Hepatocellular Carcinoma Presentation & Management , A Prospective Study in the Medical City Baghdad - Iraq .

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ABSTRACT:

BACK GROUND :

The development of HCC is a major global health problem ' It's incidence has increased world wide and nowadays it constitute the 5th most frequent cancer representing around 5% of all cancers, and estimated to rank 4th in terms of mortality of cancers incidence world wide , it accounts for 80 –90% of all primary liver tumors . The Etiology of this tumor is multifactorial , certain viral, environmental & hereditary causes of cirrhosis have a strong correlation with HCC . HCC is a highly malignant tumor with poor prognosis .

OBJECTIVE:

To evaluated the Etiological , Epidemiological , Patho physiological , Diagnostic series , Therapeutic approaches & Advanced studies in detection and prevention of HCC .

PATIENTS AND METHODS :

Across sectional study of (57) patients with HCC (43 males , 14 females) during the period from January 2000 to December 2002 . The patients were collected from medical & surgical units of Baghdad teaching hospital & the gastroenterology & hepatology teaching hospital .

History taken from these patients & physical examination , Lab investigation ,CBP, liver function test ,Virology study , serum AFP. Titer ,U/S study , MRI , CT scan . Ascitic fluid tapping , Liver biopsy. Modalities of treatment : Palliative Treatment, Chemotherapy, Injection of Alcohol , Hemilobectomy ,Segmental resection , Debulking resection of tumor in the liver, Conservative treatment , any complications or hazards during surgical procedures were recorded.

RESULTS :

Male to female ratio is approximately (3:1), The mean age of (57.1) yr . more common between (51-60) yrs old (28.25%) , Most of the patients were from Baghdad (47.4%) . Increasing no. of patients from 2000 (21.1 %) to 2002 (45.6 %). (84%) have previous history of chronic liver disease & (16%) haven't such a history . Most of chronic liver diseases are due to previous history of hepatitis B- infection (41.6%) . High level of AFP (66.6%), all of them are of standard type of HCC. Ascitic fluid cytological study bloody (14%) & positive malignant cells (17.2%) . Liver biopsy (82.7%) had chronic liver diseases, and (96.5%) moderate to poorly differentiated type of standard HCC,(3.5%) fibrolamellar type .Outcome of treatment , Conservative (35%), Injection therapy (3.5%) , Chemotherapy (28%), Surgical procedures (16%) , Segmental & Right lobectomy (3.5%) for each , Debulking (9%) .

CONCLUSION :

AFP and U/S study are very important in the early detection and follow up of the patient with HCC , Liver biopsy - very important study to detect various type of HCC , Surgical resection is the only potentially curative treatment of HCC .

KEY WORDS : hepatocellular carcinoma , presentation , management .

INTRODUCTION:

Hepatocellular carcinoma (HCC) is also known as primary liver cancer or hepatic tumor or hepatoma – the 4 terms are interchangeable [1] , It accounts 80-90% of all primary liver tumors [2] .

The development of HCC is a major global health problem[3] . Despite new therapies & attempt at early detection of primary liver cancer , the by far most common form , HCC , the disease with a poor prognosis[4]. The mortality rates are accordingly high in relation to incidence – world wide HCC has the 5th highest cancer incidence but the 3rd highest cancer mortality [5] . In Europe, which is considered as a low endemic area , HCC was estimated to be the 14th most common cancer in 2006 but had the 7th highest mortality [4] .

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Primary HCC although less common in North America , it is most common malignant neoplasm in endemic areas including Sub-Saharan Africa , South east Asia & Japan [3] .
The etiology of this tumor is multifactorial [6,7] . certain viral , environ- mental & hereditary causes of cirrhosis have a strong correlation with HCC , chronic viral hepatitis as a cause of cirrhosis & HCC is well known , Hepatitis B & C viruses are the leading causes of chronic liver disease , is well known around the world [8] . use of alcohol is also a common cause of cirrhosis which can indirectly lead to HCC [9] .Certain substances derived from plants , industrial pollutants & synthetic pharmacological agents have been found to cause HCC in detectable levels , Aflatoxin B confers to add ratio to HCC [10] , Vinyl chloride is the most industrial carcinogens, Estrogen , Androgen , as found in contra- ceptive pills & Anabolic steroids , Haemachromatosis carries a relative risk of HCC which can occur without cirrhosis [11] , Alpha-1 anti trypsin deficiency , and primary biliary cirrhosis , liver flukes " schistosomiasis & clonorchiasis were these infectious are endemic [12,13].
The success of its established treatment modalities is frequently limited by the advanced stage of the tumor at the time of diagnosis[14] .
Although very deficient documented epidemiological study in Iraq , a general observation that an increasing no. of cases are being diagnosed which might be due to an increased incidence as documented in other countries , as well as to increased awareness of the disease particularly it's association with chronic liver disease [15] .
The aim of this study :
1st to evaluate the main etiological causes of HCC , main presenting features & important physical findings , 2nd to study the role of AFP (alpha-feto protein) & U/S study in early detection and surveillance of HCC. 3rd to study the role of liver biopsy in various types of HCC & chronic liver disease . 4th to find the best surgical option or palliative treatment modalities for HCC which might help in the prognosis .

PATIENTS AND METHODS:

A prospective study of (57) patients with HCC (43 males , 14 females) during the period from January 2000 to December 2002 .
The patients were collected from medical & surgical units of Baghdad teaching hospital & the gastroenterology & hepatology teaching hospital.
A special formula regarding age , gender , occupation , residence , main complaints , history of present illness , social history , alcohol intake , smoking, drugs intake, history of congenital liver disease , past medical history (History of Jaundice , Hepatic disease) , history of past surgical operations .
Patients arranged for main symptometology (Abdominal pain, abdominal swelling , weight loss , weakness & fatigability , feeling of fullness & anorexia , vomiting & Jaundice) & for main physical findings (Hepatomegaly , splenomegaly , Ascitis , Jaundice , Fever & Hepatic bruit) .
Laboratory investigations including : complete hematological & biochemical blood analysis
Virology study (for Hepatitis , B & C) , serum AFP. Titer , other diagnostic series U/S study , MRI , CT scan for diagnosis, staging & localization of the tumor (Right lobe , left lobe , both, tumors metastasis to lung , bone , Regional Lymph node).
Ascitic fluid tapping done & send for cytology, culture & sensitivity , and biochemical studies .
Liver biopsy done either by Trucut needle biopsy using *chiba needle* either directly to liver tissue or under U/S guidance , or open liver biopsy by diagnostic laparoscopy or by explorative laparotomy .
The following modalities of treatment were followed in the management of the patients in this study according to the stage of the disease and general conditions of the patients : palliative treatment , chemotherapy , injection of alcohol , hemilobectomy , segmental resection , debulking resection of tumor in the liver , conservative treatment only symptomatic treatment & any complications of hazards during surgical procedures were recorded .

RESULTS:

In this study the age & sex distribution among (57) patients , (43) male (75.5%)>(14) female (24.5%) .male to female ratio is approximately (3:1), as shown in table (1) . The ages ranged from (21- 86) years with mean age of (57.1) yr. more common between (51-60) yrs old (16) out of (57) patients about (28.25%) .
In Geographical distribution from the collected data of the patients in this study . We found that most of the patients ere from Baghdad (27) out of (57) patients (47.4%) & least no. of patients were from Thiquar , Al- Ta'mim & Al-Suleimaniya , (one patient for each province) (1.8%) , as shown in table (2). From Annual distribution we found an increasing no. of patients

from 2000 (12) patients (21.1 %) to 2001 (19) patients (33.3%) to 2002 (26) patients (45.6 %) , as shown in table (3) .

In preexisting liver disease (48) out of (57) patients (84%) have previous history of chronic liver disease & (9) patients (16%) haven't such a history .

Most of chronic liver diseases are due to previous history of hepatitis B- infection (41.6%) & (9) patients (18.8 %) with positive history of hepatitis C infection , alcoholic liver cirrhosis (5) patients (10.4%) , patients with liver cirrhosis of unknown Etiology (11) patients (23%) , 2 patients with liver cirrhosis due to contraceptive pills (4.2 %) & (1) patient with liver cirrhosis due to previous history of infection with liver flukes (2 %) . Table (4) .

According to presenting features the commonest presenting symptom was upper abdominal pain mainly right hypochondrial in (52) out of (57) patients (92%) & least presenting symptom was Jaundice (5) out of (57) patients (9%) . The most common finding on physical examination was Hepatomegaly (50) out of (57) patients (90 %) & least common one is Hepatic bruit (14) out of (57) patients (25%) .Table (5) .

In Laboratory investigations, Unique alpha feto protein is found in most of the patients with positive histopathology for HCC . We found a high level of AFP in (30) out of (45) patients more than (400 ng / ml) in a percentage of (66.6%), all of them are of standard type of HCC.

From the Imaging studies using multiple diagnostic studies to the patients in this study (U/S , MRI and CT scan) , we found that most of these tumors localized to Rt. lobe (38) out of (57) patients (66.6%) & least localized to Lt. lobe (5) patients (8.8%) while both lobes (Rt. & Lt.) were involved by the tumor is (14) patients (24.6 %) , as shown in table (6) .

In categorization of the patients according to the child's classification was done in this study and we found that most patients were group C (36) out of (57) patients (63.3%) & least patients (9) out of (57) patients (15.8 %) were group A as shown in table(7) .

In (29) out of (57) patients had ascitis on presentation aspiration of Ascitic fluid done & sent for histo biochemical study , cytological study & culture & sensitivity , the findings were bloody Ascitis in (7) patients (14%) & positive malignant cells in (5) patients (17.2%) & negative results for malignant cells (24) patients (82.8%) .

Liver biopsy done either by Per-cutaneous needle biopsy directly or under U/S guidance by *chiba needle* or by diagnostic laparoscopy or explorative laparotomy " open liver biopsy " to (52) patients , the result were (43) out of (52) patients (82.7%) had associated chronic liver diseases , and (50) out of (52) patients (96.5 %) , the results of histopathology ranged from moderate to poorly differentiated type of standard HCC , while (2) out of (52) patients (3.5 %) , the results of biopsy was fibrolamellar type . Outcome of treatment, (10) patients discharged on their responsibility without proper treatment, (8) patients underwent diagnostic laparoscopy for staging & open liver biopsy was taken, (3) patients underwent explorative laparotomy for diagnosis , staging & also liver biopsy was taken, (2) patients treated by injection of alcohol therapy and one of them died because of septicemia, (5) patients underwent segmental resection perfectly & discharged well , two of them their histopathological results was of fibrolamellar type of HCC, (2) patients underwent right hemi hepatectomy or right lobectomy & one of them died because of acute liver failure, (2) patients underwent debulking surgery of right lobe & one of them died because of aspiration pneumonia, (16) patients sent for chemotherapy to the chemotherapeutic center to complete their management, (20) patients with locally advanced metastasis (or metastasis to lung , bone …etc) considered for conservative therapy) or to conservative approaches at medical and surgical wards , as shown in table (8) . Follow up of (25) patients was difficult because they didn't attend regularly for consultation regarding their disease .

Table 1 : Age & gender distribution of HCC

Age group	Male	%	Female	%	Total	%
21-30	2	3.5	2	3.5	4	7
31-40	3	5.25	2	3.5	5	8.75
41-50	6	10.5	2	3.5	8	14
51-60	13	23	3	5.25	16	28.25
61-70	10	17.5	2	3.5	12	21
71-80	6	10.5	3	5.25	9	15.75
81-90	3	5.25	0	-	3	5.25
Total	43	75.5	14	24.5	57	100%

Table 2: Distribution of HCC among Iraqi provinces

Province	No. of patients	percentage
- Baghdad	27	47.4
- Diyala	5	8.6
- Babylon	4	7
- Najaf , Basrah	3 for each	5.3 for each
- Maysan , Wassit , Saladdin , Mosul , Qadisiya , Anbar	2 for each	3.5 for each
- Thiquar , Ta'mim , Suleimanyia	1 for each	1.8 for each

Table 3: Incidence of HCC in 3 years study

Year	Number of patients	%	Male	%	Female	%
2000	12	21.1	9	15.8	3	5.25
2001	19	33.3	15	26.3	4	7.0
2002	26	45.6	19	33.4	7	12.25
Total	57	100%	43	75.5	14	24.5

Table 4: Etiology of HCC

Causes	Types	No. of patients	%
History of chronic liver disease	-Hepatitis B infection -Hepatitis C infection -Alcoholic liver disease -Cirrhosis of unknown Etiology -History of contraceptive pills used -History of Schistosomiasis	20 9 5 11 2 1	41.6 18.8 10.4 23 4.2 2
		Total :48	84%
No history of chronic liver disease	-	9	16%

Table 5 : Common presenting symptoms & physical findings in HCC .

Findings	Average incidence	No. of patients
Symptoms - abdominal pain - Abdominal swelling - Weight loss - Generalized weakness - Feeling of fullness & anorexia - Vomiting - Jaundice	92 % 40% 33% 30% 25% 10% 9%	52 23 20 17 25 6 5
Physical examination - Hepatomegaly - Splenomegaly - Ascitis - Jaundice - Fever - Hepatic bruit	90% 70% 50% 35% 40% 25%	50 40 29 20 23 14

Table 6 : Localization & distribution of HCC in the liver

Site	No. of patients	%
Right lobe alone	38	66.6
Left lobe alone	5	8.8
Both right & left lobe	14	24.6

Table 7: Child's classification of hepatocellular function in HCC

Groups	No. of patients	%
Group A	9	15.8
Group B	12	21
Group C	36	63.2

Table 8 :Outcome of medical & surgical treatment of HCC

Types of Treatment	No. of patients	%
Conservative	20	35%
Injection therapy	2	3.5%
Chemotherapy	16	28%
Surgery	9	16%
1- Segmental	(2)	(3.5%)
2- Rt. Lobectomy	(2)	(3.5%)
3- Debulking	(5)	(9%)

Note :10 patients discharge on their responsibility (17.5 %)

DISCUSSION:

Hepatocellular Carcinoma is one of the most common cancers in the world .It is one of the most deadly with a 5 years survival rate less than 5% without treatment [16] .

In this study we found:- that males are more commonly affected than females (43) (75.5 %) & (14) (24.5%) respectively in a ratio of (3:1) & age ranged from (21- 86) year, with mean age of (57.1) year the commonest age group affected was (61-70) years old (16) patients (28.25 %) . Which is approximately consistent with Flickinger J. & Sherlock's [9,17] , who stated that male to female ratio is about (4:1) and age incidence between (60 -70) years old especially in subsaharan Africa & Asia .

In our study most of the patients were from Baghdad (47.4%) . This may be , due to the fact that data collected only from Baghdad teaching hospital and the Gastroenterology and Hepatology teaching hospital not from all Iraqi hospitals .

Also we found , there is a rising incidence of HCC during the period of the study from (2000 – 2002) , this may be due to the improving techniques & experience in the diagnosis of this disease .

Data collected in this study showed most of the patients (84%) has previous history of chronic liver disease & (16 %) of patients have no such a history developed HCC of unknown Etiology , this is in agreement with many studies stated that there is a common association of HCC with chronic liver disease[18] .

Our study showed viral hepatitis B previously infected patients are more prone to develop HCC (41.6%) , other causes of HCC was previous history of hepatitis C infection (18.8%) . (10.4%) have alcoholic cirrhosis & patients with liver cirrhosis of unknown etiology develop HCC (23%) and the less common cause of HCC were the use of contraceptive pills seen in two patients (4.2%) & liver flukes " Schistosomal infection " seen in (1) patient of Egyptian nationality immigrated previously to Maysan province was not treated properly developed liver cirrhosis & portal hypertension & he presented with advanced HCC .

These results are approximately similar to H. Kuper , A. Tzonon study stated that chronic infection with either of two viruses hepatitis B virus (HBV) or hepatitis C virus (HCV) has been shown to be an important causes of HCC [19] .

According to patients presenting symptomatology abdominal pain was the commonest presenting symptoms-upper abdominal pain (92 %) , abdominal swelling (40%) , weight loss (33%) , Generalized weakness (30%) , feeling of fullness & anorexia (25%) , vomiting (10%) and least common presenting symptoms were jaundice (9%).

And also findings of physical signs shows hepatomegaly was the most common physical signs in (90%) with palpable liver below costal margin , Splenomegaly (70%) , Ascitis (50%) , jaundice (35%) , fever (40%) and least physical signs were hepatic bruit (25%) , This result similar to data from Flickinger et al [17] .

In our study we found high levels of AFP in (45) out of (57) patients . The level was > (400 ng / ml) in (3o) patients (66%) .

Sherman M. in his study stated that AFP percentage occur between (70- 90%) of patients with HCC , in (70 %) of patients with HCC in the United States and in (85%) of such patients in Africa [20] .

According to serial diagnostic approaches for tumor localization in those (57) patients in our study , we found that the right lobe affected in (66.6 %) & the left lobe in (8.8%) & both lobes (right & left) (24.6%) & these detected by aids of U/S , CT scan & MRI study .

The child's classification allows an easy method of describing the severity of liver disease & allows comparison of treatment for patients with chronic liver disease [21] . According to our results , we found that most of patients belong to group C with advanced , metastatic hepatoma because most of patients presented to us lately with signs & symptoms of metastasis to bone , lung or locally advanced cancer .

Regarding patients with Ascitis (29) out of (57) patients , ascitic tap done & sent for biochemistry , cytological study & culture and sensitivity , findings were bloody " Hemorrhagic " ascitis in (24 %) of patients & positives malignant cells in (17.2%) patients this is similar to Alkasir & Juredini study [15] , This is in contrast to the reported highly incidence of exudative ascitis in HCC [22] , cell count & cytology are not very helpful in the diagnosis which is in general agreement with other studied abroad [23] , and in our country [24] .

Cor needle liver biopsy study done specially by *Chiba* needle for (52) patients either directly or by U/S guidance & also by open liver biopsy (Explorative laparatomy , diagnostic laparoscopy , findings were (82.7 %) of patients were associated with chronic liver disease & (17.3%) of patients are not associated with chronic liver disease . (96.5 %) of the patients results are moderately to poorly differentiated HCC & (3.5%) of patients HCC of fibrolamellar variant .

The course of the disease is fatal and usually rapid , most patients died within 3 – 6 months from Gastrointestinal haemorrhage , progressive cachexia or hepatic failure [25] .

There are no studies comparing the available curative treatment options resection , liver transplantation & percutaneous ablation …. against no treatment or amongst themselves , thus there is no data to establish the first line treatment in patient with HCC in compensated cirrhosis . Each group , center & country should establish the preferred schedule taking into account the results of Cohort studies and the available resources [26,27]

Surgical resection is the only potentially curative treatment of HCC unfortunately most lesions are not respectable due to tumor spread or underlying cirrhosis , prognostic factors that influence factors that influence long term survival following resection including tumors size , tumor multiplicity , encapsulation , completeness of resection , portal or hepatic vein invasion & histological differentiation , the 5 years survival after resection approximate (25%) , survival rate of (50 – 70 %) have been reported for small tumors , liver transplantation for HCC in cirrhotic patients that can not undergo partial hepatic resection yield similar survival rate , tumor recurrence most frequently in the liver following either resection or transplantation [3,15] .

In present study most of patients presented in a late stage – advanced , metastitc stage (35%) , in (17.5%) of patients discharged on their responsibility refusing any medical or surgical treatment & (3.5 %) of patients underwent injection therapy of alcohol under U/S guidance & one of them died because of septicemia & (28%) of patients sent for chemotherapy to complete their management .

Patients underwent surgical treatment are (9) out of (57) patients that equal to (16%) , in five of them segmental resection done by resection of one or two liver segments , (2) patients underwent Rt. Lobectomy of liver , one of them died because of acute liver failure , (2) patients underwent debulking surgery of Rt. Lobe one of them died because of aspiration pneumonia .So early resection is the only potentially curative treatment of HCC .

CONCLUSION:

1. The main Etiological causes of HCC were history of chronic liver diseases and the main cause past history of Hepatitis B. and Hepatitis C. viral infection and liver cirrhosis of unknown Etiology.
2. The most common presenting symptoms abdominal pain and abdominal swelling and the least one is Jaundice. And the most common

physical examination finding were Hepatomegaly and Splenomegaly and the least one is Hepatic bruit.

3. AFP and U/S study are very important in the early detection and follow up of the patient with HCC.

4. Liver biopsy - very important study to detect various type of HCC, standard type of HCC are more common in our study than Fibrolamellar type of HCC.

5. Surgical resection is the only potentially curative treatment of HCC, unfortunately most lesions are not resectable due to tumor spread or underlying cirrhosis.

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