

# Clinico-Pathological Features and Survival of Patients Presenting with Hepatic Metastases: A Retrospective Analysis

Pages with reference to book, From 99 To 102

Atif Shafqat, Mahmood Merchant, Imtiaz A. Malik ( National Cancer Institute, Clifton and Department of Medicine, The Aga Khan University Hospital, Karachi. )

## Abstract

Retrospective analysis of 135 patients who presented with liver metastases at the NCI-Free Cancer Clinic and the Aga Khan University Hospital, Karachi is presented. The mean age was 55 years and there was no significant sexual predilection. Commonly observed primary sites were gall bladder (13%), pancreas (11%), breast (10%), colorectum (8%) and lung (8%). In 41 cases (30%), primary location remained undetermined. Most common histologic type was adenocarcinoma in both sexes. Majority (83%) had multiple metastases. Amongst those with solitary metastasis, 78% had right lobe involvement. Almost half of the patients presented with constitutional symptoms alone, while 31% had signs and symptoms related to hepatic involvement. Overall, the most commonly deranged laboratory tests were LDH (93%), albumin (84%), gamma glutamyl transferase (78%) and alkaline phosphatase (76%). Chemotherapy was offered to most cases. Majority of patients expired, mostly due to hepatic failure. Median survival was 30 days and was shorter in those who presented with multiple metastases. These findings are compatible with previous reports and may assist in the management of these patients (JPMA 46:99,1996).

## Introduction

Metastatic liver disease occurs in more than 50% of patients who ultimately die of cancer. This high incidence is explained by large size of the liver, its dual blood supply and a multitudinous array of local factors that are still incompletely understood. Liver is second only to lymph nodes as the most frequent site of metastases. with the exception of primary brain tumors, virtually all malignant neoplasms have been 'reported to metastasize to the liver<sup>1,2</sup>.

Metastatic involvement of liver may occur through the portal vein, hepatic artery, lymphatics or by direct spread<sup>3</sup>. Metastatic disease is by far the commonest malignancy involving the liver and in general, it signifies incurability. Despite years of trials utilizing radiotherapy and/or chemotherapy, there is little evidence that either has made any significant impact on survival<sup>2</sup>. Surgical intervention may be beneficial for solitary metastasis<sup>4-5</sup>. However, for majority of patients with multiple metastases, surgery has little role in the management of these patients<sup>6</sup>. Hepatic arter infusional chemotherapy as well as combined modality approach may offer certain degree of palliation<sup>2</sup>.

Assessing the impact of any intervention on the natural history of metastatic liver disease has been problematic because of heterogeneity of the disease process. However, despite the diversity of primary disease processes, several observations have been made regarding the extent of hepatic involvement at the time of diagnosis and its correlation with certain laboratory and radiologic parameters and impact on survival. Most of these data, however, are reported from the western countries. Due to paucity of such data from the developing countries, we performed a retrospective analysis of patients with metastatic liver disease to better define the clinicopathologic characteristics and their correlation with subsequent management and survival.

## **Patients and Methods**

All patients seen at the NCI Free Cancer Clinic and the Aga Khan University Hospital between January, 1989 to August, 1992 and discovered to have hepatic metastasis at initial presentation were eligible for the study. Liver metastases was confirmed by histologic means and/or pm-operative findings. However, radiologic evidence in a patient with a histologically proven cancer elsewhere, were also eligible. These patients were coded by the indexing and coding unit of the hospital who were the source of initial information. Subsequently, medical records were obtained and reviewed. Patients whose medical records could not be retrieved, had incomplete records, who left against medical advice during admission and not enough information was available, and patients with only clinical suspicion of hepatic metastases without confirmation by histologic or radiologic means were excluded from the analysis.

The Aga Khan University Hospital is a tertiary care facility with well-established oncology service. It has both surgical and medical oncology, however, there are no facilities for radiation therapy. Most of the patients attending the hospital belong to upper-middle or high socio-economic groups. NCI-Free Cancer Clinic is a voluntary non-profit organization offering free services to the indigent patients.

## **Results**

One hundred and thirty-five patients were eligible for the study (Table I).

**Table I. Clinical characteristics of patients (n=135).**

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<b>Mean (SD) Age in years</b>	
Males	56.4 (11.4)
Females	51.9 (11.0)
<b>Sex</b>	
Males	53.3%
Females	46.7%
<b>Signs and symptoms</b>	
Constitutional	54.8%
Related to liver disease	30.9%
Asymptomatic	14.8%
<b>Metastatic sites</b>	
Liver only	55.6%
Lymph nodes	28.1%
Bones	11.9%
Lungs	8.1%
Peritoneum	8.1%

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There were 72 males and 63 females (age range 25 to 76 years) Mean age was 51.9±11 for females and 56.4±11.4, years for males. More than half of the patients presented with only constitutional symptoms. Only one-third had signs or symptoms suggestive of active liver disease. Majority of the patients had multiple metastases (Table II).

Table II. Pathologic, radiologic and laboratory findings

<b>Histologic sub-type</b>	
Adenocarcinoma	68%
Squamous cell	13%
Small cell	10%
Unspecified	5%
Others (Sarcoma, melanoma, etc)	5%
<b>Radiologic test performed</b>	
Ultrasound	80%
CT scan	24%
Nuclear scan	4%
<b>Radiologic appearance</b>	
Multiple metastases	83%
Solitary	17%
Left lobe	22%
Right lobe	78%
<b>Abnormal laboratory tests</b>	
High LDH	93%
Hypoalbuminemia	84%
High gamma GT	78%
Increased alkaline phosphatase	76%
Raised SGOT	71%
Raised SGPT	39%
Prolonged PT/PTT	57%
Raised bilirubin	53%

Amongst those with solitary metastasis, 78% had right lobe involvement. More than half had hepatic involvement alone without any other site of disease. Other commonly involved sites were lymph nodes, bone, lungs and peritoneum. Some commonly deranged laboratory tests included LDH, albumin, gamma glutamyl transferase and alkaline phosphatase. Major ity of the patients had diagnosis

established by ultrasonography (Table II). C.T. Scans were performed in 24.4% of the patients. Overall, common primary cancers were breast (10%), gall bladder (13%), colorectal (8%), pancreatic (11%), bronchogenic (8%), ovarian (4%) and gastric (6%) (Table III).

**Table III. Type of underlying malignancy.**

Tumor type	Males (%)	Females (%)
Breast	-	22
Gall bladder	4	22
Pancreas	17	5
Lung	15	5
Colorectal	5	11
Stomach	8	3
Ovarian	-	8
Others	11	8
Unknown	39	21

In a significant number of patients (30%), the primary site remained undetermined. The most common cancers in females were breast and gallbladder followed by colorectal and ovarian. Primary remained unknown in 13 out of 63 females (21%). In males, a large percentage (39%) had unknown primary. Pancreas, lungs, stomach and colon were other common sites. The most common histology was adenocarcinoma (68%), followed by squamous cell carcinoma (13%). Most patients (64%) received only supportive care (Table IV).

Table IV. Management and survival.

Treatment	
Surgical	nil
Chemotherapy	35%
Hormonal done	1%
Palliative	64%
Survival	
Overall	30 days
with solitary metastases	60 days
with multiple metastases	21 days
Cause of death	
Liver failure	58%
Primary cancer	30%
Other cause	13%

Chemotherapy was employed in one-third of the patients. Only a small number had some subjective or objective improvement in their liver disease. Majority of the patients expired. Underlying cancer (other than hepatic involvement) was the cause of death in 29.6% of the patients while liver failure accounted for most of the deaths. The median survival was only 30 days and was shorter in those with multiple (21 days) than with single metastasis (60 days) (Table IV).

### Discussion

Despite significant therapeutic advances made in the management of cancer, there has been little impact on survival in patients who develop hepatic metastases<sup>4</sup>. Many patients present with liver metastases at the time of initial diagnosis. They are often asymptomatic or have only constitutional symptoms. Most develop liver metastases during the course of their disease. Patients in this study were diagnosed to have liver metastases on initial presentation. Almost half of them had only constitutional symptoms; mostly fever or weight loss. It is likely that non-localizing nature of their symptoms contributed to a delayed diagnosis with subsequent poor outcome. However, it is well recognized that patients presenting with liver metastases have an extremely unfavourable outcome<sup>1,2</sup>. Cancers of the

colon, stomach, pancreas, gall bladder, lung, breast, ovary, testis and melanoma are some of the common primary neoplasms reported in the western literature to cause liver metastasis<sup>2</sup>. Underlying cause, however, would depend upon the relative frequency of different cancers in a community. Additionally, liver metastases are more commonly caused by intra-abdominal tumors primarily of gastrointestinal tract origin<sup>1,2</sup>. A similar pattern was observed in our study but not in the same order. Breast and gall bladder carcinomas were the leading primaries in women while pancreas and lungs in men. There are differences in the relative frequency of different cancers between Pakistan and the Western countries. In Pakistan, gall bladder cancer is a very common malignancy and is the second commonest tumor of gastrointestinal origin<sup>7</sup>. This high incidence is reflected in our patients with liver metastases. Interestingly, adenocarcinoma with unknown primary was commonly observed in our patients, particularly in males. This is a well-recognized entity, although it accounts for only 5-7% of all cancers in the Western countries<sup>8</sup>. It appears to be disproportionately frequent in our patients with liver metastasis. It is unlikely that inadequate investigations would have contributed to the high incidence of adenocarcinoma with unknown primary. This particular group of individuals were thoroughly investigated using CT scans and barium studies. It is important to emphasize that our study involves patients who presented with liver metastasis as against those who develop liver metastasis during the course of their disease. This may account for the differences in relative frequency of different cancers.

Adenocarcinoma is reported as the commonest histologic type seen in patients with liver metastasis. A similar pattern was observed in our patients. The laboratory tests most often observed to be deranged in patients with hepatic metastases include elevated levels of alkaline phosphatase and LDH<sup>2</sup>. Similar results were seen in the present study. In addition, albumin was very low in majority of our patients. This probably reflects advanced stage of the disease and overall poor nutritional status of these patients. Ultrasonography and CT scans are commonly used as primary tools in assessing liver metastasis. Although no significant difference has been observed in the sensitivity or specificity of scintigraphy, ultrasound or CT scan, CT scan is generally the preferred study<sup>9</sup>. Improved detection of hepatic metastasis may be possible with the help of delayed hepatic CT scanning<sup>9,10</sup>. Magnetic resonance imaging (MRI) has been suggested to be significantly superior to conventional CT scans for detecting hepatic metastases<sup>11</sup>. In our study, ultrasound was the most commonly used test which probably is due to its wider availability and lower cost. However, whenever needed, additional tests were carried out. Metastases to the liver are mostly multiple. When single, usually right lobe is affected. This is consistent with our findings. Patients who develop liver metastases are generally incurable. Palliation, however, can be achieved by chemotherapy alone or in combination with other modalities<sup>2</sup>. In this study chemotherapy was the main form of treatment. Curative resections were not carried out in any patient. Most patients with solitary lesions were ineligible for curative surgery due to the anatomic extent of involvement or other reasons such as liver dysfunction, poor general medical condition etc. It may also reflect more conservative approach on the part of the health care providers. Intrinsic factors that influence survival include the primary tumor type, histologic sub-type, degree of differentiation and whether lymphatic dissemination of the hepatic metastasis has occurred<sup>12</sup>. Survival also depends upon the number of metastases and is regardless of the treatment given. An improved survival was observed in our patients with solitary metastasis.

Despite improvements in surgical techniques and ability to deliver hepatic radiation and chemotherapy, there has been no significant impact on survival<sup>2</sup>. Chemotherapy in our study resulted in subjective benefit for some patients, however, objective responses were observed in less than 20% of all patients. It didn't influence survival. More innovative treatment approaches such as intra-arterial chemotherapy etc may result in an improved outcome.

In conclusion, retrospective analysis of our patients who presented with liver metastases suggests that

most of the patients are middle aged to elderly and usually present with constitutional symptoms. Although clinical hepatic dysfunction is uncommon, most have laboratory evidence of hepatic disease. Type of underlying cancer is somewhat different than reported elsewhere particularly adenocarcinoma with unknown primary and gall bladder cancer are more frequently observed. Overall survival is poor. More innovative approaches are required to improve survival.

## References

1. Weinman, MD. and Chopra, S. Tumours of the liver, other than primary hepatocellular carcinoma. *Gastroenterol. Clin. North Am.*, 1987; 16:627-50.
2. Niederhuber, J.E. and Ensminger, WD. Treatment of metastatic cancer to liver. In: DeVita VT, Heliman, S., Rosenberg, S.A., eds, *Cancer-Principles and Practice of Oncology*, 4th edition, Philadelphia, J.B. Lippincott Company, 1993, pp. 2201-2222.
3. Poste. G. and Fidler, I.J. The pathogenesis of cancer metastasis. *Nature*, 1980;283:139-146.
4. Webber, B.M., Soderberg, C.H. and Leone, L.A. A combined treatment approach to management of hepatic metastases. *Cancer*, 1978;42:1087-1095.
5. Friedman, M., Cassidy, M., Levine, M. et al. Combined modality therapy of hepatic metastases. *Cancer*, 1979;44:906-913.
6. Sherman, D.M., Weichselbaum, R., Order, SR. et al. Palliation of hepatic metastasis *Cancer*, 1978;41,2013-2017.
7. Abmad, .M., Khan, A.H. and Mansoor, A. The pattern of malignant tumours in Northern Pakistan, *J, Pak. Med. Assoc.*, 1991;41:270-73.
8. Greco, F.A. and Hainsworth, J.D. Cancer of unknown primary site. In: DeVita, VT., Heilman, S., Rosenberg, S.A. eds, *Cancer- Principles and Practice of Oncology*. 4th edition, Philadelphia, J.B, Lippincott Company, 1993, pp:2027-2092.
9. Berman, C.G. and Clark, R.A. Diagnostic imaging in cancer. *Prim. Care*, 1992;19(4):677-713.
10. Bernardino, ME., Ermin, B.C., Steinberg, H.V. et al. Delayed hepatic CT scanning: Increased confidence and improved detection of hepatic metastases. *Radiology*, 1986;159:71-74.
11. Reinig, J.W., Dwyer, A.J, Miller, DL. et al. Liver metastases detection: Comparative sensitivities of MR Imaging and CT Scanning. *Radiology*, 1987;162:43-47.
12. August, D.A., Sugarbaker, PH. and Schneider, PD. Lymphatic dissemination of hepatic metastases- Implications for the follow- up and treatment of patients with colorectal cancer. *Cancer*, 1985;55:1490-1494.