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Metastases of Hepatocellular Carcinoma to Unusual Sites: A 10 Year Case Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author BU did the literature search, data acquisition, data analysis, manuscript preparation and editing. Author ND came up with the concept, did the literature search, data acquisition and manuscript editing and author ZA reviewed and edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Hepatocellular carcinoma is the most common primary tumor of the liver, usually arising in a background of chronic hepatitis and cirrhosis. It is the fifth most common cancer worldwide comprising almost 6% of all newly diagnosed cancers.
Aim: The aim of our study is to report unusual metastasis of HCC seen in our practice.
Methods and Results: Data of 10 years were collected. A total of 30 cases diagnosed as metastatic hepatocellular carcinoma during the period 2004-2013 were retrieved and reviewed from files of the Section of Histopathology, Aga Khan University Hospital. Cases presenting with metastases to the lungs were excluded from the data. Age range of the patients was 31-84 years with mean age of 59.1 years. There were 28 males and 2 females. The most frequent unusual site of extrahepatic metastases was bone (n= 23), followed by soft tissue of the gluteal region (n=2), posterior triangle of neck (n=1), inguinal region (n=1), iliopsoas muscle (n=1), parotid region (n=1) and the eyeball region presenting as retrobulbar mass (n=1).

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Conclusion: Lung and bone metastases are frequently seen in patients with HCC. However, HCC sometimes metastasizes to unusual sites/organs. An early diagnosis of these metastases by appropriate diagnostic modalities is essential and can improve the quality of the patient's life.

Keywords: Hepatocellular carcinoma; unusual metastatic sites; extrahepatic sites.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver, usually arising in a background of chronic hepatitis and cirrhosis. Chronic Hepatitis B and C (HBV & HCV) infections accounting for majority of the cases in underdeveloped countries while alcohol consumption eventually leading to cirrhosis is a major culprit in developed nations. Other less common conditions which can progress to HCC include Autoimmune Hepatitis, Primary biliary cirrhosis, Sclerosing cholangitis, Wilson's disease, Hemochromatosis etc. It is the fifth most common cancer comprising almost 6% of all newly diagnosed cancers worldwide. Incidence of HCC also varies geographically. It is rare in United States (USA) but very common in all African countries, South of Sahara and in Southeast Asia which is mostly attributable to endemic nature of HBV and HCV infection [1,2]. Hepatocellular carcinoma has a dismal prognosis. Factors that affect the prognosis of patients with hepatocellular carcinoma are tumor stage at the time of diagnosis, general health of the patient, hepatic synthetic function and efficacy of the treatment [3]. like all cancers, early diagnosis is essential for better survival. However, unfortunately, HCC is frequently diagnosed at an advanced stage resulting in high mortality rates. Although the mainstay of therapy in HCC is surgical resection of the tumor, other available treatment options which can be successfully employed in appropriately selected patients include liver transplantation and some locally ablative and locoregional therapies in the form of percutaneous ethanol injection, radiofrequency ablation, transcatheter arterial chemoembolization and radioembolization [4]. Prognosis of the patient after successful treatment is worsened by two factors, intrahepatic recurrence or extrahepatic metastases, of which extrahepatic metastasis carries worse prognosis because of limited treatment options available [5]. Recently two large randomized controlled trials involving Sorafenib, an oral multikinase inhibitor has decreased improved survival in patients with advanced HCC and now Sorafenib is widely used in the treatment of such patients [6,7]. The most frequent site of extrahepatic metastases are the lungs followed by abdominal lymph nodes, bones, adrenal glands, peritoneum, diaphragm, brain, cervical lymph nodes, skin and muscle. In most cases, extrahepatic metastasis correlate with advancing intrahepatic tumor stage but it may be the initial presenting feature especially in cases where the tumor metastasizes to an unusual site. HCC metastases to unusual sites have been reported in a few case reports [8-11]. This series illustrates the notorious nature of HCC to metastasize to unusual sites.

2. MATERIALS AND METHODS

Data were collected over a period of 10 years, from 2004-2013. All cases diagnosed with metastatic HCC during the period 2004-2013 were retrieved and reviewed from pathology files of the Section of Histopathology, Aga Khan University, Hospital, Karachi. Cases presenting with metastases to the lungs were excluded since lung is a common site of metastasis in HCC.

Out of total 30 cases, only one patient was a known case of HCC while two patients were clinically diagnosed with HCC. In the remaining cases, there was no previous history of HCC. In 6 cases, there was clinical suspicion of a metastatic lesion. In most of the remaining cases, there was history of mass lesion at the site of presentation (Table 1). All cases were stained with H&E. Following histologic examination, a panel of immunohistochemical stains was performed on each case to confirm the diagnosis.

Table 1. Demographic characteristics and presentation of the patients (n=30)

Case no	Age & gender	Presentation of the patients
1	50/Male	Growth involving the angle and ramus of the mandible
2	56/Male	Growth C6 (cervical) vertebra with clinical suspicion of Tuberculosis
3	51/Male	Growth L4 (Lumbar) vertebra with the clinical suspicion of metastatic lesion
4	56/Male	Growth humerus
5	66/Male	Growth right shoulder, MRI suggestive of soft tissue sarcoma
6	63/Male	Known case of HCV, clinical suspicion of Hepatoma, presented with left shoulder mass
7	55/Female	Known case of HCV, presented with mass in big toe
8	65/Male	Right lower limb weakness, MRI showed extradural mass at T7 (thoracic) vertebra
9	52/Male	Right eye pain and difficulty in vision, MRI showed retrobulbar mass
10	61/Male	Known case of Hepatocellular Carcinoma, presented with paraplegia, MRI showed mass with collapse of T4 & T5 vertebrae
11	70/Male	Mass in the forehead region, MRI showed extradural lesion eroding the frontal bone
12	60/Male	Mass right chest wall involving the sternum. Patient also had an enlarged axillary lymph node
13	48/Male	Known case of HBV, patient presented with leg pain, MRI showed sacral mass compressing the nerves
14	60/Male	Known case of HBV , MRI showed osteolytic lesion in right Scapula
15	75/Male	Soft tissue mass in the posterior triangle of neck, with clinical suspicion of metastasis
16	58/Male	Weakness of the lower limbs, MRI showed enhancing lesion of C3 vertebra
17	64/Male	Painful inguinal lymphadenopathy
18	55/Male	Weakness of the lower limbs, MRI showed highly vascular extradural lesion involving T2 & T3 vertebrae
19	84/Female	Growth in the gluteal region
20	64/Male	Biopsy from thoracic vertebra, CT scan of the patient showed a 71 mm echogenic mass in the liver
21	55/Male	Biopsy from iliopsoas region, CT scan showed soft tissue mass in paraspinal region
22	65/Male	MRI showed a mass involving the T6 vertebra
23	34/Male	Presented with swelling in the parotid region
24	55/Male	Weakness of the lower limbs, MRI showed spinal tumor
25	60/Male	Biopsy from posterior chest wall with clinical suspicion of metastasis
26	56/Male	Biopsy from humerus, no clinical information provided
27	67/Male	Swelling in gluteal region with clinical suspicion of rhabdomyosarcoma
28	31/Male	Weakness of the lower limbs, MRI showed enhancing lesion at L5
29	75/Male	Swelling anterior chest wall for 6 months
30	62/Male	Fracture right femur after trivial trauma, biopsy from the femur

3. RESULTS

Age range of the patients was 31-84 years with an average age of 59.1 years. There were 28 males and 2 females. The most frequent unusual site of extrahepatic metastases was bone (n=23), followed by soft tissue of the gluteal region (n=2), posterior triangle of neck (n=1), inguinal region (n=1), iliopsoas muscle (n=1), parotid region (n=1) and the eyeball region presenting as retrobulbar mass (n=1) (Table 2). Among the cases involving the bone, the most common site was vertebral column (n=11), followed by humerus and the shoulder joint (n=4), chest wall (n=3), scapula (n=1), frontal bone (n=1) and phalanx (n=1) (Table 3). Except in one case, the metastasis was the first manifestation of the disease. Immunohistochemical stains used to confirm the diagnosis included Cytokeratin AE1/AE3, Cytokeratin CAM5.2, Hep Par 1, CK7 and CK20, Alpha Fetoprotein (AFP) etc. To exclude some of the differentials based on the morphology, additional immunohistochemical stains were used which included TTF-1(to exclude lung origin), S-100 (to exclude tumors of neural differentiation), Melan A (to exclude malignant melanoma), PSA (to exclude carcinoma of prostate), NSE, chromogranin, CD56 (to exclude neuroendocrine tumors) etc. (Table 4).

Table 2. Unusual metastatic sites of hepatocellular carcinoma in our series (n=30)

Sites	No: and percentage
Bone	23 (76%)
Soft tissue of gluteal region	2(6%)
Posterior triangle of neck	1(3%)
Inguinal region	1(3%)
Iliopsoas muscle	1(3%)
Eyeball	1(3%)
Parotid region	1(3%)

Table 3. Sites of bone metastases (n=23)

Sites	No: and percentage
Vertebral column	11(47.8%)
Humerus and shoulder joint	4(17%)
Chest wall	3(13%)
Scapula	1(4%)
Frontal bone	1(4%)
Phalanx	1(4%)
Mandible	1(4%)
Femur	1(4%)

Table 4. Results of immunohistochemical (IHC) staining

Case no	Biopsy site	IHC stain results	
1	Mandible	Hep Par 1	+
		Ck 7	--
		CK20	--
2	C6 vertebrae	CK AE1/AE3	+
		Hep Par1	+
		CK7	--
		CK20	--
		TTF 1	--
3	L4 vertebrae	CKAE1/AE3	--
		CK CAM 5.2	--
		Hep Par 1	+
		PSA	--
4	Right humerus	CK CAM5.2	+
		Hep Par1	+
		CK7	--
		CK20	--
5	Right shoulder joint	Hep Par1	+
		CK7	--
		CK20	--
		S100	--
6	Left shoulder joint	CK CAM5.2	+

Case no	Biopsy site	IHC stain results	
		Hep Par1	+
7	1st phalanx of the left foot	CKAE1/AE3	+
		Hep Par1	+
		CK7	--
		CK20	--
8	T9 vertebra	CKAE1/AE3	+
		Hep Par1	+
		AFP	+
		CK7	--
		CK20	--
9	Retrobulbar region	CKAE1/AE3	+
		Hep Par 1	+
		CK7	--
		CK20	--
		CD10	--
		PSA	--
10	T4 & T5 vertebrae	Since patient was known case of HCC, no IHC stains were performed	
11	Frontal bone	CKAE1/AE3	+
		Hep Par1	+
		CK7	+
		Ck20	--
		TTF1	--
		S100	--
12	Sternum	CK CAM5.2	+
		Hep Par 1	+
		CK7	--
		CK20	--
		Vimentin	--
13	Sacrum	Hep Par1	+
		CK7	--
		CK20	--
14	Scapula	CK CAM5.2	+
		Hep Par1	+
		CK7	--
		CK20	--
15	Cervical lymph node	CK CAM 5.2	+
		Hep Par 1	+
		CK7	--
		CK20	--
16	L3 vertebra	CK CAM 5.2	+
		Hep Par 1	+
		CK7	--
		CK20	--
		TTF1	--
		Vimentin	--
		PSA	--
		CK5/6	--

Case no	Biopsy site	IHC stain results
17	Inguinal lymph node	CKAE1/AE3 +
		Hep Par 1 +
		CK7 --
		CK20 --
18	T2 – T3 vertebrae	CKAE1/AE3 --
		CK CAM5.2 +
		CK7 --
		CK20 --
		Ber EP4 +
		Hep Par1 +
		TTF1 --
19	Gluteal region	CK CAM5.2 +
		Hep Par 1 +
		CKAE1/AE3 --
		Vimentin --
		ASMA --
		EMA --
		S100 --
		Chromogranin &, NSE --
		CD 68 --
		CEA --
20	Vertebral column (exact site not mentioned)	CKAE1/AE3 +
		Hep Par1 +
21	Iliopsoas region	CK CAM 5.2 +
		Hep Par1 +
22	T6 vertebra	CK CAM 5.2 +
		Hep Par 1 +
		AFP +
		CK7 --
		CK20 --
		PSA --
23	Parotid region	CK CAM 5.2 +
		AFP +
24	Vertebral column (exact site not mentioned)	CK CAM5.2 +
		Hep Par 1 +
		CK7 --
		CK 20 --
25	Posterior chest wall	CK CAM5.2 +
		Hep Par1 +
		CK7 --
		CK20 --
26	Humerus	CK CAM5.2 +
		Hep Par 1 +
		CK7 --
		CK20 --
27	Gluteal region	CK CAM5.2 +
		Hep Par1 +
		CK7 --
		CK20 --

Case no	Biopsy site	IHC stain results	
		Vimentin	--
28	L5 vertebra	CKAE1/AE3	+
		CK CAM5.2	+
		Hep Par 1	+
		Vimentin	+
		CK7	--
		CK20	--
		PSA	--
29	Anterior chest wall	CK CAM5.2	+
		Hep Par1	+
		CK7	--
		CK20	--
		Vimentin	--
		Desmin	--
30	Right femur	CKAE1/AE3	+
		Hep Par1	+
		CK7	--
		CK20	--

CK: cytokeratin, PSA: prostate specific antigen, ASMA: Alpha smooth muscle actin, EMA: epithelial membrane antigen, TTF-1: thyroid transcription factor, AFP: alpha fetoprotein

4. DISCUSSION

In the past distant metastases in HCC were not as well studied as those of other cancers, possibly due to shorter life span of patients and the high mortality rate associated with HCC. However, recent evolution in the treatment of HCC together with advances in imaging techniques have made it possible to diagnose and manage the primary tumor as well as the deleterious effects associated with it at early stages. Hepatocellular Carcinoma is an aggressive tumor known for its propensity to directly invade the hepatic and portal veins.

The most frequent site of metastases of HCC is lung, while less frequently the abdominal lymph nodes, bone and the adrenal glands are involved. Terada & Maruo [12], in their series examined unusual metastatic sites from hepatocellular carcinoma in autopsy and surgical cases. In autopsy cases (n=31) extrahepatic metastases were present in 68% (21 cases) and most of them involved the lungs (18 cases). Other sites included abdominal lymph nodes, bones, diaphragm, pancreas, gallbladder, stomach, colon, adrenal gland, pleura, peritoneum, cervical lymph nodes, soft tissue of shoulder etc. Many of the patients had more than one metastatic focus. In surgical cases (n=21) also, lung (76%, 16 cases) was the most common site of extrahepatic metastases. Unusual sites in surgical cases included bones, brain, skin and oral cavity [12] Katyal et al. [13] in their series found extrahepatic metastases in 148 (37%) of the 403 living patients with HCC. The most common sites were lung (55%), followed by lymph nodes (53%), bone (28%), adrenal glands (11%) and peritoneum (11%). Rare sites of metastases in their series included brain, rectum, spleen, diaphragm, duodenum, esophagus, pancreas, seminal vesicles and bladder. In a study of 151 living patients with HCC by Uka et al. [14] lung (47%) was found to be the most common site of metastases, followed by lymph nodes (45%) and bone (37%).

Cancers of the breast, lung and prostate usually metastasize to the bone but bone metastasis in HCC is not well studied. In our case series, bone was the most common site of HCC metastases (lung cases were excluded from the data) (Figs. 1A and 1B). Among the bones, sites in order of frequency were the vertebral column, humerus and the shoulder joint, chest wall, scapula, frontal bone and the phalanx. Fukutomi et al. [15], studied the increased incidence of bone metastases in HCC patients in two decades and found that bony metastases are present in 12(4.5%) out of 269 patients between 1978-1987 and in 52(12.9%) out of 404 patients between 1988-1997. The most common sites of bone metastases in their series were the vertebrae, followed by pelvis, rib, skull, humerus, sternum, scapula, clavicle, tibia and mandible in order of frequency [15].

In the present series, other unusual sites with HCC metastases included soft tissue of the gluteal region, posterior triangle of neck, inguinal region and the retrobulbar region. There are only very few case reports of HCC metastases in these unusual sites [16-19]. Majority of our patients received chemotherapy and radiotherapy. Average survival in our series ranged from 1 week to 1 year after diagnosis.

Morphological patterns seen in our cases included trabecular, sinunsoidal, pseudoglandular/acinar and compact composed of large polygonal cells with round to oval nuclei exhibiting coarse chromatin and single prominent nucleoli (Figs. 1A,B and 2A-D). Intranuclear inclusions were also present in many cases. Bile formation was seen in few cases; a feature which is very suggestive of hepatocellular carcinoma.

Hep Par 1 immunostain which is relatively specific and a very sensitive marker for HCC was performed in almost all cases to confirm the diagnosis (Figs. 1C and 1D). Alpha Fetoprotein (AFP) immunostain is also quite specific but rather insensitive marker for HCC and is present only in one quarter of the cases [20,21]. Due to this reason, this stain was performed in a few cases where there was diagnostic dilemma on morphological grounds.

The prognosis of patients with hepatocellular carcinoma is unsatisfactory and not well known. One of the limitations of our study was relatively small number of cases, due to which it is difficult to analyze out the impact of treatment modalities on patient's survival. A multicentric study with larger number of patients is required to analyze response of metastatic HCC to therapy.

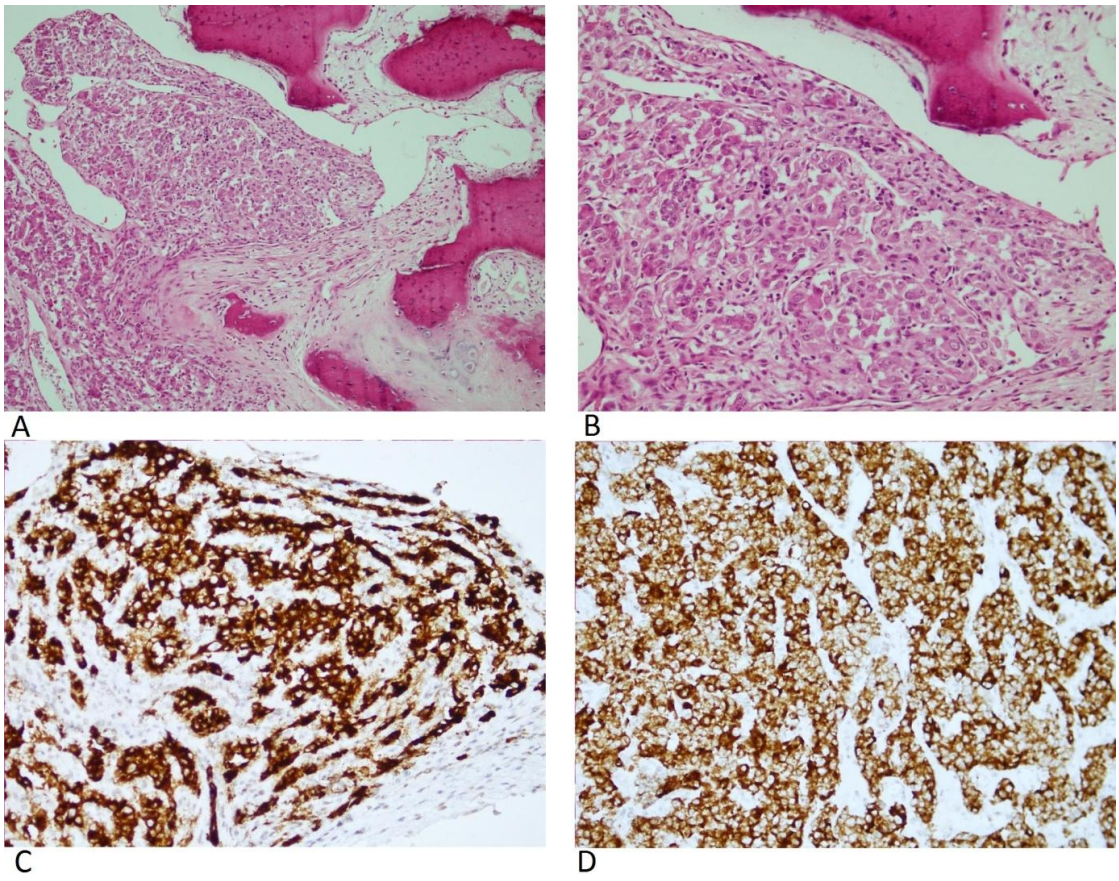

Fig. 1. A: The bone metastases of hepatocellular carcinoma, H&E 20X; B: Nests of hepatocytes with eosinophilic cytoplasm and pleomorphic nuclei invading the bony trabeculae, H&E 40X; C&D: Bone metastases of hepatocellular carcinoma with strong Hep Par 1 positivity, H&E 20X(A7B) & 40X(C7D) respectively

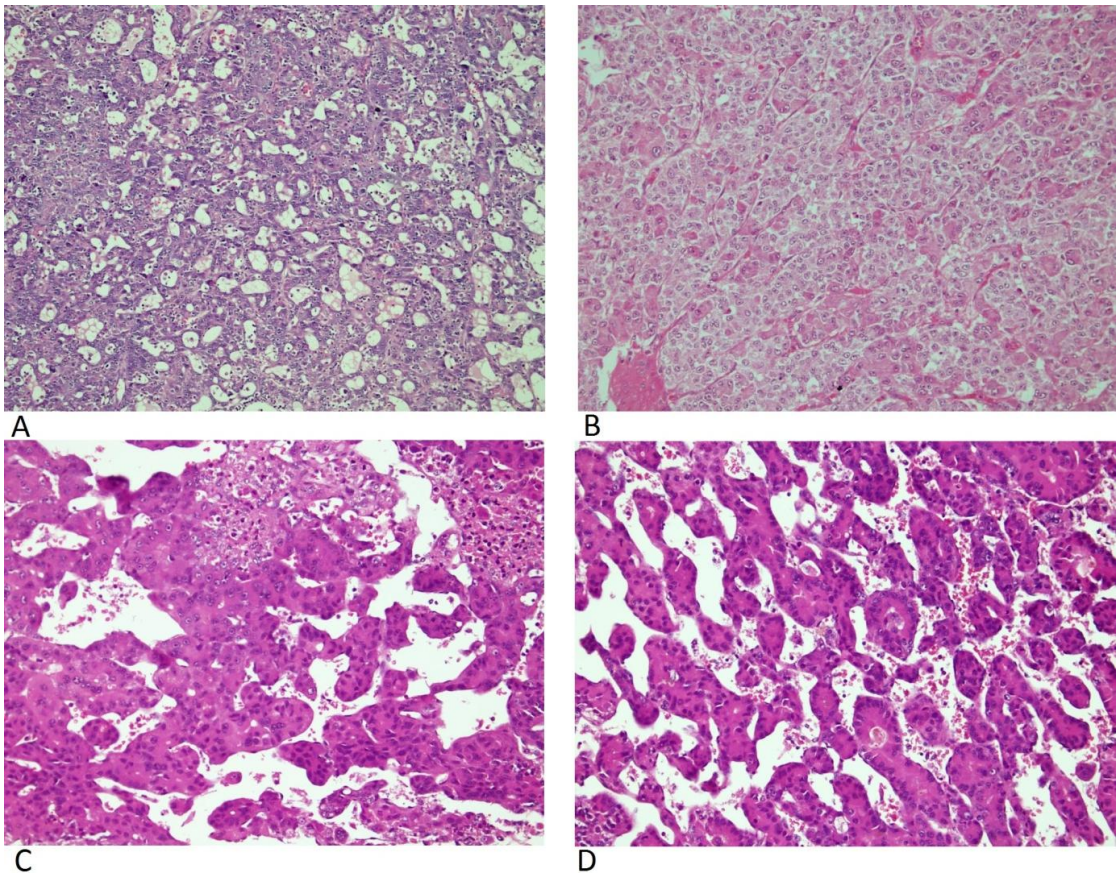

Fig. 2. Extrahepatic metastases of hepatocellular carcinoma showing the A: pseudoglandular/acinar pattern; B: compact arrangement; C: trabecular/pseudoglandular pattern D; trabecular pattern with occasional tubule formation, H&E 20X

5. CONCLUSION

Lung and bone metastases are frequently seen in patients with HCC. Hepatocellular carcinoma however can metastasize to any organ/tissue in the body. Hep Par 1 immunostain is a relatively specific marker to confirm the diagnosis of extraheptic metastases to unusual sites. The prognosis of HCC patients with extrahepatic metastases is not well known. HCC patients should be carefully followed for possible metastases to usual and unusual sites.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

All of the authors declare that there is no conflict of interest.

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