scintigraphy, X-ray, CT scan and/or MRI.

Treatment

Chemotherapeutic regimens were delivered in multiple protocols for 16 patients. The most common used therapeutic agents include capecitabine (Xeloda®) 1,000 mg/m² PO twice daily on days 1–14 every 3 weeks, cisplatin 80 mg/m² IV weekly and anthracycline 60 mg/m² IV every 3 weeks. Medical supportive care was delivered to patients with poor general condition.

Palliative radiation therapy for bone metastasis was delivered with a Cobalt-60 and/or linear accelerator, utilizing 6 MV photon beams and/or 9 MV electron beam. The treatment volume covered the gross tumor volume (GTV), which was identified with imaging data, adding a margin of 1.5 to 2 cm in all directions. If vertebral bodies were targeted for treatment, the treatment volume included the involved vertebral bodies, plus one additional segment in both the cephalad and caudal directions. Enlarged fields were utilized according to CT scan and/or MRI with the presence of soft tissue extension. Various palliative radiation doses were used, 3 Gy x 10 fractions (46 lesions), 4 Gy x 5 fractions (30 lesions) or 7 Gy x 1 fraction (8 lesions).

Statistical analysis

Overall survival (OS) was calculated from the radiographic diagnosis of metastasis until death or until the date of last follow-up visit for patients who were still alive. Cumulative survival rate was assessed by the Kaplan-Meier method and the differences were evaluated by the log rank test. Cox proportional hazard model analysis was performed to identify the prognostic factors for OS. Variables with a p<0.05 in univariate analysis were included in the multivariate survival analysis. A p-value <0.05 was considered statistically significant. Analyses were performed using the Statistical Package for the Social Science (SPSS, Chicago, IL USA, V-12) software package.

3. Results

Ninety-six bony lesions (72 axial lesions and 24 appendicular lesions) were detected by plain x-ray, CT scan, MRI and/or bone scintigraphy and showed osteolytic lesions of the bony framework. Infiltration into the surrounding with soft tissue formation was detected in 57 sites. From those patients, five patients were presented with clinically palpable mass (3 in the chest wall, 1 in the gluteal region and 1 in the shoulder). Bone pain and tenderness with limited mobility was the main problem for all metastatic patients.

None of the metastatic patients had surgical interference after the detection of extra-hepatic metastasis. Local therapy was performed in 3 (4.8%) patients with Child-Pugh grade A and PS<2 presented with asymptomatic solitary appendicular skeletal metastasis (radiofrequency in 2 patients and TACE in 1 patients). Chemotherapy was given to 16 (25.4%) patients. The received cycles varied between 2 to 4 cycles according to the tolerance of the patients. On the other hand, 44 (69.8%) patients presented with Child-Pugh grade B-C and/or PS≥2 received supportive care.

Palliative irradiation was given to a total of 84 (87.5%) metastatic sites. Spine was the most common site (54 lesions), followed by upper and lower extremities (11 lesions), pelvic bones (9 lesions), scapula (4 lesions), skull (3 lesions) and the ribs (3 lesions). The full dose was delivered to all treated patients according to the decided plans. The main indications for palliative irradiation were pain (100%); associated soft tissue formation (67.9%); neurological complications due to cord compression (64.3%) and instable lesions with increased risk of pathological fracture (13%). Irradiation with single fraction was given for patients with poor general condition and carrying bad prognosis because of a limited life expectancy.

Response to radiation therapy varied for all treated patients. Concerning pain relief, patients

reported >50% improvement for 59 lesions (70.2%). Re-irradiation was done for 6 patients after a median time 2.5 (range, 1-4) months.

At the time of analysis, we identified 61 patient deaths (96.8%). The median survival period for all patients from the time of initial diagnosis of metastatic HCC was 7 (range 2-18) months with 1-year survival rate 20.1%, Fig (1).

The median survival period of patients diagnosed with primary HCC and metastasis synchronously or metachronously were nearly the same, 7.8 (range 2-18) months and 8.6 (range 3-17) months respectively (p=0.82).

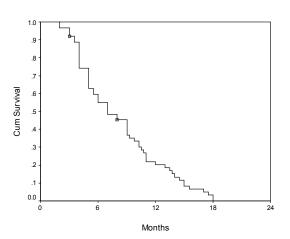


Fig (1): Overall survival rate for all patients with bone metastasis

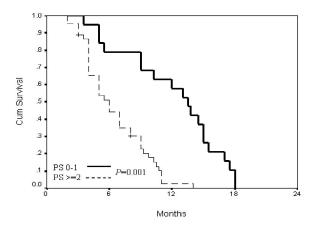


Fig (2): Overall survival rate for all patients with bone metastasis according to performance status

After initial diagnosis of extrahepatic skeletal metastases, identified factors influencing survival in a univariate analysis were: PS, (p<0.0001); Child-Pugh score, (p<0.0001); size of the primary intra-hepatic tumor (p=0.029); portal venous thrombosis, (p=0.0008); CLIP score (p=0.022); intra-hepatic T stage (p=0.0043); number of metastatic systems (p=0.0002) and number of metastatic lesions, (p=0.043). When multivariate analysis was performed, the following variables were independent determinants of survival: PS (p=0.001) and Child-Pugh score (p=0.0006) (Figs 2 & 3 and Table 4).

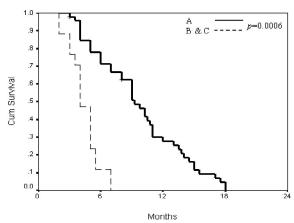


Fig (3): Overall survival rate for all patients with bone metastasis according to Child-Pugh score

Table (4): Univariate and multivariate analysis of prognostic factorsCharacters

	,		Univariate analysis		Multivariate analysis	
		No	Median survival (months)	<i>p</i> -value	95%CI	<i>p</i> -value
Age	<60 ≥60	38 25	7.9 8.4	0.647	-	-
Sex	Male Female	54 9	8 8.7	0.680	-	-
Performance status	<2 ≥2	19 44	12.1 6.4	<0.0001*	1.79 – 9.87	0.001*
Child-Pugh score	A B & C	46 17	9.5 4.4	<0.0001*	1.96 – 11.86	0.0006*
Size of primary tumor	≤5 cm >5 cm	35 28	9.2 6.7	0.029*	-	NS
AFP	<400 ≥400	30 33	9.2 7	0.133	-	-
PV thrombosis	+ve -ve	18 45	5.7 9	0.0008*	-	NS
CLIP score	<4 ≥4	54 9	8.5 5.6	0.022*	-	NS
Intra-hepatic T stage	1 2-3	32 31	9.6 6.5	0.004*	-	NS
Number of metastatic systems	Skeletal Skeletal + others	46 17	9.1 5.4	0.0002*	-	NS
Number of metastatic lesions	Solitary Multiple	16 47	10.4 7.3	0.043*	-	NS
Time for development of metastasis	Synchronous Metachronous	40 23	7.8 8.6	0.821	-	-

CI: Confidence interval; AFP: Alpha Fetoprotein; PV: Portal vein; CLIP: Cancer of the Liver Italian Program; *: Significant *p*<0.05; NS: Non-significant

4. Discussion

In the present study, the incidence of extrahepatic metastases from HCC was 35%. The most frequent metastatic sites were the lymph nodes, bone, lung, adrenal gland and brain. Concerning the skeletal metastasis, it was presented in 17.9% of all HCC patients and constitutes 51.2% of all metastatic patients. The most common sites were the vertebrae with the main complain was pain and neurological symptoms. All of the bony lesions were osteolytic with associated soft tissue formation in 59.4% of the lesions. Most of the skeletal metastasis (63.5%) was presented at the initial diagnosis of HCC.

Many studies reported extrahepatic metastases to occur in 13.5%-42% of HCC patients $^{(24,32\cdot34)}$. Concerning skeletal metastases, Fukutomi *et al.*, $^{(35)}$ & Ahmed *et al.*, $^{(36)}$ reported that the incidence of bone metastasis was 3-20% with definite upward trend due to recent progress made in both the diagnosis and treatment of the disease. Bone metastasis being symptomatic and can occur before the other clinical manifestations of HCC become apparent. The most common sites are the vertebra and pelvis $^{(20,34,36)}$.

All bone metastases from HCC are osteolytic in nature. They tend to be expansile and lytic in appearance on plain radiograph and CT scan. (32, 38) Leung *et al.*, (39) concluded that if a patient presents with an expansile osteolytic bone lesion, bone metastasis from HCC should be considered in addition to renal cell carcinoma and thyroid carcinoma. Kim *et al.*, (20) studied the association of soft tissue formation with bony lesions and reported their presentation in 85.4% of all cases.

Katyal *et al.*, (32) and Natsuizaka *et al.*, (24) reported

Katyal *et al.*, ⁽³²⁾ and Natsuizaka *et al.*, ⁽²⁴⁾ reported that patients with advanced HCC develop extrahepatic metastases significantly more frequently than those with less advanced HCC. On the other hand, our study identified 32 (50.8%) patients with skeletal metastatic HCC had early intra-hepatic tumor stage (T1), 16 patients at the initial diagnosis of HCC and 16 patients were treated previously for intra-hepatic HCC.

The prognosis of HCC patients with extrahepatic metastases is unsatisfactory ^(24, 25). Though there is no standard treatment for extrahepatic metastases of primary HCC, some reports have described successful treatment of extrahepatic metastases because of hepatic reserve or intra-hepatic tumor stage ⁽⁴⁰⁻⁴²⁾.

The clinical features of our patients varied widely. Most of our patients (69.8%) had symptomatic metastasis and were presented with Child-Pugh grade B-C and/or PS\ge 2. So, they received supportive treatment. Localized palliative radiation therapy was given to a total of 84 (87.5%) metastatic sites with reduction in pain severity in 70.2% of the lesions. Local hepatic therapy was performed for 3 (4.8%) patients presented with asymptomatic solitary skeletal metastasis and had Child-Pugh grade A and/or PS\le 2.

The median survival period from the time of initial diagnosis of skeletal metastasis was 7 (range, 2-18) months with 1-year survival rate 20.1%. On analysis of factors affecting survival, we identified that performance status and Child-Pugh score were the independent prognostic factors (p=0.001 & p=0.0006, respectively)

Uka et al., (26) concluded that extrahepatic metastases with early intra- hepatic tumor stage can spread during the relatively long survival period. So, successful treatment of extrahepatic metastases in HCC patients with early intra-hepatic tumor stage might improve the prognosis. However, these selected patients must have good hepatic reserve, intra-hepatic tumor stage: T0-T2, and are free of portal venous invasion.

Attili *et al.*, ⁽⁴³⁾ reported that the presence of bone only metastasis confers a better prognosis than metastasis at other sites, and all such patients need to be offered chemotherapy and at least one of bone directed therapies, either local radiation in case of localized disease or bisphosphonates in the presence of extensive disease.

Seong *et al.*, ⁽⁴⁴⁾ investigated the effectiveness of palliative radiation therapy for bone metastasis from HCC with a median total dose of 30 Gy. There was pain relief in 73% of the lesions. The median survival period from the occurrence of a bone metastasis was 5 months, with a 1-year survival rate of 15%. Also, Kim *et al.*, ⁽²⁰⁾ reported 5 months median survival period from the occurrence of a bone metastasis.

5. Conclusion

HCC should be considered in the differential diagnosis in patients presenting with bone metastasis especially in areas with a high incidence of HCC. Considering the possibility of extrahepatic metastases, HCC patients with early intra-hepatic tumor stage should be followed up carefully, particularly those who have been treated for intra-hepatic HCC. Selected HCC patients with skeletal metastases could undergo treatment for intra-hepatic lesion. However, these selected patients must have good hepatic reserve and have good performance status. Further studies are needed to improve the prognosis of HCC patients with skeletal metastases.

6. Corresponding author

Alaa Mohamed Maria

Clinical Oncology Department, Faculty of Medicine, Tanta University, Al Gaish St., Tanta, Gharbia 11312, Egypt.

alaamaria1@hotmail.com

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