

Extrahepatic Metastasis in Hepatocellular Carcinoma: A Review Article

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Abstract : Hepatocellular carcinoma (HCC) is most common primary tumour of the liver and prevalence is higher in developing countries than in developed countries. High incidence in Asian countries is believed to be because of high prevalence of Hepatitis B and C infection though chronic alcoholism still remains most common causative factor. Extrahepatic spread (EHS) is commonly seen in hepatocellular carcinoma. Common extrahepatic sites are lungs, abdominal lymph nodes and bones though spread to rare sites like brain, heart, parotid, peritoneum, gall bladder, spleen, pharynx, etc is also reported. Mode of spread is usually haematogenous but lymphatic spread can also occur. In a meta analysis of various randomized control trials information on extrahepatic spread EHS was missing from most of these trials while it ranged from 7% to 68% in trials reporting EHS. Various classification systems like TNM classification, CLIP classification, OKUDA classification and Barcelona clinic liver classification (BCLC) are devised for staging and treatment of HCC with EHS but none is universally accepted. Patients with extrahepatic metastasis have more advanced intrahepatic disease. Majority of patients with extrahepatic spread have intrahepatic tumour stage T₃ or T₄ as per TNM classification. Vessel invasion is also more common in patients with EHS. Advanced diagnostic and treatment modalities have improved outcome in these patients and EHS which was once considered to be a terminal event in the disease process has shown prolonged survival with treatment options like surgical resection, transcatheter arterial chemoembolization (TACE), percutaneous ablation and liver transplantation and introduction of a novel agent called sorafenib. Despite significant advances in treatment of intrahepatic lesions, long term prognosis in patients with EHS still remains poor.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the common malignancies of the liver. It is most common primary tumour of the liver and a leading cause of cancer death. Its prevalence is 16-32 times higher in developing than developed countries¹. Incidence is high in Asian countries including Japan^{2,3}. It is the 5th most common cancer in the world especially in south east Asia⁴. Probable cause of this is high prevalence of Hepatitis B and C infection in Asian countries. Hepatocellular carcinoma (HCC) usually develops in a liver that has chronic disease like cirrhosis secondary to hepatitis B or hepatitis C virus infection⁵. Extrahepatic spread is commonly seen in HCC and 30-50% cases of HCC have extrahepatic metastasis⁶. Most common extrahepatic site is lung (55%) followed by abdominal lymph nodes (41%) and bone (28%)⁷. In the study by Katyal et al a majority of patients with extra hepatic HCC had intrahepatic stage IV A (76%) or an interhepatic stage III tumour (11%). HCC was earlier diagnosed usually at late stages of disease with poor prognosis⁸. However early diagnosis because of close surveillance and advanced diagnostic tools coupled with advanced treatment options like surgical resection, transcatheter arterial chemoembolisation (TACE), percutaneous ablation and liver transplant have improved the prognosis in these patients⁹⁻¹³. However in patients with extrahepatic spread (EHS) prognosis is poor¹⁴ but survival has been prolonged with the introduction of sorafenib, a multikinase inhibitor, which is now regarded as a standard treatment for patient of HCC with extrahepatic spread^{15,16}. In the recent years extrahepatic spread of HCC seems to have been observed more frequently than in the past even as few data exists in the literature on prevalence, clinical picture and prognosis in patients of HCC with EHS. This review is aimed at underlining the main concerns

and pitfalls in keeping in mind the rare sites of EHS in HCC while treating these patients.

Causative factors :

1. **Common**
 - Hepatitis B virus infection
 - Hepatitis C virus infection
 - Chronic alcoholism with alcoholic cirrhosis
2. **Uncommon**
 - Aflatoxin ingestion
 - Haemochromatosis
 - Wilson's disease
 - Metabolic syndrome and obesity
 - Type 2 diabetes mellitus
 - Anabolic steroid use

Causative factors in children:

More common in children with congenital disorders like:

- Biliary atresia
- Infantile cholestasis
- Glycogen storage diseases

Causative factors vary from country to country. In countries where hepatitis B and C infection is more prevalent like in China, it is major cause of HCC¹⁷. Otherwise alcohol abuse remains a major factor in the development of HCC. HCV infection is an upcoming risk factor for HCC development as a large number of people afflicted with HCV worldwide serve as reservoir of transmission to others. It is estimated that HCV accounts for 25% of HCC cases worldwide¹⁸.

Diabetes mellitus is associated with a high risk of HCC which is independent of alcohol use or viral hepatitis¹⁹. Metabolic syndrome with its liver effects in the form of non alcoholic fatty liver disease (NAFLD) is upcoming as a cause of HCC and more and more cases of HCC may be seen in future secondary to NAFLD²⁰.

HCC is uncommon in children but children having congenital liver disorders are more susceptible to development of HCC²¹. Aflatoxin B₁, a product of *Aspergillus* fungus, is found in a variety

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of grains stored in hot and humid places where peanuts and rice are stored in unrefrigerated conditions. It plays a causative role in 4.6 to 28.2% of global HCC cases¹.

PATHOGENESIS AND MODE OF SPREAD

The mode of spread from HCC is usually haematogenous but it may also spread through lymphatic path. As far as haematogenous spread is concerned there are two main routes. The first is involvement of major vessels like hepatic artery leading to widespread metastasis frequently to lungs. The 2nd pathway called Batson’s pathway²² consists of a pathway of rich anastomosis of paravertebral veins (called Batson’s plexus – a connection between the azygos and hemiazygos veins and the vertebral venous system) that lack valves and may be capable of by-passing other venous systems such as pulmonary, caval and portal system. Possible mechanism of bony metastasis is thought to be through portal vein – vertebral plexus because of portal vein thrombosis or portal hypertension which explains the frequent site of bone metastases in craniospinal and pelvic bones. However case reports of upper and lower limb involvement²³ are not in line with view.

Lymphatic spread is through hepatic node and then thoracic duct.²⁴ At the site where thoracic duct joins venous system probable back pressure leads to metastatic cell deposition in nearby cervical lymph nodes.

In oncology metastatic formation is the spread of cancer cells from a primary tumour to organs and distant sites in cancer patient’s body. This process is end result of different series of genetic alteration, epigenetic events and host responses. The tendency of primary growth to form metastases is hallmark of malignancy. Metastatic formation is final step in tumour progression and has prognostic value. Prognosis and treatment are largely dictated by tumour stage at the time of diagnosis and scenario is complex in case of HCC.

SITES OF SPREAD

In a meta analysis of various randomized control trials information on EHS was missing from most of these while it ranged from 7% to 68% in trials reporting EHS.^{15,16,25-31}

Katyal et al⁷ reported 148 patients with EHS out of total of 403 patients of HCC. As per their findings lungs (55%), lymph node (63%) and bone (28%) were common sites of spread.

Natsui zaka et al³² reported 65 patients with EHS out of total 482 patients with HCC with lungs (54%), lymph node (39%) and bone (34%) being common sites of spread.

Uka et al³³ reported 151 patients with EHS out of total 995 cases of HCC in which lungs (42%), lymph nodes (40%) and bones (34%) were common sites of spread.

Apart from above studies literature shows case reports of extrahepatic metastasis from HCC to various uncommon sites. These sites are Paroid³⁴, Peritoneum³⁵, gall bladder³⁶, spleen³⁷, pharynx³⁸, oesophagus³⁹, tonsils⁴⁰, skull^{41,42}, brain⁴³, facial subcutaneous tissue⁴⁴, orbit⁴⁵, pituitary gland, sphenoidal sinus and cavernous sinus⁴⁶, nasal cavity and maxillary sinus⁴⁷, epidural space⁴⁸, colon⁴⁹, kidneys⁵⁰, pancreas⁵¹, heart⁵² and skin.^{53,54}

Table 1: Sites of extrahepatic spread (EHS)- N(%)

Sr. no		Katyal et al no. of patients with EHS (N=148) Total 40	Natsui zaka et al (n=65) Total 482	Ukas et al (n=15) Total 995
1	Lungs	81 (55%)	35 (54%)	63 (42%)
2	Lymph node	787 (53%)	22 (34%)	60 (40%)
3	Bone	41 (28%)	25 (38%)	51 (34%)
4	Adrenal gland	16 (11%)	11 (17%)	16 (11%)
5	Peritoneum &/or omentum	16 (11%)	6 (9%)	1 (0.7%)
6	Brain	3 (2%)	5 (8%)	-
7	Skin	-	4 (6.2%)	-
8	Rectum	2 (1.35%)	-	-
9	Spleen	2 (1.35%)	-	-
10	Duodenum	1 (0.7%)	-	-
11	Esophagus	1 (0.7%)	-	-
12	Pancreas	1 (0.7%)	-	1 (0.7%)
13	Seminal vesicles	1 (0.7%)	-	-
14	U. Bladder	1 (0.7%)	-	-
15	Nasal passages	-	-	1 (0.7%)

SUMMARY OF EXTRA HEPATIC SPREAD SITES IN 3 STUDIES

Metastasis have also been reported from oral soft tissue and jaws being frequently the first manifestation of HCC^{40,55-57}. Soft tissue lesions in mouth may be painful or painless but bleeding is often a constant early symptom⁵⁸. Case reports of cervical lymph node metastasis and specially left supraclavicular lymph node involvement are also there^{6,59}.

Classification and staging system:

Various classification system, incorporate four patterns that are recognized as determinants of survival.

1. Severity of underlying liver disease.
2. Tumour burden (number and size of nodules, portal invasion and EHS).
3. Patient’s general condition (performance status)
4. Treatment efficacy

A number of systems have been proposed to predict the prognosis of HCC⁶⁰⁻⁶⁸ but none of these is universally adopted⁶¹.

Prognosis and treatment are largely dictated by tumour stage at the time of diagnosis and scenario is complex in the case of HCC⁶⁹. Natural history of HCC is also variable^{70,71} and treatment results reported in literature are difficult to interpret because, the survival, as primary end point may reflect more of basic disease than its progression.

Classification systems

Table 2: TNM staging system:

Stage	Definition
Primary tumour	
T _x	Primary tumor cannot be assessed
T ₀	No evidence of primary tumour
T ₁	Solitary tumour <2 cm without vascular invasion
T ₂	Solitary tumour ≤2 cm with vascular invasion, or multiple tumours in one lobe, none ≥2 cms, with vascular invasion or a solitary tumour >2 cm without vascular invasion.
T ₃	Solitary tumour >2 cm with vascular invasion; or Multiple tumours in one lobe none >2 cm with vascular invasion; or Multiple tumours in one lobe any >2 cms with or without vascular invasion
T ₄	Multiple tumours in >1 lobe; or Tumours involving a major branch of portal or hepatic vein (s).
Regional lymphnodes	
N _x	Regional lymph nodes cannot be assessed
N ₀	No regional lymph node metastasis
N ₁	Regional lymph node metastasis
Distant metastasis	
M _x	Presence of distant metastasis cannot be assessed
M ₀	No distant metastasis
M ₁	Distant metastasis
Stage group	
Stage I	T ₁ N ₀ M ₀
Stage II	T ₂ N ₀ M ₀
Stage III	T ₁ N ₁ M ₀
	T ₂ N ₁ M ₀
	T ₃ any N M ₀
Stage IVA	T _x any N M ₁
Stage IVB	T ₁ any N M ₁

Table 3: CLIP CLASSIFICATION

Variables	Points		
	0	1	2
1. Tumour number	Single	Multiple	-
2. Hepatic replacement of tumour (%)	<50	<50	>50
3. Child Pugh score	A	B	C
4. Alfa fetoprotein level (ng/ml)	<400	≥400	-
5. Portal vein thrombosis (CT)	No	Yes	-

Clip stages – (Score = sum of points)

(Clip 0 – 0 point; Clip 1 – 1 point; Clip 2 – 2 points; Clip 3 – 3 points)

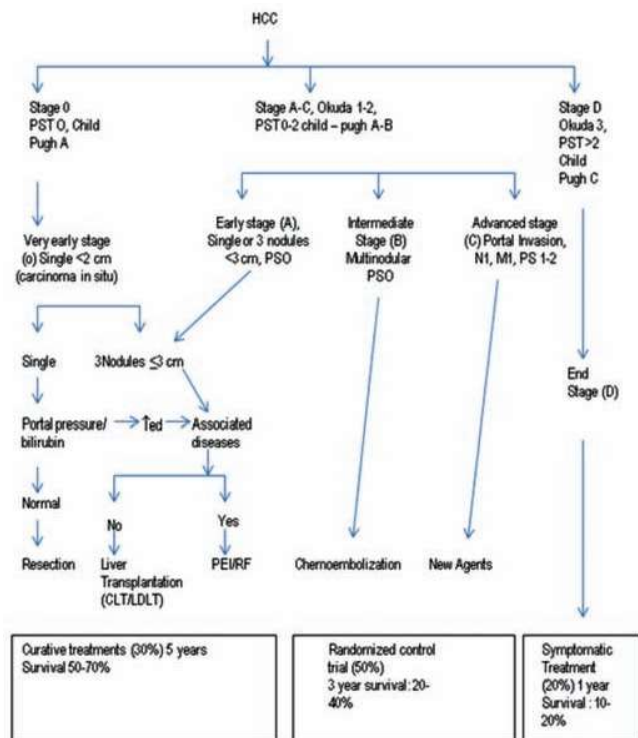
CLIP – Cancer of liver Italian Programme

Table 4: OKUDA Classification

Tumour extent		Ascites		Albumin g/dl		Bilirubin mgm/dl	
>50%	<50%	+	-	≤3	>3	≥3	<3
(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)

Okuda Stages : Stage 1 – All (-); Stage 2 – 1 or 2 (+); Stage 3 – 3 or 4 (+)

BCLC staging and treatment schedule



(Adapted from Llovet et al. Lancet 2003)⁹⁹

BCLC = Barcelona clinic liver classification

The treatment algorithms in Europe and North America have been prepared based on Barcelona Clinic Liver Cancer Classification⁷². BCLC classifies patients from stage 0 to D^{15,67,73}. Stage 0 is very early disease, defined as solitary liver cancer that is ≤2cm without tumour invasion into surrounding tissue. Stage A is early disease patients who exhibit preserved liver function with a solitary hepatocellular carcinoma ≤5 cm size or upto 3 tumours each of which is ≤3 cm in size. Patients with stage 0 or A can be treated with therapies like surgical resection, liver transplant or by subcutaneous ablation methods including Percutaneous Ethanol Injection (PEI) and radiofrequency ablation (RFA). With these therapies 5 years survival is 50 to 70%.

The BCLC intermediate stage (stage B) consists of asymptomatic

patients with well preserved liver function and multinodular or large tumour extension without macrovascular invasion or extrahepatic spread. These type B patients can be treated with transarterial embolization (TAE) or transarterial chemoembolization (TACE).

Patients with mild related symptoms and/or macrovascular invasion or EHS are classified as advanced stage (BCLC Stage C) patients and sorafenib is considered to be standard treatment for these patients^{15,16}.

Patients with cancer symptoms, related to progressed liver failure, tumour growth with vascular involvement, EHS or physical improvement (performance status ≥2) are classified as stage D (end stage disease). They do not benefit from anticancer treatment and should get only supportive care.

TREATMENT OF PATIENTS WITH EHS

Distant metastases and macrovascular invasion indicate advanced stage of disease as per BCLC classification. Chemotherapy has no encouraging results and mortality from toxicity of chemotherapeutic drugs is high. There is no standard therapy for these patients⁷⁴. Some studies^{15,16} have shown encouraging results with sorafenib as far as mortality benefit is concerned and it improves the survival duration in patients at this stage. Sorafenib is Raf kinase and vascular endothelial growth factor receptor (VEGFR) inhibitor. Other patients with isolated distant metastasis like in lymph node, bone and brain may be treated with surgical resection of lymph node or radiotherapy of bone/brain metastasis as a palliative procedure so as to lessen the mortality without much affecting the survival rates.

CONCLUSION

Hepatocellular carcinoma is a common primary tumour of liver. Chronic alcoholism, hepatitis B and C infection remain common causative factors. Extrahepatic spread is commonly seen in hepatocellular carcinoma. Though common sites are lungs, abdominal lymph nodes and bone, spread to rare sites in the body is known. Various classification systems have been devised for staging and treatment of these patients but none is universally adopted. Advanced diagnosis and treatment modalities have improved outcome in these patients and EHS which was once considered to be a terminal event in disease process has shown prolonged survival. Despite significant advances in management of intrahepatic lesion long term prognosis in patients with EHS still remain bleak.

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