Proceedings S. Z. P. G. M. I. Vol. 2 (1988), pp. 58- 63

A Middle Aged Man with Primary Hypatocellular Carcinoma

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HISTORY

H.M.A. a male of 44 years, labourer from Pakpatten Sahiwal, presented in the surgical out patient dept. on 22-07-1987 with the following complaints

- Pain right upper quadrant of abdomen —— 7 years
- Loss of weight —— 18 months
- Swelling anal region —— 15 days

The pain in the abdomen was coliky in nature, lasting for 3–4 hours, usually associated with vomiting. It started in right upper quadrant and involved whole of abdomen. It had no relation with meals.

Patient had loss of appetite for the last 18 months. During this period he lost about 25 Kg. He also complained of easy fatigueability since than.

He was aware of ch. constipation for the last one and a half years. He noticed streaks of blood in stools three months back and haemorrhoids which were reducible for the same time.

There was no history of fat intolerance, hunger pains, malena, or drug intake.

He had two episodes of jaundice lasting for one to two months during the past two years. He was not hospitalised, got treatment from a G.P. and recovered.

EXAMINATION

On General Physical Examination, he was thin, wasted emaciated and pale. His pulse was 88 per min. B.P. 110&0, Temp. 98°F He was not jaundiced

On examination of the abdomen, the liver was enlarged 5cm below right costal margin. It had a smooth surface, well defined margins and was tender. No viscera other than liver was palpable. The bowel sounds were normal.

Rectal examination revealed 3rd degree haemorroids at 3,7, 11 O'clock. There was no active bleeding but these were very tender.

The examination of his chest, cardiovascular system and central nervous system was unremarkable.

INVESTIGATIONS

His haemoglobin was 12.6gm/dI, W.b.C.. 11500, E.S.R. 50 mm 1st hour. His blood urea, serum creatinine, blood glucose and urine examination were within normal limits. He had normal liver function tests and normal bleeding profile. HBsAg was negative. Alpha feto protein was raised to 400 ng/mI (upper limit of normal:20 ng/ml)

His X-ray chest was normal & X-ray plain abdomen showed enlarged liver shadow. His barium enema was carried out to rule out any intestinal malignancy but it did not show any filling defect.

Abdominal ultrasound showed enlarged liver 6.2 cm below right costal margin and a ill defined hyper echoic mass (61. x 8.0 cm) in right lobe of the liver. Gall bladder was contracted and contained gall stones and had thickened walls. The lesion in liver was suspected to be malignant.

C.T. Scan of abdomen was advised. It confirmed presence of tumour in right lobe of liver. (Fig 1)

OPERATION

The patient was planned for right lobectomy of liver. Usual pre-operative preparations were carried out.

A bilateral subcostal incision was made. On exploration, liver was enlarged. A large mass was present in right lobe. The gallbladder was full of stones and had firm adhesions with liver. The hepatic flexure of colon also had firm adhesions with liver and gallbladder. There was no enlargement of lymphnodes at portahepatis. All other abdominal viscera were normal & there was no ascites.

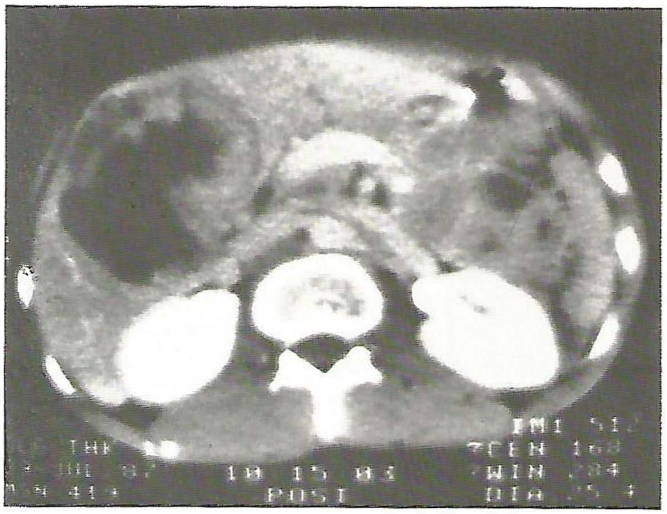

Fig: 1. Pre-operative CT Scan of liver showing large tumour in right lobe

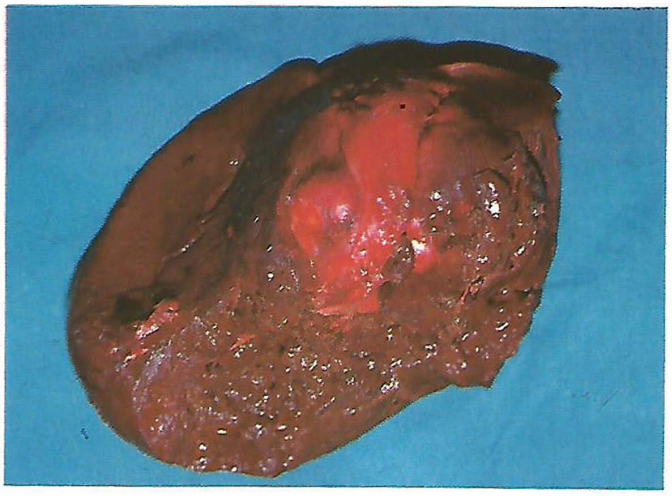

Fig: 3. Removed Rt. lobe of liver, posterior view.

The liver was mobilized, common bile duct, right & left hepatic ducts identified. Common hepatic artery, its right & left branches identified Portal vein, its right & left division identified.

Right hepatic artery, right hepatic duct and right division of portal vein ligated and divided. Vascular clamps applied to left hepatic artery & left division of portal vein. The liver dissected by finger fracture technique. Right & middle hepatic veins ligated and divided. Right extended lobectomy performed with cholecystectomy. Suction drains left in subphrenic space.(Fig 2, 3 & 4)

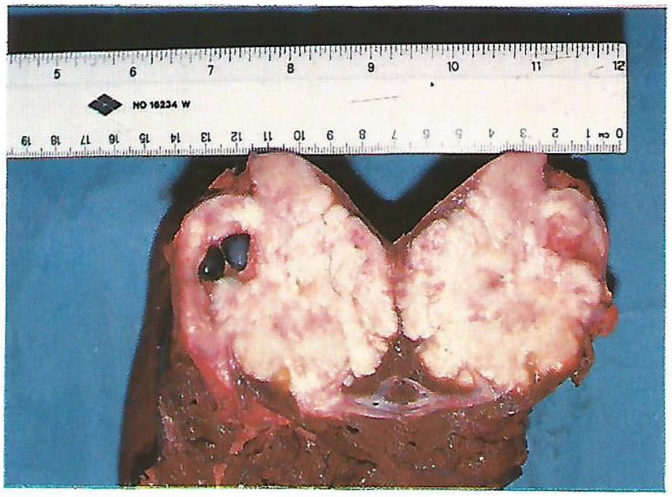

Fig: 4. Cut section of tumour.

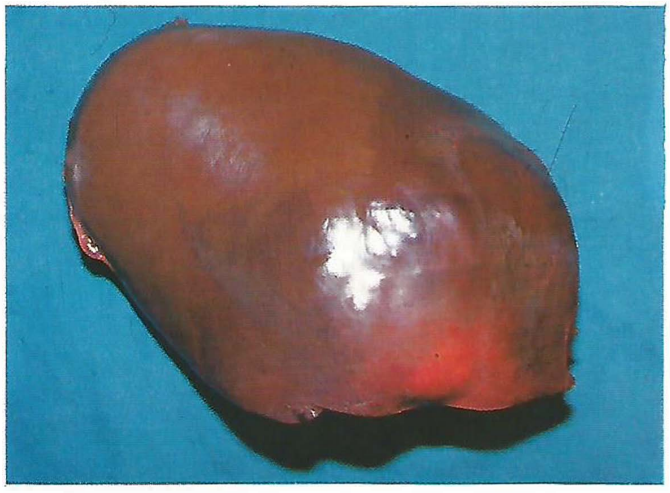

Fig: 2. Removed Rt. Lobe of liver, frontal view.

HISTOPATHOLOGY

On gross examination, multiple serial sections of the liver showed pale, greish rounded tumour having a diameter of 7.0 cm and occupying almost half of specimen. The cut surface of tumour showed haemorrhagic punctations. The gallbladder had thickened walls and multiple jet black stones were present in it.

The microscopic examination revealed a section of liver part of which was replaced by malignant epithelial neoplasm. The neoplastic cells showed marked variation in size and shape and were arranged in trabecular pattern. The surrounding liver cells had no changes of cirrhosis.

The diagnosis of hepatocellur carinoma was made (Fig 5).

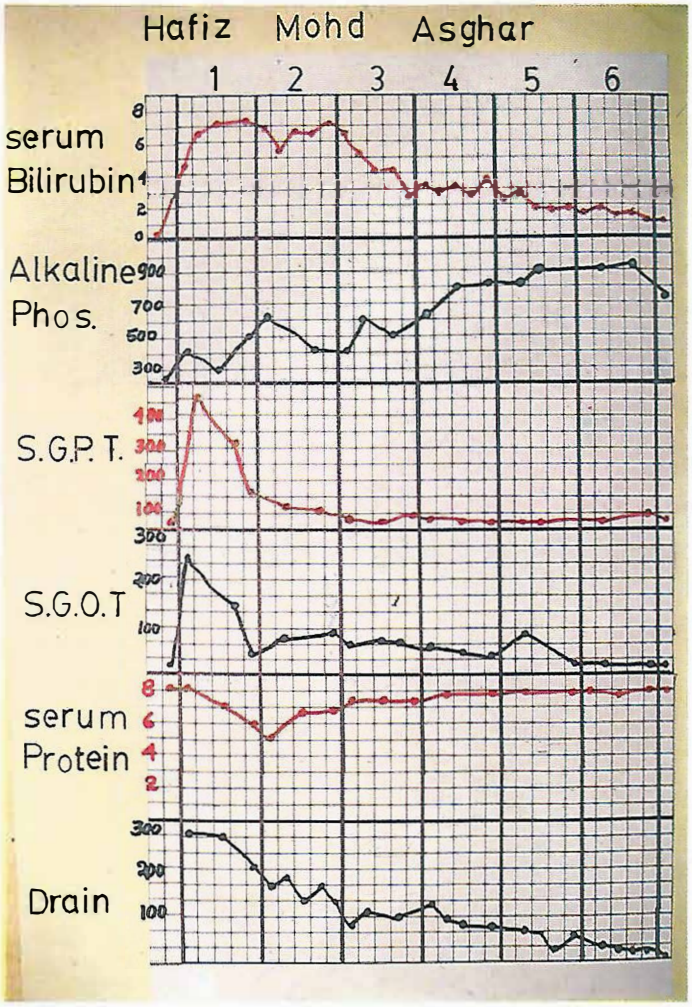

Fig: 5. Post operative course.

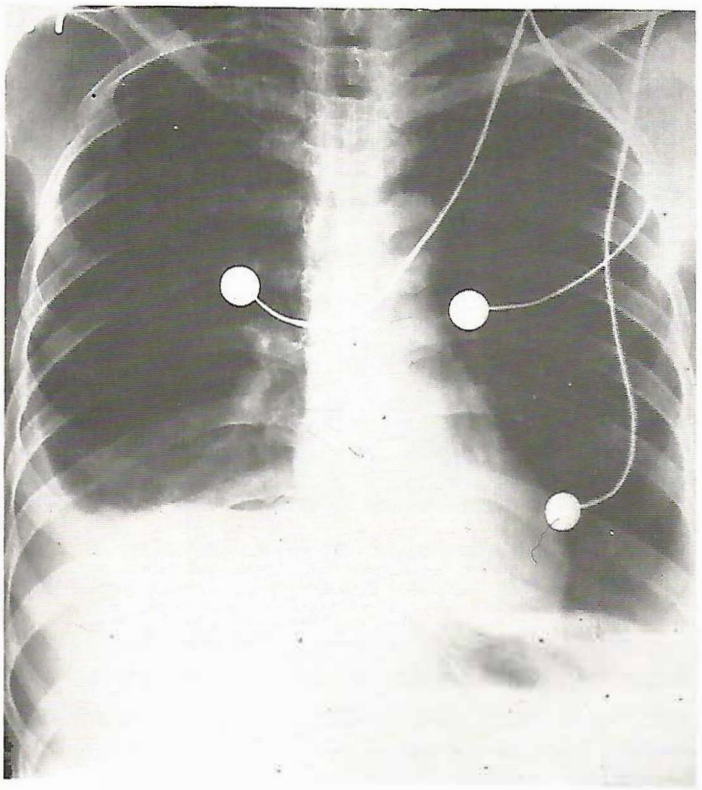

Fig: 6. Post-operative X-Rays chest showing elevation of Rt. hemidiaphragm.

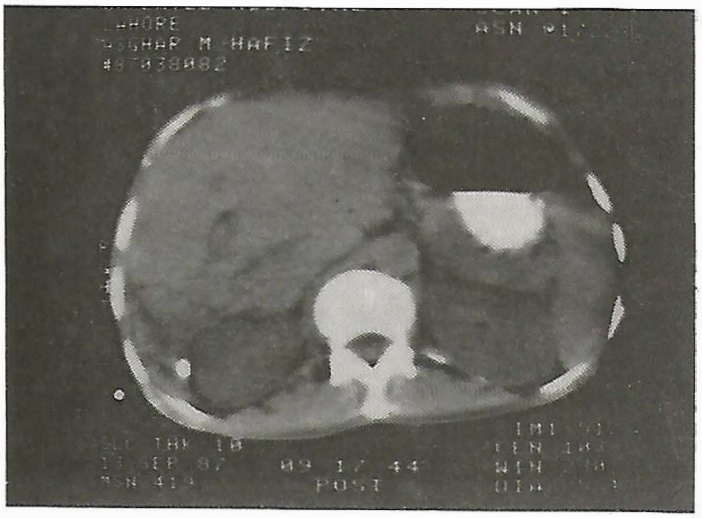

Fig: 7. C.T. Scan after 7 weeks. showing regeneration of liver.

POST-OPERATIVE COURSE

After the operation, the patient was kept in I.C.U. for 24 hours where his vital signs & intake, output were monitored carefully. On 5th post-operative day air entery was reduced on base of right hemidiaphragm with mild pleural effusion, About 400 ml of clear fluid was tapped & set for culture & sensitivity but it did not show any growth (Fig 6).

During the first six post operative weeks, his liver function tests were monitored carefully along with drainage.

During 7th post operative week, C.T. Scan of abdomen was repeated. There was enormous regeneration of left lobe of live. It attained almost the size of a normal live (Fig 7).

DISCUSSION

Hepatocellular carcinoma is common in Africa and south east Asia. Its incidence varies from 98 per 100,000 population in Mozambique to 64 in Singapore, 10.5 in Spain, 2.5 in New York, 2.7 in India & 1.5 in England. The high risk areas are characterized by a tropical or subtropical environment and rural poverty. Male to female

ratio is 2–3:1

Hepatitis B Virus – In Africa and Asia 90% of patients with hepatocellular carcinoma are HBV carriers. The infection is acquired in utero and its persistance may be due to immunological impairment or tolerance. The virus may be directly oncogenic, although HBV infection has been linked with liver cell dysplasia– a probable pre-cancerous change in cirrhosis. In low risk areas only 30% of patients with hepatocellular carcinoma have ch. hepatitis B infection.

Cirrhosis often precedes hepatocellular carcinoma in developed countries, whereas in tropical countries, cirrhosis and hepatocellular carcinoma occur almost simultaneously.

Aflatoxins are the toxic metabolites of Aspergillus flavus. The contamination rates appear to parallel the incidence of hepatocellular carcinoma. The effects range from acute massive necrosis to liver cell dysplasia.

Steroids – There is an association between oral contraceptives and hepatic adenoma. Some malignant tumours of liver have been reported in women taking oral contraceptives. The risk is also associated with male sex hormones.

Thorotrast an obsolete radiological contrast medium produces liver tumours particularly angiosarcoma.

Hepatocellular carcinoma accounts for about 90% of malignant liver tumours. *The common features are:*

- Unexplained deterioration of cirrhotic patient.
- Acute symptoms like liver abscess.
- Painless hepatic mass.
- Intraperitoneal haemorrhage with peritonitis due to rupture.
- Jaundice.
- Ascites.

Uncommon features of HCC include:

- Paraneoplastic manifestations
- Carcinoid syndrome
- Hypercalcaemia, production of chorionic gonadotrophins, ACTH & neuroendocrine hormones.
- Hypoglycaemia due to production of insulin like substance.

Hepatocellular carcinoma may be solitary or multifocal and spreads by invading hepatic or portal veins or by lymphatic permeation. Porta hepatic lymph nodes are commonly involved. Lung and bone metastasis are uncommon. There is often local invasion of diaphrague and other surrounding structures.

The confirmation of presence of space occupying lesion is by ultrasound and C.T. Scan. The resectability is assessed by C.T. Scan, hepatic angiography, spleenoportography, inferior vena cavography and laparoscopy.

The pre-operative criteria of irresectibility include:

* Extensive tumour anatomically nonresectable
* Bilat. hilar vascular invasion
* Peritoneal or distant metastasis
* invasion of inferior vena cava
* Cirrhosis (relative contra-indication)

For resectable lesions, pre-operative biopsy is not essential but the histopathology of non-resectable lesions must be confirmed by Tru cut biopsy or fine needle aspiration guided by ultrasound

Alpha fetoprotein is produced by 85–90% of HCC. Testicular teratoma, benign liver diseases, or hepatic metastasis may also produce raised AFP. Levels greater than 1000 ng/ml are highly suggestive of HCC. AFP is a useful tumour marker to monitor patients after resection or for screening patients in high risk areas.

Treatment

Surgical resection of malignant liver tumours offers the only hope for long term survival. Improved anaesthesia and surgical technique has reduced the risk of haemorrhage, bile leak and post operative derangements to acceptable level.

Unfortunately, only 10% of Asian patients with HCC are resectable. Cirrhosis presents problems such as impaired haemostasis, decreased reserve of remaining liver, poor regenerative capacity and multicentric growth which is common in cirrhotic livers.

A formal lobectomy or extended lobectomy is necessary for curative resection.

The complications include intra-abdominal haematoma, hypoglycaemia, hypoalbuminaemia, and clotting disorders.

DR. G.R. QURESHI (*Histopathologist*): Two things are important in this case. Firstly it was in a non cirrhotic liver. Majority of patients with HCC have a cirrhotic liver. We took a lot of sections of liver and tried our best to find any area with cirrhosis but there was none. Secondly his gallbladder was examined thoroughly, It showed changes of ch. cholecystitis with cholelithiasis.

As a surgeon is confronted with a tumour in the liver so is a pathologist, from a different angle. Liver is a very

common seat of secondaries. It should be always kept in mind especially when it is a non cirrhotic liver. Some of patients with HCC are HBsAg negative. Although we do see cases of post necrotic cirrhosis secondary to HBV commonly.

The specimen we recieved had peritoneal reaction which is a good sign. Some times it may lead to ascites but our patient did not have it. Tumour was projecting on the surface of specimen. The cut section showed a well circumscribed tumour with a few setallite cells at margins but it was still a single mass. It was a very hard tumour, difficult to cut, had a gritty feel and showed areas of haemorrhages. because it was a very vascular tumour.

On microscopic examination, it had multiple atypical mitoses and pleomorphism. The hepatocytes were forming trabecular pattern. There was multinucleation of cells which is characteristic of HCC. One to two portal areas are present in each field in normal liver but in this case we had absolutely no portal areas. There was Kupffer cell hyperplasia and intracellular collection of bile. This leaves no doubt that we are dealing with HCC.

DR. JAWED SIDIQUI *(Radiologist)*: This patient had very good radiological workup. The patient presented with enlarged liver. First investigation was X-ray plain abdomen, which showed enlarged liver shadow. Ultrasound examination which showed a hyper echoic lesion in liver. It was more dense than the rest of the liver substance suggesting a solid tumour. There was no associated intrahepatic or extrahepatic dilatation of bile ducts.

C.T. Scan was done to differentiate from necrotic liver tissue and a large abscess.

The margins of this tumour were very rugged. In the case of abscess, there is a thick wall and margins are usually well defined. It was unlikely a cyst or locular cyst because there were no septa.

Post operative C.T. Scan showed considerable regeneration of liver substance, fig No. 6

DR. ANWAAR *(Gasttroenterologist)* HCC is wrath for countries of Africa and South East Asia. The incidence is 90 times higher as compared to West and U.S.A. The problem has been studied and investigated by leaders in hepatology like Mac Sween in England, Geddes and Falkson have reported 124 cases where it occured on a back ground of liver cirrhosis.

The association of HBV and HCC has been well documented. This association is not evident over here. It might be due to the technique we use, i.e. ELISA rather than radio-mmune assay. Secondly the cirrhosis might be due to Non A Non B virus. There is about 20% incidence of HCC associated with cirrhosis, haemachromatosis and post necrotic cirrhosis. In a cirrhotic background, HCC is multicentric, therefore very difficult to approach by surgery. In non-cirrhotic livers we dont know the etiology of HCC.

The HBV implication has been recently well studied and Jay Hoofnagle from NIH U.S.A. has reported that there is genetic change in the hepatocytes. Even if the patient clears viral B antigen, the changed genetic code may persist and ultimately over the ensuing 10–15 years develop HCC. This has raised a great concern among the carriers of HBsAg, that they may be potential candidates for developing HCC ultimately.

The surgical approach in Mayo Clinic series showed that out of 60 patients operated, the survival was 30% over 5 years, which is very good in HCC because without surgery the patient is usually dead in 2–3 months.

The medical treatment has not been promising. The medications which have been mostly useful in other GIT tumours like 5FU, CCNU and streptozotocin, have not shown good results. Adriamycin has shown response of 60% with prolongation of survival to 18 months.

The effect about post-operative rise in liver function studies has been well documented in paitents who have partial lobectomy, especially in trauma cases. About 80% of liver can be simply resected and we can see very nice improvement of abnormal liver function tests correlating the regeneration of liver. In about 3–4 weeks there is decline in serum bilirubin. Serum transaminases suddenly rise and fall to normal within the first two weeks, which shows rapid regeneration.

DR. IQBAL *(Pulmonologist)*:: There was long history of 7 years of RHC pain, may I ask Dr. Anwar what is doubling time of this tumour ?

DR. ANWAAR (*Gastroenterologist*) : The doubling time for this tumour is approximately 2 months. If a patient with cirrhosis, suddenly gets worse and develops ascites, please think about HCC. Patients with back ground of cirrhosis have compromised liver functions so HCC causes death with in a few months. In answer to a question of causation of pain in RHC, I think it was due to gall stones but not due to HCC otherwise it should have shown itself much earlier.

DR. SULTAN TARAR *(Gen. and Vascular Surgeon):* Hepatocellular carcinoma is the predominanat malignant tumour of the liver. The liver is such a vascular organ that operative bleeding has plagued the surgeons for a century. Recent improvements in the operative techniques and better understanding of anatomy have made hepatic resections very safe. Advances in diagnosis include alpha fetoprotein monitoring, ultrasonography and computed tomography.

I would like to mention one type of hepatocellular carcinoma that is fibrolamaller. This is associated with paraneoplastic manifestations. Disproportionate rise of alkaline phosphatase as compared to other LFTs points towards hepatocellular carcinoma. Before hepatic resection, BSP retention should be done and patient having BSP retention greater than 30% are not suitable for resection.

Alpha-feto protein level over 500ng/ml except for pregnancy or intrauterine fetal death is highly suggestive of primary HCC. The HBsAg is positive in about 30–40% of these cases in West and 80% of cases in South East Asia and Africa.

Isotope scan are also useful in reaching the diagnosis. The HIDA scan shown cold spots in liver scan but Gallium scan which should be preferred shows hot spots on scan.

The C.T. scan is helpful except in lesions which are less than 2cm in size. The most accurate test for detection of HCC is hepatic angiography. It can show lesions which are less than 1.5 cm in diameter.

Laparotomy is the only way to determine resectability which cannot be assesed by any other mean.

As Dr. Anwaar has already mentioned, without surgery these patients are dead with in 3–4 months. The only chance of survival is in radical surgical resection. The survival is better in patients with out cirrhosis. All patients with cirrhohis undergoing hepatic resection are practically dead with in three years.

The patients with positve HBsAg and alpha protein levels of 200–300ng/ml but having no tumour in liver on organ imaging should undergo hepatic angiogram because ultimately they will devalop HCC. This is agreed by most of authorities in the world including Prof. Wong from University of Hongkong who presented over 800 cases in 1980 when he was given honourary fellowship of American College of Surgeons, Prof. Stig Bengmark from sweden and Prof.. Blumgart from London.

Systemic chemotherapy has not been really helpful. One has to consider quality of life and associated morbidity in those patients who have only 2–3 months to live. Intra-arterial chemotherapy, ligation of hepatic artery or therapeutic embolization have not really prolonged the survival that much.

In the series of Starzl, which consists of 144 liver transplants till 1980 and out of these 19 were for primary HCC. Out of 19, 18 cases were alive at the end of one year. This appears to have good promise in future but has not been applied to metastatic liver disease.

Due to some unknown reasons Tagamet reduces the symptoms of pruritis in patients with HCC.

Flagyl, 5FU and Mitomycin are being used to radiosensitize the tumour.

Recent developments like ultrasonic scalpel and the laser beam scalpel might take all the thrill of major hepatic resection but these modalities are still too expensive although, they reduce the operative blood loss considerably.

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