*DISSERTATION ON*

# ROLE OF TRANSARTERIAL CHEMOEMBOLIZATION IN UNRESECTABLE HEPATOCELLULAR CARCINOMA

*Submitted in partial fulfillment of*

*Requirements for*

**M.D. DEGREE**

**BRANCH VIII RADIODIAGNOSIS**

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**MADRAS MEDICAL COLLEGE AND**
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# CERTIFICATE

**Certified that this dissertation titled "ROLE OF TRANSARTERIAL CHEMOEMBOLIZATION IN UNRESECTABLE HEPATOCELLULAR CARCINOMA" is a bonafide work done by Dr.K.GOPINATHAN M.D.(RADIODIAGNOSIS), Post graduate student of Barnard Institute of Radiology, Madras Medical College, Chennai, under the guidance and supervision of PROF. T.S.SWAMINATHAN, MD., DMRD., FICR., during the academic year 2003 – 2006.**

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# DECLARATION

**I declare that this dissertation titled "ROLE OF TRANSARTERIAL CHEMOEMBOLIZATION IN UNRESECTABLE HEPATOCELLULAR CARCINOMA" has been conducted by me under the guidance and supervision of Prof. T.S. SWAMINATHAN, M.B., MD., DMRD., FICR, Director, Barnard Institute of Radiology, MMC. It is submitted in part of fulfillment of the requirement for the award of the M.D., Radiodiagnosis, September 2006 examination to be held under Dr.M.G.R. Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other University.**

**Dr. K. GOPINATHAN**

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# CONTENTS

# INTRODUCTION

**Hepatocellular carcinoma (HCC) is one of the most common fatal malignancies worldwide. Incidence is more than 530,000 patients annually. It is common in certain geographic areas particularly in Japan, South East Asia, and Sub Saharan Africa. In India HCC is more common in southern states with a male female ratio of 5-7:1. The prevalence of HCC is rapidly increasing as a result of the spread of chronic infections with Hepatitis B&C.**

**The main therapeutic modalities used for HCC are primary hepatic resection and loco regional therapies. Whenever liver function permits, resection should be considered the first choice. But only less than 30 % of patients are suitable candidates for surgery and also 70% of patients who undergo surgery will develop new liver tumors during the first 3 years of follow up. Since most of the patients present in late stage, surgical options are not possible. Hence loco regional therapies are the main stay in treatment.**

**In loco regional therapy, liver can be targeted through a vascular approach, injecting the active product through feeding vessels or by a direct approach to the tumor by delivering the treatment directly inside the mass lesion.**

**Loco regional therapy can be**

**1) Vascular**

**2) Direct**

**<u>Vascular Approach Procedures</u>**

- **Hepatic arterial chemotherapy**
- **Trans arterial chemoembolization (TACE)**

- **Hepatic injection of loaded embols (drug and radiation)**
- **Intra portal drug delivery**
- **Isolated liver perfusion**

**Direct Approach Procedures**

- **Percutaneous ethanol injection(PEI)**
- **Radio frequency ablation(RFA)**
- **Cryo ablation**
- **Micro wave and laser ablation**

**When the lesions are small or less than 3 in number with less preserved hepatic reserve PEI / RFA is indicated. In large lesions or more lesions with well preserved hepatic reserve TACE is indicated.**

**Chemoembolization combines simultaneous infusion of a concentrated dose of chemotherapeutic drugs and embolization particles. Chemoembolization causes tumor drug concentration manifolds than that achieved by infusion. Hepatic artery embolization renders the tumor ischemic, depriving it of nutrients and oxygen. The dwell time of the chemotherapy agent within the tumor is markedly prolonged, with measurable drug levels present as long as one month after procedure. Because most of the drug is retained within the liver, systemic toxicity is reduced.**

# AIM

1. **To evaluate the role of Transarterial chemoembolization in unresectable hepatocellular carcinoma patients as a palliative care.**

   **This is done by assessing**

   - **1 year survival benefit of TACE patients.**
   - **Pain reduction and performance status of TACE patients.**

2. **To assess the safety of TACE in unresectable HCC patients with portal vein thrombosis.**

# REVIEW OF LITERATURE

**Since 1977, TACE has been performed in Japan, where it is regarded as standard treatment in unresectable HCC. In Western nations, the procedure was introduced in the mid-1980s.**

***In 1989 Bockmeyer et al*** **have done trans arterial chemoembolization of unresectable HCC with lipiodol , epirubicin, cisplatin in 22 patients and repeated TACE after storage subsided. They found 6 month ,12 month survivability of 73% and 54% respectively.**

**Seven hundred thirty-nine patients with unresectable HCC have been treated by TACE using gelatin sponge particles soaked in a solution of Mitomycin C and Adriamycin by *Uchida H, et al* of Japan in 1990. They found this therapy can be equal or superior to surgical resection and serves both as embolic therapy and targeted chemotherapy.**

***In 1989 Nakamura H et al*** **Japan, did TACE with doxorubicin hydrochloride, iodized oil, and gelatin sponge was used in 100 patients with HCC. They found TACE to offer better survival rate than chemo infusion. One year survival rate is 53%, 43% in chemoembolization and chemo infusion patients respectively.**

***In 1990 Uchida H et al[7] Japan*** **, carried out segmental Lipiodol-TAE in 54 patients with hepatocellular carcinoma .Better therapeutic results were obtained in 47 cases. They concluded that lipiodol -TAE doesn't have adverse effect on the normal liver tissue.**

***In 1990 Pelletier G et al[8],*** **carried out randomized trial of hepatic arterial chemoembolization in 42 patients with unresectable hepatocellular carcinoma. Patients received either repeated chemoembolization with gelfoam powder and doxorubicin (group 1) or symptomatic treatment (group 2). They noticed no significant increase in survival rate in chemoembolization group even though partial response is noted in chemoembolization.**

***In 1991 Li GQ et al[9]*** **china, in their study included 60 cases of which 31 had Stage II and 29 had Stage III lesions. Adriamycin or cisplatin infusion was carried out, followed by chemoembolization therapy of tumor vessels using mixture of ethiodized oil or iophendylate and mitomycin C. Finally, gelatin sponge block was used for proximal arterial embolization. After the treatment procedure, abdominal pain was relieved, tumor reduced in size, AFP, r-GT, AKP and LDH declined to various degrees and the survival time was prolonged. The 3-, 6- and 12-month survival rates were 93.3% (56/60), 67.3% (37/49) and 33.3% (9/27), respectively. It is indicated that TAI and TAE, being safe and effective, is the treatment of choice for patients with unresectable HCC.**

***Aoyama K et al[10]*****, in their study of 18 patients with hepatocellular carcinoma (HCC) treated by transcatheter arterial embolization (TAE) with a 4'-epi-doxorubicin (EDX)-lipiodol emulsion. Results are compared with TAE with gelfoam only. They noticed significant survival rates in TAE with doxorubicin.**

***Hasan et al*** **in germany -50 mg/m2 epirubicin, 30 mg/m2 cisplatin, 8 ml fatty acid ethyl ester of iodinated papaver oil and 10 ml nonionic contrast medium were injected under fluoroscopy into the proper hepatic artery in 16 HCC patients. Partial remission was achieved in 10 patients after a median of 4 months. The median survival time was 9 months.**

***In 1993 Park JH et al[11]*****, in their study of TACE done in 87 patients with recurrent HCC . One- and 2-year survival rates after TACE of the 87 recurrent HCCs were 74.7% and 55% respectively. They found significant increase in survival rate when compared with control group.**

***In 1993 Hashimoto T et al[12]*****, The anticancer drug adriamycin, mixed with lipiodol injected via hepatic artery, accumulates in HCC and shows a good anti-cancer effect. TCE with Lipiodol also improved the prognosis. They found TCE without adding gelfoam had increased survival than symptomatic therapy.**

***In 1993 Daniels JR et al[13] ,*** **performed Chemoembolization with 10 mg/mL of cross-linked collagen, 10 mg/mL of mitomycin, 3 mg/mL of doxorubicin, and 3 mg/mL of cisplatin in ten patients of HCC with portal vein thrombosis. Eight patients responded to treatment, including two long-term survivors (> 2 years). They concluded that portal vein thrombosis should not be considered an absolute contraindication to hepatic chemoembolization. Hepatic chemoembolization can be performed safely in the presence of adequate collateral circulation.**

***In 1994 Lu CD et al[14],*** **studied Fifty-two patients with unresectable hepatocellular carcinoma, Group A (n = 24) received lipiodolization with gelatin sponge and group B (n = 28) lipiodolization alone. They found the therapeutic effects of lipiodolization without gelatin sponge for patients with high risk were significantly superior to those of lipiodolization with gelatin sponge. They concluded that the modality of hepatic arterial chemoembolization should be chosen according to the patient's clinical conditions.**

***In 1994 Bronowicki JP et al[15],*** **studied TACE done in 127 advanced HCC patients. The results were compared with symptomatic therapy. Survival in the treated group were 64%, 38%, 27%, and 27% at 1, 2, 3, and 4 years, respectively; those for the untreated group were 18%, 6%, and 5% at 1, 2 and 3 years, respectively ($p < 0.0001$). The survival was significantly increased in patients with Okuda Stage I and II disease ($p < 0.0001$), but not in those with Stage III.**

***Katsumori T et al[16],*** **Segmental TAE was performed in nine patients with hepatic cirrhosis and advanced HCCs accompanied by portal vein thrombosis. The cumulative survival rates were 67% at 6 months, 44% at 1 year, and 22% at 2 years. This therapeutic approach is thought to be a useful treatment for HCC with PTT, because it reinforces anticancer effects and can be performed more safely than conventional TACE.**

***In 1995 Yamada R et al[17],*** **a large series of 1310 patients noticed TACE and related procedures greatly increased survival benefits in unresectable HCC patients than resectable HCC patients.**

***In 1996 Bayraktar Y et al[18]*, mitomycin C mixed with Lipiodol and arterial embolization using Gelfoam was done. The mean survival of those receiving TACE was 13.0 months. Chemotherapy without embolization yielded a mean survival of 7.2 months. The mean survival of the patients receiving no specific anti-cancer treatment was only 6.9 months. The mean survival of the group receiving TACE was significantly greater than that of either of the other two groups ($p < 0.005$).**

***Cheng L et al[19] ,* followed the effect of TAE on hepatocellular carcinoma . In there patients treated with TAE 1, 2, 3, 5, 7 years survival rates were 58.1%, 34.0%, 24.4%, 13.7%, 9.1% .This results indicate therapy is a treatment of choice for patients with advanced HCC.**

***Rose DM* , In 39 patients underwent TACE, overall actuarial survival was 35%, 20%, and 11% at 1, 2, and 3 years with a median survival of 9.2 months, which was significantly higher than over the group receiving supportive care only ($p < 0.0001$). Median survival for the group receiving supportive care was less than 3 months.**

***Kashima Y* TACE did TACE in three advanced HCC patients with hepatic vein thrombosis. They found significant reduction in size of tumor .**

***In 2000 Mizoe A et al,* did TACE in two patient with advanced HCC. Noticed gross reduction in tumor size. Following resection showed complete necrosis of tumor which indicates the efficacy of TACE.**

***Caturelli E et al* conducted TACE in 115 patients. They found TACE does not induce significant long-term worsening of liver function in patients with class A or B cirrhosis.**

***Roche A et al ,* found that TACE can be recommended in Okuda I or II patients, the sessions being prolonged after the second one only for the responders who do not present which severe side effects.**

***Liu H et al*** **, did trans arterial chemoembolization in 40 HCC patients with portal vein thrombosis. Follow up CT showed decrease in size of tumor thrombus 24patients out of 36 patients. Survival is more than 1 year in 20 patients. They found TACE seems to be valuable for the treatment of intra portal tumor thrombi with massive HCC.**

***Lo CM et al[33] ,*** **From March 1996 to October 1997, 80 out of 279 Asian patients with newly diagnosed unresectable HCC treated with a variable dose of an emulsion of cisplatin in lipiodol and gelatin-sponge particles injected through the hepatic artery (chemoembolization group, 40 patients) or symptomatic treatment (control group, 40 patients). Chemoembolization was repeated every 2 to 3 months unless there was evidence of contraindications or progressive disease. Survival was the main end point. Chemoembolization resulted in a marked tumor response, and the actuarial survival was significantly better in the chemoembolization group (1 year, 57%; 2 years, 31%; 3 years, 26%) than in the control group (1 year, 32%; 2 years, 11%; 3 years, 3% ( p =.002 ).**

***In 2002 Kim KM et al[1],*** **separated 182 patients who belong to child criteria A and UICC stage T1-3N0M0, into two groups . One group was treated with chemoembolization and other group treated with hepatic resection. They found similar survival rates in both the groups.**

***Masutani et al[28] ,*** **used four chemotherapeutic agents including epirubicin along with lipiodol without embolization(chemolipidolization) ,and repeated every four week in a case of HCC with portal vein thrombosis patient and good response was noted.**

**In the study of *Maeda S et al* ,Complete and partial responses were obtained in 83 cases (53.2%) in the lipiodol-cisplatin suspension alone group compared to 60 cases (62.5%) in the lipiodol-cisplatin suspension and transcatheter arterial embolization group. The survival rate of the former was 29.6% at 5 years, and of the latter was 24.2% at 5 years**

***In 2003 Romano M*****, [30] found a intraarterial administration of lidocaine before and**

**during chemoembolization is a safe and effective method for preventing or reducing peri and post procedural pain and dosage of narcotic analgesics in patients with HCC with respect to group B patients.**

***In 2003 Wu YP et al,*** **studied the efficacy of TACE combined with portal venous chemoembolization (PVCE) in the treatment of moderate and advanced stages of PLC. The half-year survival rates were 93.1% in TACE/PVCE group and 72.0% in TACE group (P< 0.05). The 1-year survival rates were 43.1% in TACE/PVCE group and 51.7% in TACE group.**

***In 2003 Schwartz JD, Beutler AS et al*** **reviewed 44 randomized trials investigating non-embolization-based therapies in unresectable HCC. Hepatic artery infusion of [I]lipiodol appears safe; initial studies suggested a survival benefit and efficacy comparable to more toxic embolization-based therapies. Cytotoxic chemotherapy may confer a modest survival benefit in advanced HCC including oral fluoropyrimidines, and hepatic arterial or i.v. cisplatin and doxorubicin.**

**In 2004 more recently published, well-conducted studies demonstrate a survival benefit conferred by TACE. Chemoembolization likely confers a benefit greater than that associated with embolization without chemical agents. There is limited evidence and consensus regarding optimal choice and dosage of chemical agents utilized for TACE.**

**Recently in *2005 Walser et al* [37] in their study involving 42 patients of hepatocellular carcinoma with compromised portal venous flow found TACE group survival is longer when compared to control group who received symptomatic therapy alone (413 vs67 days). They used PVA particles, oily contrast, doxorubicin and mitomycinC. They compared the average tumor size, MELD score and survival data.**

***In 2005,Georgiades et al*[36]** **in John Hopkins university , conducted study in 31 patients with unresectable HCC and portal vein thrombosis using Cisplatin , Mitomycin, Doxorubicin,**

**Lipiodol , PVA particles and found median survival rate of 5.1months which was better than those who received symptomatic therapy alone.(3.7 months). They observed 5 months median survival rate in child class B and 12 months in child class A.**

# IMAGING AND VASCULAR ANATOMY OF LIVER

**A thorough knowledge of vascular and segmental anatomy of liver is essential for therapeutic planning, like segmental resection or loco regional therapies.**

## Vascular Anatomy[39]

**The liver receives 15 to 20% of the cardiac output and constitutes a significant reservoir for blood. The liver receives dual blood supply from 1) the hepatic artery, which provides systemic arterial circulation, 2)the portal vein which returns blood from the spleen and gut. Arterial flow is primarily nutritive and provides about 20% of the blood supply; the remainder is supplied by the mesenteric portal drainage. The relative contribution of blood flow to the liver varies and depends upon hormones, neural stimulation (sympathetic, vagal), nutritional state (including fasting or postprandial), and the presence of hepatic parenchymal disease.**

## Hepatic Artery

**The celiac artery gives rise to the common hepatic, splenic and left gastric arteries at the level of T12-L1. The common hepatic artery courses along the upper border of the pancreatic head, anteriorly and to the right, behind the posterior layer of peritoneum of the lesser sac. After giving the gastroduodenal artery, it continues along the upper margin of the duodenum as proper hepatic artery and enters the subperitoneal space of the hepatoduodenal ligament. It ascends to the liver anterior to the portal vein and medial to the common bile duct. After entering the porta hepatis, the proper hepatic artery divides into a right, a left and occasionally a middle hepatic artery. The right lobe is supplied by the right hepatic artery, the medial segment of the left lobe is supplied by the middle hepatic artery augmented by the branches of the left hepatic artery and the lateral segment of left lobe receives blood from left hepatic artery. Branches of the right hepatic artery nourish the caudate lobe, but in some cases the left or even middle hepatic artery contributes. The right hepatic artery also gives off the cystic artery which supplies the**

**gallbladder.**

**The vascular schema described above is present in only 55% of patients. Normal variants include (1) the right hepatic artery partially (18%) or completely (14%) replaced by superior mesenteric artery; (2) the entire hepatic artery arising from the superior mesenteric artery (2 to 4%); (3) the left hepatic artery having a partially or totally replaced origin from the left gastric artery (18% to 25%); and (4) the left hepatic artery giving rise to the middle hepatic artery in 4-5%.**

## Portal Vein

**The main portal vein arises behind the pancreatic neck at the junction of the splenic and superior mesenteric veins. The main portal vein courses to the right and superiorly in the hepatoduodenal ligament, along with the hepatic artery and common bile duct, anterior to the foramen of Winslow. At the porta hepatis, the portal vein divides into right and left branches. The right branch of portal vein courses horizontally before bifurcating into anterior and posterior branches. The left branch of portal vein is shorter as it ascends anterior to caudate lobe before it courses ventrally to the left intersegmental fissure, where it divides into branches supplying the medial and lateral segments of the left hepatic lobe.**

## Hepatic Veins

**The hepatic veins lie in intersegmental & interlobar connective tissue. The right hepatic vein is usually the largest and courses obliquely between the anterior and posterior segments of the right lobe. The middle hepatic vein lies in between superior aspect of the right and left lobes. The left hepatic vein courses between the medial and lateral segments of the left lobe. All these veins course obliquely and superiorly and drain into the inferior vena cava, near its entrance into the right atrium. The right hepatic vein usually enters the inferior vena cava separately from the middle and left hepatic veins. The last two veins typically form a common trunk as they enter the**

**vena cava.**

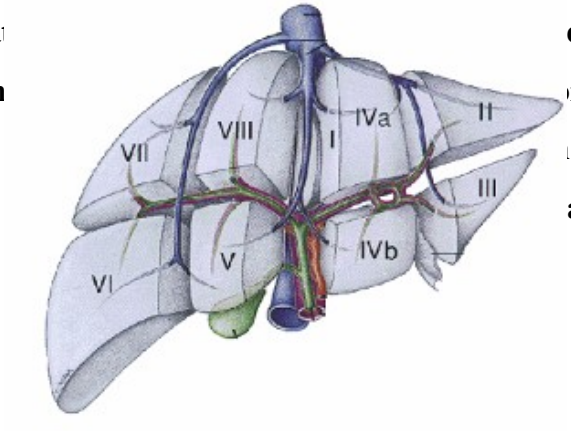
**Lobar and Segmental Anatomy**

**The segmental anatomy of the liver is eloquently depicts on cross-sectional imaging. Delineation of this anatomy is essential for the localization of focal hepatic pathology before surgical, angiographic or percutaneous intervention. Hepatic segmental topography is best appreciated radiologically by identification of the vascular and fissural anatomy. The portal venous, hepatic arterial and biliary radicles travel together within hepatic segments and lobes (intrasegmental). The main hepatic veins course between segments and lobes (intersegmental).**

**The right hepatic vein separates the posterior and anterior segments of the right lobe. The middle hepatic vein superiorly and the interlobar fissure inferiorly separate the right and left lobes of the liver. The medial and lateral segments of the left hepatic lobe are divided by three readily discernible structures: the ligamentum teres (inferiorly), the ascending portion of the left portal vein and the left hepatic vein (superiorly).**

**Advances in surgical techniques and percutaneous intervention have popularized the use of the subsegmental anatomic classification of Couinaud, with the modification of Bismuth and colleagues, to define intrahepatic location more precisely. In this system, the liver is divided into one segment and eight subsegments. Segment 1 is the caudate lobe. The well-known vertical divisions along the planes of hepatic veins are maintained, but each segment is further divided into superior and inferior subsegments by a transverse fissure (a plane through the right and left portal veins). The subsegments are numbered in a clockwise fashion when viewing the liver in the frontal projection except for segment 4a.**

**The caudate lobe is central hepatic lobe that has certain unique features. The anterior border of the cauda ent of the left lobe by the fissure for the ligamentum ven rtal vein resides at the apex of this fissure. Fat in this the fissure for ligamentum teres. Posteriorly caudate a. Inferiorly caudate lobe forms the**



**superior margin of foramen of Winslow.**

# HEPATOCELLULAR CARCINOMA

## EPIDEMIOLOGY

**HCC is the most common primary malignancy of the liver with a marked geographic variation .In terms of relative frequencies it ranks eighth in the world, seventh among men (5.6 % of all cancer deaths) and eleventh among women (2.7 % of all cancer deaths). In developing countries it is the third most common cancer among men after stomach and lung cancer. Largest concentration is found in Asia, especially in the coastal areas of South East Asia, China and Japan. Asia alone accounts for 70 % of all cases.**

It is common in South India. Male : Female ratio in India is 5-7:1[41]. Mortality / Incidence ratio reported by the cancer registries is close to 1 indicating that majority of cases do not survive beyond 1 year.

## PATHOLOGY

**Eggel classified HCC into three types.**

I. **Solitary massive**

II. **Multicentric small nodular**

III. **Diffuse infiltrating or cirrhotic form.**

**CLASSIFICATION BY HISTOLOGIC GRADES:**

**a) WELL DIFFERENTIATED HCC**

**These are characterized by irregular thin trabecular patterns and fatty change. The HCC cells lack distinct cellular and nuclear atypia .Its common among HCCs < 2cms in diameter. It corresponds to grade I carcinoma of Edmonston – Steiner classification.**

**b) MODERATELY DIFFERENTIATED HCC**

**Classic trabecular pattern with tumor cells arranged in several layers and pseudoglandular patterns seen. This corresponds to grade II and III of the Edmonston –Steiner classification and is most common among advanced HCCs.**

**C) POORLY DIFFERENTIATED HCC**

**These tumors show a compact solid growth pattern, loss of trabecular pattern increased nuclear cytoplasmic ratio and frequently show pleomorphism. Corresponds to Grade III and IV of Edmonston – Steiner classification.**

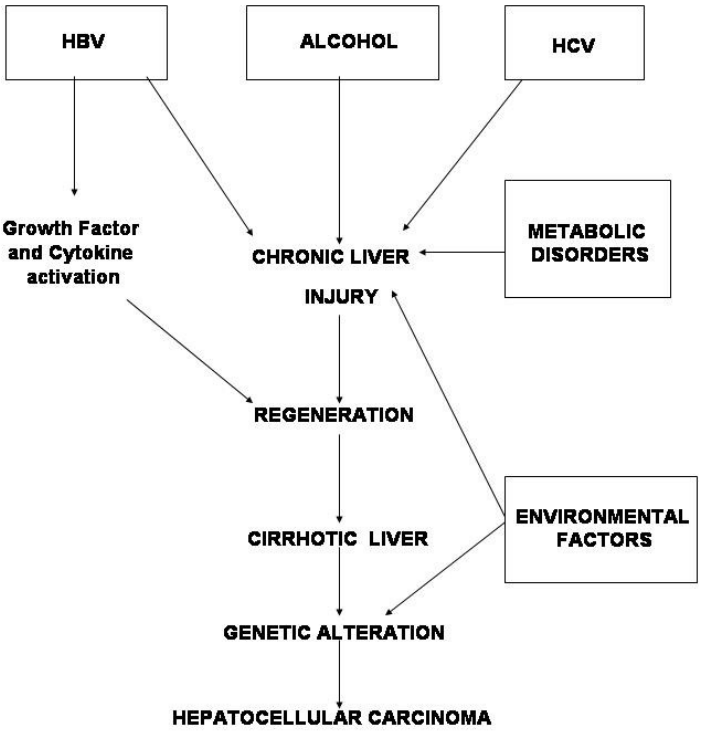
**d) UNDIFFERENTIATED CARCINOMA**

**The tumor cells have scant cytoplasm with short spindle shaped or round nuclei, and proliferate in a solid or medullary pattern. This Corresponds to Stage IV of Edmonston – Steiner classification.**

**Based on histologic features, the World Health Organization has classified HCC as trabecular, acinar, compact and scirrhous types.**

**Etiologic factors involved in pathogenesis**

**of Hepatocellular Carcinoma**[35]




## CLINICAL FEATURES

**HCC is clinically silent in its early stages and the onset of symptoms is usually insidious. HCC developing in a liver without underlying chronic liver disease can grow to an enormous size, whereas HCC in a markedly shrunken cirrhotic liver has no time to grow larger before the patient dies from hepatic failure.**

**Patients present with**

1. **Dull abdominal pain.**
2. **Malaise.**
3. **Anorexia.**
4. **Loss of weight, which is more common in HCC without cirrhosis**

   **Weight loss greater than 25 % carries a poor prognosis.**
5. **Ascites – occurs in over half of cases and indicates a poor prognosis.**
6. **Palpable mass.**
7. **Jaundice is usually a late manifestation and it can be obstructive jaundice due to tumor extending into bile duct or due to lymph node causing obstruction of a major duct or hepatocellular jaundice due to hepatic failure.**
8. **Bone pain.**

**Berman described five patterns of clinical presentation**

A. **Frank cancer.**
B. **Occult cancer.**
C. **Acute abdominal Cancer.**
D. **Febrile Cancer.**
E. **Metastatic Cancer.**

   A. **Frank cancer 63 % - Signs and symptoms are referred to liver in patients with previously good health. Clinical presentations are asthenia, loss of weight,**

**abdominal pain, tender enlarged liver and jaundice. This was common in Japan before early detection by screening was introduced.**

**B. Occult cancer 16 % -HCC was found during examination for complaints other than those attributable to liver.**

**C. Acute abdominal cancer 8 % - Most patients were in good health and suddenly developed features of an acute abdomen. Abdominal muscular exertion or forceful palpation would occasionally precipitate rupture of a superficial tumor nodule. Hepatic arteriography will demonstrate the bleeding artery and it should be embolised. Immediate surgery results in 18 % survival rate, otherwise the outcome of acute bleeding of HCC is often fatal.**

**D. Febrile Cancer 8 % - The clinical picture is that of an enlarged liver abscess. A nodular abdominal mass with a tendency to central necrosis is noted. This form is usually of a poorly differentiated HCC with sarcomatoid feature. It is most common in Africans.**

**E. Metastatic cancer – 5% , The symptoms due to metastases in remote organs completely over shadow those of the primary lesion and may be the only manifestation of an otherwise unsuspected HCC . Dissemination to lungs in early stages mimics tuberculosis, but there is a heavier distribution in lower zones.**

**HCC can be staged by using the Okuda staging system** [35.]

**OKUDA STAGING SYSTEM FOR HCC RELATE TO SURVIVAL AFTER TREATMENT**

| | | | |
|---|---|---|---|
| **1.** | **Tumor hepatic replacement** | **>50%**<br>**< 50 %** | +<br>_ |
| **2.** | **Ascites** | **Present**<br>**Absent** | +<br>_ |
| **3.** | **Albumin** | **< 3 g/dl**<br>**> 3 g/dl** | +<br>_ |
| **4.** | **Bilirubin** | **>3 mg/dl**<br>**< 3 mg/dl** | +<br>_ |

| | | | |
|---|---|---|---|
| | | | **Median survival** |
| **Stage I** | **All negative** | **Not advanced** | **8.3 Months** |
| **Stage II** | **1 or 2 +** | **Moderately advanced** | **2 Months** |
| **Stage III** | **3 or 4 +** | **Very advanced** | **0.7 Months** |
| | | **Overall Median survival** | **1.6 Months** |

**Because most patients with HCC have underlying cirrhosis, it is important to use clinical criteria to classify the severity of cirrhosis, which has a considerable bearing on therapeutic decisions. The Child classification system is usually used to stage cirrhosis into group A, group B, or group C.**

## MODIFIED CHILD PUGH CLASSIFICATION FOR LIVER FUNCTIONAL STATUS

| Parameter | Score | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Bilirubin (mg/dl) | < 2.0 | 2.0 – 3.0 | > 3.0 |
| Albumin (g/dl) | > 3.5 | 2.8_ 3.5 | < 2.8 |
| Ascites | None | minimal | Moderate to severe |
| Encephalopathy | None | mild | Moderate to severe |
| Prothrombin time[seconds increased] | 1-3 | 4-6 | >6 |

| Total numerical score | Child Pugh class |
|---|---|
| 5-6 | A |
| 7-9 | B |
| 10-15 | C |

**Child Pugh group A disease has the best prognosis, and Child Pugh group C has the worst prognosis.**

## TNM CLASSIFICATION

**Tx - Primary tumor cannot be assessed.**

**To - No evidence of primary tumor .**

**T1 - Solitary, less than 2 cms, without vascular invasion.**

**T2 - Solitary, less than 2 cms, with vascular invasion.**

**Multiple, single lobe involved, without vascular invasion.**

**Solitary, more than 2cms, without vascular invasion.**

**T3 - Solitary, more than 2 cms, with vascular invasion.**

**Multiple, single lobe less than 2cms, with vascular invasion.**

**Multiple, single lobe, 2cms.**

**T4 - Multiple, more than one lobe.**

**Invasion of major branch of portal or hepatic vein.**

**N0 - No nodal involvement**

**N1 - Presence of regional nodal involvement**

**M0 - Indicates no distant metastasis**

**M1 - Indicates metastasis present beyond the liver**

## STAGING

| | | | |
|---|---|---|---|
| **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** | **N 0/N1** | **M 0** |
| **Stage IV a** | **T 4** | **N 1** | **M 0** |
| **Stage IV b** | **Any T** | **N 1** | **M 1** |

## LABORATORY INVESTIGATIONS

**Abnormal LFT with raised SGOT, SGPT, alkaline phosphatase, decreased albumin with the exception of bilirubin level corresponds to the severity of cirrhosis . Alpha-fetoprotein (AFP) is elevated in 75% of cases. The level of elevation correlates inversely with prognosis. An elevation of greater than 400 ng/mL predicts HCC with specificity greater than 95%. In the setting of a growing mass, cirrhosis, and the absence of acute hepatitis, many centers use a level greater than 1000 ng/mL as presumptive evidence of HCC (without biopsy).**

## IMAGING :

**The role of imaging INCLUDES screening, diagnosis, staging, interventional therapy and post operative follow up.**

**Diagnostic imaging depicts not only the primary hepatic disease but also ascites, lymph node metastases, and thrombosis of portal and or hepatic veins.**

**Morphologic features that are characteristic of HCC include the tumor capsule, internal mosaic pattern, venous invasion, fatty metamorphosis and occurrence within a cirrhotic liver. Presence of capsule carries a better prognosis, as the tumors are amenable to surgical resection and also respond better to trans arterial chemo-embolization. The extent of tumor in relation to segmental anatomy and to surgically critical structures like IVC, major bile ducts and portal vein should be assessed.**

**Plain Radiograph: Plain films are nonspecific but may show a mass in the upper abdomen if the HCC is large. Rarely calcifications can be detected in HCC.**

### Ultrasonogram (USG) :

**Ultrasonogram is the most commonly used screening method as it is cheap, widely available and non-invasive. Sensitivity ranges from 84 to 91 %., with most missed lesions being under 2 cms in diameter. Intraoperative ultrasound has 96 % sensitivity. Ultrasonography can detect extremely small tumors and when combined with serum alpha-fetoprotein assays, serves as an excellent screening method for high risk patients with long standing cirrhosis. Sonography, in conjunction with colour and duplex Doppler, is an excellent tool for diagnosing tumor thrombus in the portal and hepatic veins as well as the inferior vena cava.**

**The most common finding is a discrete lesion of uniform echogenicity, usually hypoechoic or isoechoic and detected by the hypoechoic halo corresponding to the tumor capsule, mosaic**

**pattern, septum formation and posterior echo enhancement also occur. Lesions less than 3 cms are usually hypoechoic.**

**In tumors with diffuse pattern, disorganization of normal echo pattern with multiple areas of increased and decreased echogenicity are seen throughout the distorted liver without distinct margins.**

**Hypoechoic lesion corresponds to a solid tumor without necrosis. Lesions with a mixed pattern are partially necrotic. Hyperechoic lesion is caused by fatty metamorphosis or severe sinusoidal dilatation .Fibrous septa and scars appear as hypoechoic linear structures. Ultrasonic documentation of venous involvement favors HCC over metastases.**

DOPPLER:

**Colour Doppler ultrasound has been used to assess the vascularity of HCC because HCC tumour nodules are supplied by hepatic artery. Lesions show both intratumoral and peritumoral flow. A basket pattern (a fine blood flow network surrounding the tumour nodule) was observed in HCC. In lesions less than 2 cms it is difficult to detect the flow pattern. In lesions >2 cms, intralesional pulsatile flow with peak systolic velocity (PSV) more than 40 cms/s with relatively normal hepatic artery flow is strongly suggestive of HCC.. Arterial branches supplying HCCs tend to show an irregularly tortuous course, and the tumour vessels have widened, sclerosed lumina and shows increased PSV. Demonstration of hepatofugal flow and arterial flow within the thrombus by Doppler indicates a tumor thrombus.**

**COMPUTED TOMOGRAPHY:**

**Proper technical performance of CT with imaging in the hepatic-arterial, portal-venous phases and delayed-contrast phases are important in detecting HCC. CT appearance of HCC varies depending on the tumor size and the imaging phase. The most common attenuation pattern is iso-hyper-isoattenuation on pre-, arterial, and venous phases, respectively. In the**

**hepatic-arterial phase, lesions typically are hyperdense (relative to hepatic parenchyma) as a result of hepatic-arterial supply. In the portal-venous phase, small lesions may be isodense or hypodense and difficult to see, since the remainder of the liver also increases in attenuation. Larger lesions with necrotic regions remain hypodense. In the delayed-post contrast phase, small lesions may be inconspicuous. Delayed phase scans may show a tumor capsule, one of the more specific signs indicating HCC.**

**Tumor thrombus in Portal vein and IVC is readily depicted but subsequent invasion through the vessel wall cannot be predicted. Dynamic CT can demonstrate parallel thin neovasculature along the vessel in tumor thrombus.**

**Endovenous tumor is persistently radiolucent, although arterial phase enhancement may occur as a result of tumor vascularity. Frequently there is linear periportal arterial phase hypervascularity (TRAM – TRACK PATTERN) on contrast enhancement. Other signs of portal vein occlusion are straight line sign, and transient hepatic attenuation defects.**

CT ARTERIOGRAPHY: (CTA)

**It maximizes the principle of arterial phase contrast imaging. In patients with cirrhosis, CTA detects substantially more HCC nodules than helical arterial phase CT. Early and rapid tumor enhancement is directly related to angiogenesis .Increased microvessel density has been shown to correlate with poor prognosis, with higher rates of metastases and poor patient survival.**

CT–ARTERIAL PORTOGRAPHY: (CTAP)

**It is a sensitive technique for detection of HCC and metastases in non-cirrhotic patients. Contrast medium is selectively injected into SMA. This technique enhances normal parenchyma maximally while neoplasms supplied by the hepatic artery are enhanced minimally. Lesion as small as 0.5 cms can be detected .With severe cirrhosis and altered portal venous blood flow CT–AP either fails to opacify the liver or results in too many " pseudo-lesions" to be of clinical use .**

LIPIODOL CT SCAN:

**It can detect HCCs as small as 3.7 mm in diameter and this technique is predominantly used in Japan where it has been reported to be approximately as sensitive as CT-AP. About 4 to 10 ml of lipiodol is injected into the hepatic artery and CT is done 7 – 14 days later. It is retained by HCC and hypervascular metastases. Retention is due to the absence of kuppfer cells &lymphatics, hypervascularity and alteration in the sinusoidal spaces in HCC. Tumor vessels allow passage of substances with large molecules like macromolecular lipiodol than the vessels in normal tissue. Retention makes the nodules an excellent target for biopsy under CT guidance.**

ANGIOGRAPHY:

**Angiography is a useful tool in delineation of arterial anatomy before surgery and in therapeutic applications like embolization and delivery of chemotherapeutic agents.**

**Angiography shows a hypervascular mass with neovascularity, enlarged tortuous feeding arteries, early draining vein and a marked tumor blush due to delayed clearance. Arterio-venous shunting causes early opacification of portal or hepatic veins .Tumor thrombus is directly demonstrated by a parallel thin neovasculature along the vessels (Thread and streaks sign) and indirectly as filling defect in the vessels. Small HCCs less than 2 cms are often hypovascular and may not be detectable by angiography.**

**MRI:**

**HCC appearance varies on MRI depending on the multiple factors, such as hemorrhage, degree of fibrosis, histologic pattern, degree of necrosis, and the amount of fatty change. HCC on T1-weighted images may be isointense, hypointense, or hyperintense relative to the liver. On T2-weighted images, HCCs usually are hyperintense. Pre and postcontrast MRI have a 70-85% chance of detecting a solitary mass of HCC. MRI can help differentiate cirrhotic nodules from HCC. Gadolinium-enhanced MRI typically demonstrates that HCCs densely enhance, usually in**

**the arterial phase and particularly if they are small. Visualization of the capsule (RIM SIGN) is characteristic of HCC .Capsule usually appears as a low intensity ring on T1W images or as an internal low intensity and external high intense ring on T2W images.**

**Gradient echo sequences are quite sensitive to changes in blood flow patterns and can identify tumor thrombus within IVC and portal vein.**

**MRI can differentiate a large regenerating nodule from a small HCC as the former is hypointense or isointense on T2W images.**

**In the diffuse infiltrative form, the disease is more evident in T2W images .A nodule within nodule appearance suggests early HCC in a cirrhotic liver .MRI seems to be slightly superior than contrast enhanced CT in detection of lesions 2 cms or less in size. Contrast enhancement and increased signal on T2W images are the imaging correlates of the increased microvascular density and vascular permeability that occurs with angiogenesis.**

## NUCLEAR MEDICINE:

**HCCs are usually depicted as a photopenic region on sulphur colloid scintigraphy. 70-90% of HCCs are gallium avid and moderately well differentiated tumors show the strongest uptake. 99m Tc labeled macro aggregated albumin injected into hepatic artery demonstrates lesions as small as 5mm.**

## TREATMENT

**In the presence of extra hepatic metastasis, intra arterial chemotherapy is indicated with no significant improvement in the survival. Hepatic resection is the treatment of choice when the tumor is smaller (<3 cms), < 3 in number, confined to one lobe, without involvement of hepatic vein and portal vein. Hepatic transplantation is superior to hepatic resection, but the option is not easily available.**

**When the tumor is not surgically resectable, loco regional therapies play a major role. Locoregional therapies like PEI / RFA or TACE should be carried out, depending on the tumor size and numbers.**

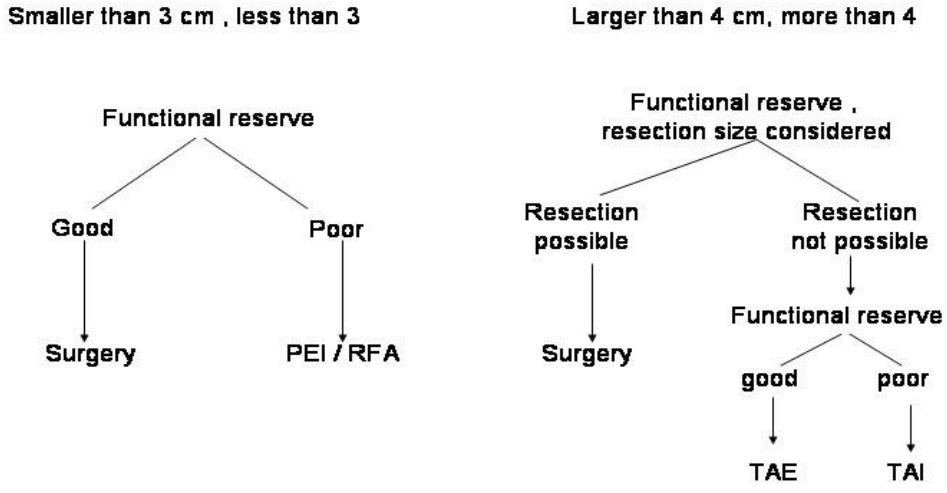
**If the tumors are large( > 4cm)or more than 4 lesions or if the resection is not possible, and if the functional reserve of the patients is good as indicated by Child Pugh criteria, Trans arterial chemo embolization is the treatment of choice.**

**If the lesion is smaller than 3cm and less than 3 in number with very poor functional reserve, PEI/ RFA are the only available options using chemical or physical destruction. RFA is more efficient than PEI.**

**Loaded Embols , These are recently introduced therapeutic materials, that are used in the same principle of chemo embolization.. The materials used are glass spheres loaded with yttrium_199 or gelatin spheres loaded with doxorubicin.**

**Lastly 131 iodine – labeled lipiodol can be injected intra arterially for nonresectable HCC with portal vein thrombosis. It is also useful to lower recurrence after surgical resection.**

## TREATMENT PROTOCOLS[42]




PROGNOSIS:

**Prognosis is correlated well with the stage of the disease and Child's score. Serum bilirubin >2mg/dl and weight loss greater than 25% of body weight are the poorest prognostic factors. Other factors of predictive value include serum AFP values, IVC or portal vein invasion**

**and presence of metastases.**

**Patients with advanced HCC live for an average of only one month from diagnosis .Okuda and associates reported that the median survival of patients with HCC who do not receive specific therapy was only 1.6 months. If limited to favorable conditions like Okuda stage I the median survival rate was 8.3 months[35].**

# TRANSARTERIAL CHEMOEMBOLIZATION

**HCC is multifocal in 76% of patients, most of whom (81-87%) have underlying cirrhosis. The percentage of patients who are candidates for surgical treatment is 3-30%, depending on the series. Patients with small, uni nodular or binodular tumors smaller than 3 cm have the best outcome. For patients undergoing hepatic transplantation, the 3-year survival rate without recurrence is 83%. The results of hepatic resection are poor.**

**Effective chemoembolization of the liver is possible because of the following factors[40].**

1. **The liver has a unique pattern of blood supply. The portal vein supplies 75% of the hepatic blood flow, while the hepatic artery supplies the remaining 25%. This backup blood supply allows the occlusion of either vessel without resultant liver infarction.**

2. **95% of the blood for both primary and metastatic hepatic tumors is derived from the hepatic artery.**

3. **The development of catheter technology allows the super selective placement of catheters for the safe and effective delivery of therapeutic agents to hepatic tumors. Microcatheters can be safely placed, even in the presence of aberrant vessels or a collateral blood supply.**

4. **When iodized poppy seed oil is injected into the hepatic artery, it remains preferentially in the neovascularity of HCC. Therefore, a vehicle exists for delivering cytotoxic agents to tumor sites in the liver. Oily contrast droplets when released in hepatic artery selectively go into the largest arteries without entering the smaller one due to tensioactive forces.**

5. **Water in oil emulsion that is chemotherapeutic drugs contained in oily contrast lipiodol, selectively enters in to the larger tumor vessel and then releases the chemotherapeutic agents into the tumor tissue.**

6. **Lipiodol is responsible for temporary embolization of the arteries and of the portal system, which it reaches through the peribiliary anastomosis, thus increases the dwell time between drug and tumor.**

7. **Embolization after chemo-lipiodol increases the efficacy of chemotherapeutic agents by providing additional ischemia to the highly hypervascularized tumor. This causes failure of transmembrane pumps, thus increasing the retention of the drugs inside the cells.**

8. **Normally Kupffer cells in liver actively capture and phagocytose iodized oil droplets in hepatic sinusoids. Since there is absence of kupffer cells in hepatoma lipiodol is retained in the hepatoma for long time.**

**Chemolipiodol embolization and gelfoam embolization are done separately because chemolipiodol particles has to go into the tumor and from the peribiliary capillaries goes retrogradely into the portal radicles causing the portal radicular occlusion. If gelfoam powder goes into the peribiliary plexus it causes biliary necrosis.**

**A further benefit is gained by regional arterial treatment, which results in lower systemic drug levels, thus reducing systemic toxicity.**

**<u>In our study TACE was done using the following methods</u>**

**A protocol based on the technique used by Bismuth et al is used.**

**Child group A or B disease are considered No extrahepatic disease should be demonstrable.**

**Preparation:**

**All patients were given inj vitamin K 1 amp i.m one day prior to the procedure. The patient receives nothing by mouth beginning midnight before the procedure.**

**Pre medication :**

**Inj Atropine**

**Inj Chlorpheniramine maleate**

**Antibiotics prophylaxis :**

**Inj Cefotaxime 1 g iv bd**

**Inj Metronidazole 500mg iv bd started one day prior to procedure**

**Sedation/ anesthesia :**

**Oral Lorazepam is used as premedication to counter anxiety. It is given one hour prior to the procedure. Local anesthesia - xylocaine 2%.**

**The intra-arterial injection of 30-40 mg of 1% lidocaine is used for analgesia and given in the selective hepatic artery directed at embolization site to prevent immediate pain syndrome.**

**Patient positioning**

**Supine**

**Approach**

**Percutaneous trans femoral**

**Technique**

**Seldinger technique femoral puncture**

## Procedure

**Angiography is an essential part of the workup performed prior to embolization or chemoembolization. After the arterial sheath catheter introduction, a celiac-axis and superior mesenteric angiogram is first obtained to identify common variations in the blood supply to the liver and to check for patency of the portal vein using 5-6F curved catheter (cobra). Selective cannulation of right / left hepatic artery is then done.. Position of the cystic artery and gastroduodenal arteries are noted to avoid their embolization. Otherwise chemical duodenitis, chemical cholecystitis can occur. Catheter is advanced as close to the tumor as possible, if not it is advanced up to the segmental level hepatic artery branches. Even if this is not possible due to lack of micro catheters then the main catheter is advanced into the right main hepatic artery distal to cystic artery origin or into the left hepatic artery.**

**Chemotherapeutic emulsions are released into the feeding vessels i.e. segmental or right main or left main artery depending upon the catheter placement.**

**After the release of chemotherapeutic agents embolization is done separately using the gel foam pledgets. After the procedure, catheter is removed and the puncture site is compressed and dressed after attaining hemostasis.**

## Post procedural follow up

**All the patients were followed up as inpatients and IV antibiotics continued for 3 days. Patients are discharged on fourth day if there is no serious complication.**

## Chemo embolizing material :

**Chemo therapeutic agents : Cisplatin (alkylating agents) 20mg/$m^2$**

**Adriamycin (anti tumor antibiotic) 20mg/$m^2$**

**Vehicle medium : Omnipaque 300mg ( 5 ml)**

**Lipiodol (8 -10ml )**

## Emulsion preparation:

**Both adriamycin powder and cisplatin are mixed with water soluble contrast medium (omnipaque). This mixture is mixed with lipiodol by alternate filling and emptying using three way stopcock with two syringes.**

## Embolising material

**Gelfoam, a water insoluble temporary haemostatic material prepared from purified skin gelatin (a non antigenic carbohydrate), is frequently used as a biodegradable, intravascular embolic agent. Correll and Wise were the first to report the haemostatic properties of Gelfoam. Histologically , Gelfoam initiates an acute full thickness necrotizing arteritis of the arterial wall and leads to thrombus formation. Gelfoam is currently available in a sheet from which sections of various size can be cut. Gelfoam, like polyvinyl alcohol, is not radio opaque and is typically mixed with iodinated contrast material before injection. The small size of the particles in gelfoam powder increases the risk of ischemia caused by the distal artery occlusion, eventually leading to biliary necrosis. So it is now recommended that gelfoam powder should not be used.**

**Pledgets cut from a sheet of gelfoam are typically larger and result in a more proximal occlusion. An additional technique is to create gelfoam slurry by mixing pledgets between two syringes via a three-way stopcock. This method will decrease the size of the injected gelfoam and allow a more distal delivery than that achieved with pledgets. The arterial occlusion induced by gelfoam is often recanalized with in weeks to months of the embolization procedure. Poly vinyl alcohol particles can be used. They cause permanent occlusion of vessels.**

## Complications:

**Embolization of solid organs causes a self-limited postembolization syndrome in the**

**majority of patients, consisting of varying degrees of pain, nausea, vomiting, and fever. This is independent of chemotherapeutic drug used, reason for embolization (eg, bleeding, tumor), and the organ treated (eg, liver, kidney, spleen, uterus). With current medical care (eg, hydration, antiemetic therapy, and pain control), postembolization syndrome is well tolerated.**

**Liver function is transiently affected with an increase in liver aminotransferase levels. These values usually peak 3–5 days after therapy and return to baseline levels by 10–14 days after embolization. There is no sustained degradation of liver function in properly selected patients. Because most of the injected drug is retained in the liver, systemic toxicity is minimized, with little bone marrow suppression. Serious adverse events occur after approximately 5% of chemoembolization procedures. The most common serious adverse events are liver abscess or liver infarction, which occur in approximately 2% of cases each. The 30-day mortality rate is 1%.**

**The major complications as noted by Sakamoto et al in 2300 patients in 1998 are, Acute hepatic failure (0.26%), Liver abscess (0.22%), Intrahepatic biloma (0.87%), Hepatic infarction (0.17%), Multiple intrahepatic aneurysms (0.26%), Cholecystitis/gallbladder infarction (0.30%), Splenic infarction (0.08%) Gastrointestinal mucosal lesion (0.22%),Pulmonary embolism/infarction (0.17%), Tumor rupture (0.04%).**

## Comparison of TACE with other techniques

## Percutaneous ethanol instillation (PEI)

**It is usually performed in patients with cirrhosis and HCC. Candidates for ethanol ablation must have tumors with a volume less than 30% of the total volume of the liver. Contraindications for this procedure include portal vein thrombosis, extrahepatic disease, Child group C, a prothrombin time more than 40% increase, and a platelet count less than 40,000/$mm^3$.PEI is inexpensive, easy to perform, and repeatable. Long-term results of PEI and surgery in the treatment of small-to-medium sized HCCs are comparable.**

**In multiple HCCs, ethanol is less toxic than chemoembolization. PEI is currently considered a reliable alternative to surgery in the management of limited-stage cancer, but unlike TACE, it is not suitable for multifocal advanced disease. Unlike with TACE, necrosis of the capsule and perineoplastic tissue have occurred with PEI.**

**Shiina and Niwa described survival rates with a potentially curable HCC treated with PEI in 131 patients at 1&2 years as 87%&70% respectively.**

## Radiofrequency Ablation

**It is suitable for patients with 4 or fewer primary or metastatic liver tumors 5 cm or smaller. The tumors should be completely surrounded by liver parenchyma, they should be at least 1 cm deep to the liver capsule, and they should be at least 2 cm or more away from major intrahepatic portal and hepatic veins. Subcapsular tumors can be ablated, but in this situation, the procedure causes more pain. RF ablation performed in tumors near the porta hepatis poses an increased risk of injury to the bile ducts and portal vein and it is generally more painful. Patients with sepsis, severe debility, and coagulopathy usually cannot be treated by using RF ablation.**

**In a prospective study of small HCCs, Livraghi and associates have shown that the rate of complete ablation was 10% higher with RF ablation than with ethanol ablation. Unlike ethanol ablation, RF ablation appears to be effective in treating both HCCs and liver metastases. RF ablation is less toxic than agents used in TACE and it is better controlled. The main disadvantage of RF ablation is the difficulty in heating normal liver tissue, and hence, tumors have a higher recurrence rate than desired.**

***Bartolozzi et al*** **noted, when combining TACE and PEI, the overall survival rates at 1, 2years were 92%, 83% respectively. These figures appear to be more positive than the results achieved with TACE or PEI alone.**

## Chemoembolization as a bridge to transplantation:

**The prevention of progression of the HCC until a donor liver becomes available is in the patient's best interest. Chemoembolization plays a critical role in permitting eventual cure in this patient subset by inhibiting tumor growth so that patients can remain on the transplant list.**

# MATERIALS AND METHODS

**This prospective study was done in Barnard Institute of Radiology during the period, Dec 2003 to Dec 2005. The patients were referred from various Government medical colleges in Chennai.**

**Forty two patients in the age group of 35 to 73 years who either refused to undergo surgery or were denied surgery due to poor general condition or due to contra-indications irrespective of portal vein involvement were chosen. Of these forty two patients, 16 patients underwent TACE and the remaining 26 patients were treated conservatively. Both these groups were selected in a nonrandomized manner.**

## Criteria for Inclusion were

**Mass more than 4 cm size**

**More than 4 lesions**

**Childs Pugh A, B**

## Criteria for Exclusion were

**Childs Pugh C**

**Extra hepatic metastasis**

**The diagnosis of HCC was established with USG guided biopsy and in some cases combining classical imaging finding with alpha protein level more than 1000 ng/ml.**

**All forty two patients underwent pretreatment ultrasound, duplex, dual phase CT to know the tumor size, extension, portal vein involvement & hepatic vein involvement.**

**Other parameters necessary for Child Pugh criteria, that is presence of ascites, bilirubin level, prothrombin level, albumin level, encephalopathy status are also noted. Cardiac profile was**

**done in all patients.**

**After selecting the patient, all the sixteen patients in the interventional group underwent trans arterial chemo embolisation with cisplatin , adriamycin, lipiodol & gelfoam. Angiography and embolization was performed using a 800MA conventional angiographic unit (siemens). 26 patients in the conservative group were given symptomatic therapy including intra venous chemotherapy. In those patients with main portal vein involvement (n=3) TACE was done with out adding gelfoam (chemo lipiodolization) Repeat TACE was done in patients with no adverse reaction to prior TACE.**

**All the patients were admitted one day prior to the procedure and discharged 3 days after the procedure. All the patients were followed up for 12 months.**

**Many of the patients presented with severe upper abdominal pain. In all patients pain intensity was classified by visual analogue scale using 0- 10 criteria starting from least possible pain to worst possible pain.**

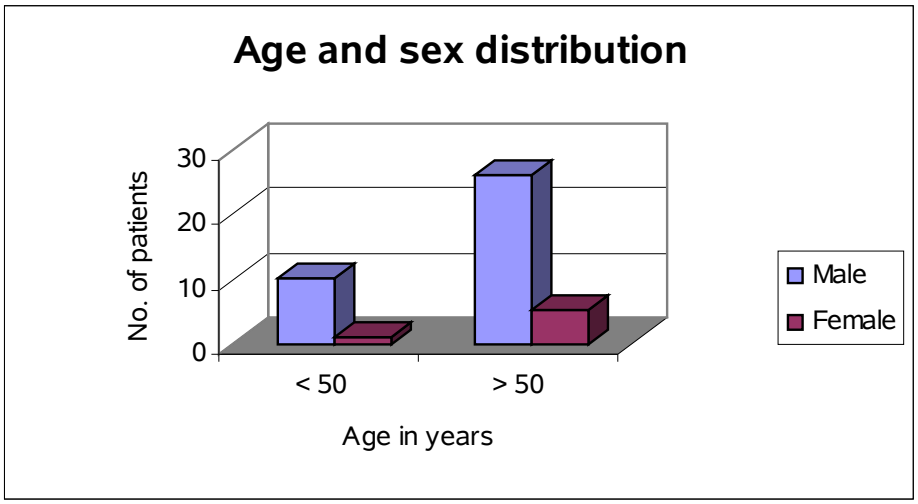
**Performance status of the patients were scored using performance status scale by ECOG. Visual analogue scale and performance status score were noted in all the patients both pre procedurally and post procedurally after one month. Contrast enhanced CT and USG with Duplex sonography were done one month after treatment to asses the tumor size and lipiodol retention. Change in tumor size in single long axis ( RECIST )was taken as a measure of response to treatment in contrast enhanced CT as noted by Therasse p et al was taken .**

# RESULTS AND ANALYSIS

## TABLE 1

## SEX DISTRIBUTION

| SEX | Treatment | | | | Total | |
|---|---|---|---|---|---|---|
| | TACE | | Symptomatic | | | |
| | Count | % | Count | % | Count | % |
| Male | 14 | 87.5 | 22 | 84.6 | 36 | 85.7 |
| Female | 2 | 12.5 | 4 | 15.4 | 6 | 14.3 |
| Total | 16 | 100.0 | 26 | 100.0 | 42 | 100.0 |



## TABLE 2

## AGE WISE DISTRIBUTION

| Age | Treatment | | | | Total | |
|---|---|---|---|---|---|---|
| | TACE | | Symptomatic | | | |
| | Count | % | Count | % | Count | % |
| 30 - 40 | 1 | 6.3 | 0 | 0.0 | 1 | 2.4 |
| 40 - 50 | 5 | 31.3 | 5 | 19.2 | 10 | 23.8 |
| 50 - 60 | 8 | 50.0 | 11 | 42.3 | 19 | 45.2 |
| 60 - 70 | 2 | 12.5 | 9 | 34.6 | 11 | 26.2 |
| 70 - 80 | 0 | 0.0 | 1 | 3.8 | 1 | 2.4 |
| Total | 16 | 100.0 | 26 | 100.0 | 42 | 100.0 |

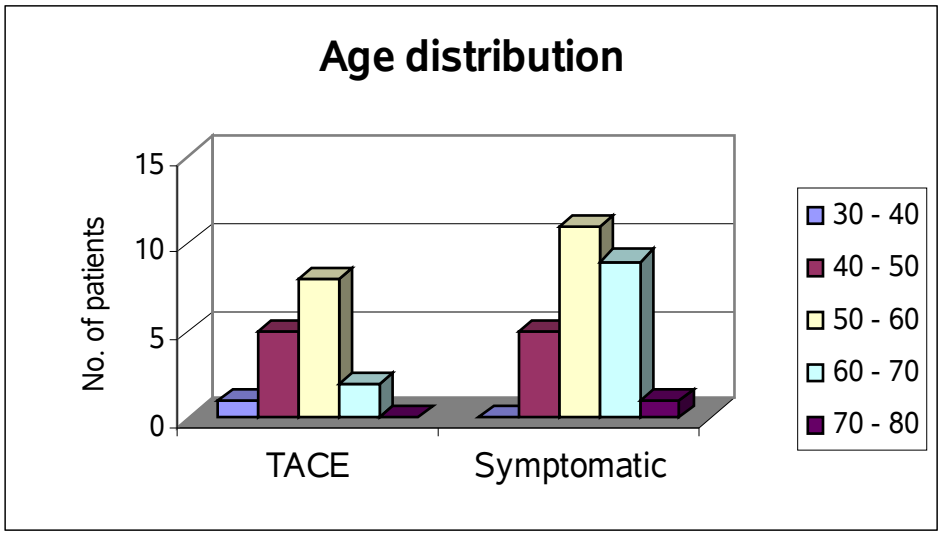
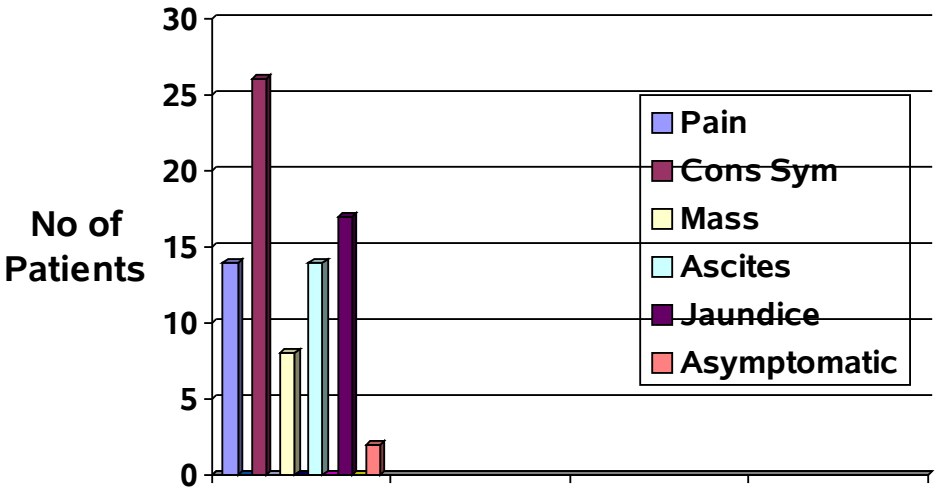


**TABLE 3**

| CLINICAL FEATURES | | |
|---|---|---|
| Upper abdominal Pain | 14 | 33% |
| Constitutional Symptoms | 26 | 62% |
| Palpable mass | 8 | 19% |
| Ascites | 14 | 33% |
| Jaundice | 17 | 40% |
| Asymptomatic | 2 | 5% |



## TABLE 4

## PORTAL VEIN INVOLVEMENT

| | Treatment | | | | Total | |
|---|---|---|---|---|---|---|
| | TACE | | Symptomatic | | | |
| Portal Vein status | Count | % | Count | % | Count | % |
| Normal | 9 | 56.3 | 9 | 34.6 | 18 | 42.9 |
| Branch vein | 4 | 25.0 | 9 | 34.6 | 13 | 31.0 |
| Main portal vein | 3 | 18.8 | 8 | 30.8 | 11 | 26.2 |
| Total | 16 | 100.0 | 26 | 100.0 | 42 | 100.0 |

## TABLE 5

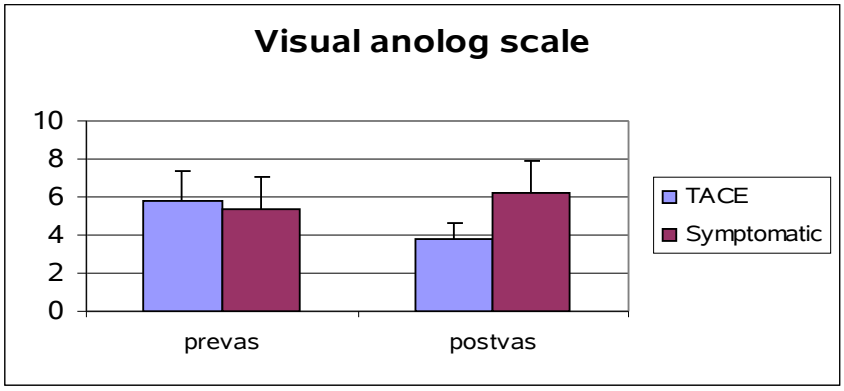
## CHILD PUGH CRITERIA DISTRIBUTION

| CHILD PUGH criteria | Treatment | | | | Total | |
|---|---|---|---|---|---|---|
| | TACE | | Symptomatic | | | |
| | Count | % | Count | % | Count | % |
| A | 10 | 62.5 | 10 | 38.5 | 20 | 47.6 |
| B | 6 | 37.5 | 16 | 61.5 | 22 | 52.4 |
| Total | 16 | 100.0 | 26 | 100.0 | 42 | 100.0 |

## TABLE 6

## COMPARISON OF VAS & PSS BEFORE AND AFTER TREATMENT

| | TACE | | | Symptomatic | | | t | df | p value |
|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | S D | N | Mean | S D | | | |
| Pre VAS | 16 | 5.81 | 1.52 | 26 | 5.38 | 1.65 | 0.84 | 40 | 0.405 |
| Pre PSS | 16 | 2.00 | 0.63 | 26 | 2.54 | 1.03 | -1.88 | 40 | 0.067 |
| Post VAS | 16 | 3.81 | 0.83 | 23 | 6.22 | 1.70 | -5.21 | 37 | 0.000 |
| Post PSS | 16 | 1.94 | 0.57 | 23 | 2.83 | 0.83 | -3.69 | 37 | 0.001 |




## TABLE 7

## TUMOR SIZE REDUCTION 1 MONTH AFTER THERAPY

| | Treatment | | | | Total | |
|---|---|---|---|---|---|---|
| | TACE | | Symptomatic | | | |
| Tumor Size | Count | % | Count | % | Count | % |
| No change | 7 | 43.8 | 8 | 34.8 | 15 | 38.5 |
| Reduced | 9 | 56.3 | 0 | 0.0 | 9 | 23.1 |
| Increased | 0 | 0.0 | 15 | 65.2 | 15 | 38.5 |
| Total | 16 | 100.0 | 23 | 100.0 | 39 | 100.0 |

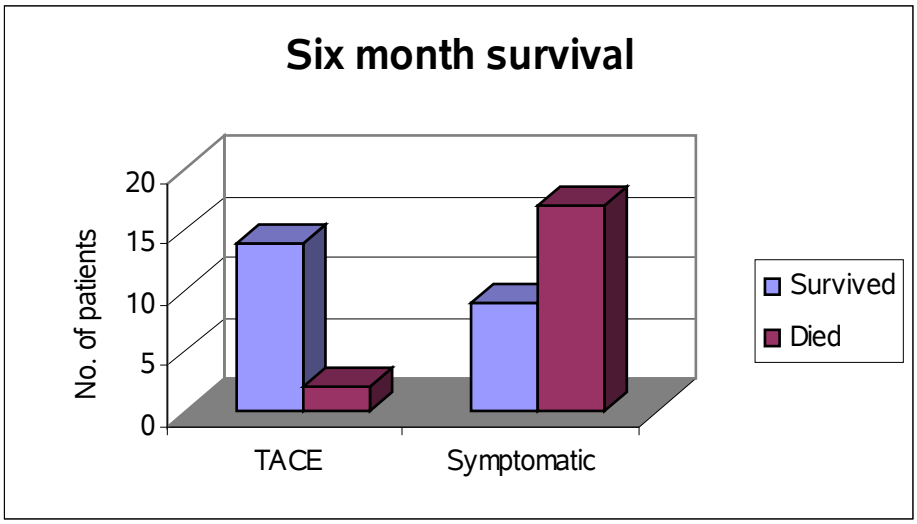
$p < 0.001$

## TABLE 8

## 6 MONTH FOLLOW UP SURVIVAL

| Follow up 6 months | Treatment | | | | Total | |
|---|---|---|---|---|---|---|
| | TACE | | Symptomatic | | | |
| | Count | % | Count | % | Count | % |
| Survived | 14 | 87.5 | 9 | 34.6 | 23 | 54.8 |
| Died | 2 | 12.5 | 17 | 65.4 | 19 | 45.2 |
| Total | 16 | 100.0 | 26 | 100.0 | 42 | 100.0 |

$p < 0.01$



## TABLE 9

## 6 MONTH FOLLOW UP RELATING TO CHILD PUGH CRITERIA

| Follow up 6 months | CHILD PUGH criteria | | | | Total | |
|---|---|---|---|---|---|---|
| | A | | B | | | |
| | Count | % | Count | % | Count | % |
| Survived | 15 | 75.0 | 8 | 36.4 | 23 | 54.8 |
| Died | 5 | 25.0 | 14 | 63.6 | 19 | 45.2 |
| Total | 20 | 100.0 | 22 | 100.0 | 42 | 100.0 |

$p < 0.05$

## TABLE 10

## 6 MONTH FOLLOW UP RELATING TO PORTAL VEIN STATUS

| Follow up 6 months | Portal Vein status | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Normal | | Branch vein | | Main portal vein | | | |
| | Count | % | Count | % | Count | % | Count | % |
| Survived | 15 | 83.3 | 6 | 46.2 | 2 | 18.2 | 23 | 54.8 |
| Died | 3 | 16.7 | 7 | 53.8 | 9 | 81.8 | 19 | 45.2 |
| Total | 18 | 100 | 13 | 100 | 11 | 100 | 42 | 100 |

$p < 0.01$

## TABLE 11

## 12 MONTH FOLLOW UP

| Follow up 12 months | Treatment | | | | Total | |
|---|---|---|---|---|---|---|
| | TACE | | Symptomatic | | | |
| | Count | % | Count | % | Count | % |
| Survived | 9 | 56.3 | 2 | 7.7 | 11 | 26.2 |
| Died | 7 | 43.8 | 24 | 92.3 | 31 | 73.8 |
| Total | 16 | 100.0 | 26 | 100.0 | 42 | 100.0 |

$p < 0.01$

## TABLE 12

## 12 MONTH FOLLOW UP RELATING TO

## CHILD PUGH CRITERIA

| Follow up 12 months | CHILD PUGH criteria | | | | Total | |
|---|---|---|---|---|---|---|
| | A | | B | | | |
| | Count | % | Count | % | Count | % |
| Survived | 11 | 55.0 | 0 | 0.0 | 11 | 26.2 |
| Died | 9 | 45.0 | 22 | 100.0 | 31 | 73.8 |
| Total | 20 | 100.0 | 22 | 100.0 | 42 | 100.0 |

$p < 0.001$

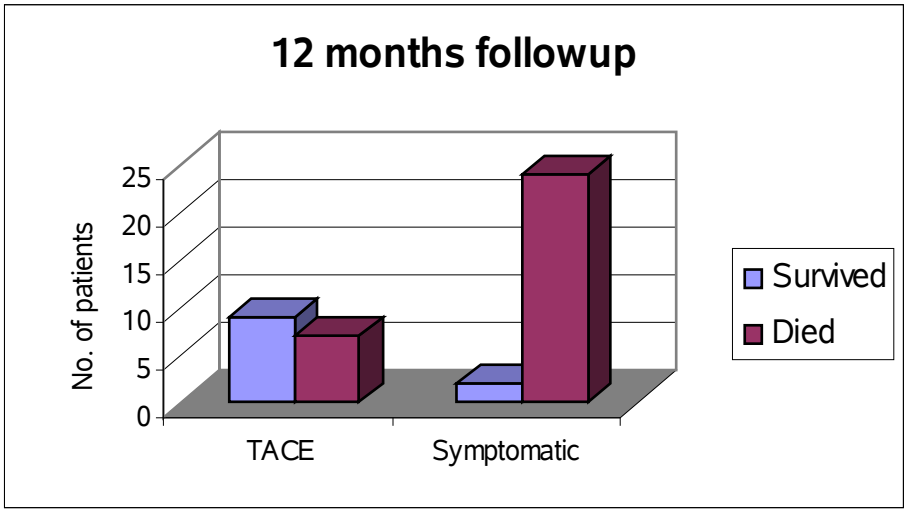
## TABLE 13

## 12 MONTH FOLLOW UP RELATING TO

## PORTAL VEIN STATUS

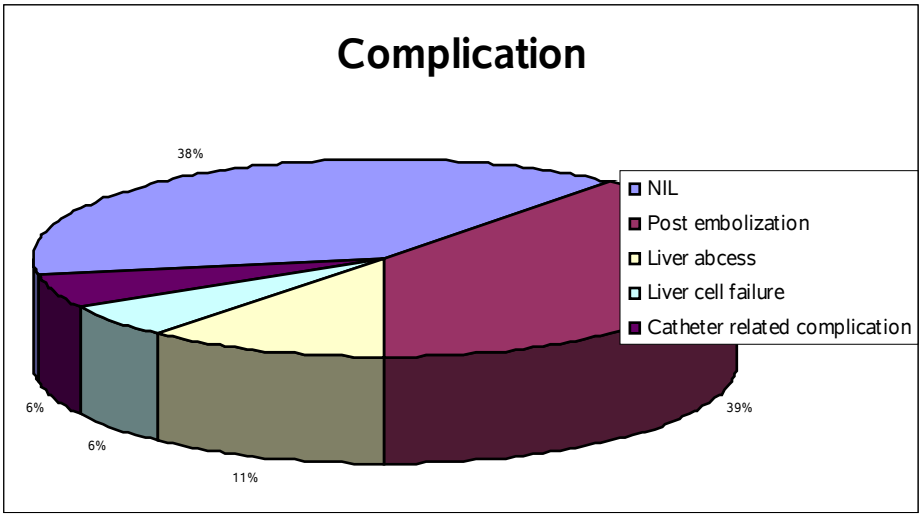
| Follow up 12 months | Portal Vein status | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Normal | | Branch vein | | Main portal vein | | | |
| | Count | % | Count | % | Count | % | Count | % |
| Survived | 10 | 55.6 | 1 | 7.7 | 0 | 0.0 | 11 | 26.2 |
| Died | 8 | 44.4 | 12 | 92.3 | 11 | 100 | 31 | 73.8 |
| Total | 18 | 100 | 13 | 100 | 11 | 100 | 42 | 100 |

$p < 0.01$



## Table 14

| COMPLICATIONS | |
|---|---|
| NIL | 7 |
| Post embolization syndrome | 7 |
| Liver abscess | 2 |
| Liver cell failure | 1 |
| Catheter related complication | 1 |



## Table 15

## 12 MONTHS SURVIVAL, PORTAL VEIN STATUS AND TREATMENT CROSS TABULATION

| Follow up 12 months | | | Treatment | | Total |
|---|---|---|---|---|---|
| | | | TACE | Symptomatic | |
| Survived | Portal Vein status | Normal | 8 | 2 | 10 |
| | | Branch vein | 1 | 0 | 1 |
| | Total | | 9 | 2 | 11 |
| Died | Portal Vein status | Normal | 1 | 7 | 8 |
| | | Branch vein | 3 | 9 | 12 |
| | | Main portal vein | 3 | 8 | 11 |
| | Total | | 7 | 24 | 31 |

p value not significant

## Table 16

## 6 MONTHS SURVIVAL, PORTAL VEIN STATUS AND TREATMENT CROSS TABULATION

| Follow up 6 months | | | Treatment | | Total |
|---|---|---|---|---|---|
| | | | TACE | Symptomatic | |
| Survived | Portal Vein status | Normal | 9 | 6 | 15 |
| | | Branch vein | 4 | 2 | 6 |
| | | Main portal vein | 1 | 1 | 2 |
| | Total | | 14 | 9 | 23 |
| Died | Portal Vein status | Normal | 0 | 3 | 3 |
| | | Branch vein | 0 | 7 | 7 |
| | | Main portal vein | 2 | 7 | 9 |
| | Total | | 2 | 17 | 19 |

p value not significant

## TABLE 17

## 6 MONTHS SURVIVAL, CHILD PUGH CRITERIA AND TREATMENT CROSS TABULATION

| Follow up 6 months | | | Treatment | | Total |
|---|---|---|---|---|---|
| | | | TACE | Symptomatic | |
| Survived | CHILD PUGH criteria | A | 9 | 6 | 15 |
| | | B | 5 | 3 | 8 |
| | Total | | 14 | 9 | 23 |
| Died | CHILD PUGH criteria | A | 1 | 4 | 5 |
| | | B | 1 | 13 | 14 |
| | Total | | 2 | 17 | 19 |

p value not significant

## TABLE 18

## 12 MONTHS SURVIVAL, CHILD PUGH CRITERIA AND TREATMENT CROSS TABULATION

| Follow up 12 months | | | Treatment | | Total |
|---|---|---|---|---|---|
| | | | TACE | Symptomatic | |
| Survived | CHILD PUGH criteria | A | 9 | 2 | 11 |
| | Total | | 9 | 2 | 11 |
| Died | CHILD PUGH criteria | A | 1 | 8 | 9 |
| | | B | 6 | 16 | 22 |
| | Total | | 7 | 24 | 31 |

# DISCUSSION

**In our prospective study group of 42 patients, the age range was 35 to 73 years with mean age being 55 years. But in western countries, the incidence of hepatocellular carcinoma is more common between 60 to 70 years. Early incidence is due to increase in infection rate of hepatitis B & C virus.**

**In 42 patients 36 patients were men and 6 patients were women with the male: female ratio of 6:1. This is comparable to the western incidence.**

**In my study, 33% patients presented with upper abdominal pain, 62% patients presented with constitutional symptoms like weight loss , malaise, 19% patients presented with palpable liver mass, 33% patients presented with ascites, 40% presented with jaundice . Majority of patients presented with symptoms, constitutional symptoms being more common. In contrast to our study, asymptomatic presentation is more common in Japan due to active screening programme.**

**Of the forty two patients TACE was done for 16 patients, the remaining 26 patients were treated with symptomatic therapy. 20 patients belonged to Child Pugh criteria A, 22 patients belonged to Child Pugh criteria B. Of these 20 patients with Child Pugh criteria A, 10 patients were treated with TACE. Six patients out of 22 Child Pugh criteria B patients were treated with TACE.**

**In sixteen patients of TACE group 9 patients had patent portal vein, 4 patients had branch vein thrombosis, 3had main portal vein thrombosis. In patients with main portal vein thrombosis embolization with gelfoam was not done, only chemolipoidolization was done.**

**In twenty six patients of symptomatic treatment group 9 patients had patient portal vein, 9 patients had branch vein thrombosis, 8 patients had main portal vein thrombosis.**

**Most of the patients tolerated well to the procedure, with post embolization syndrome noted in 7 (43%), liver abscess in 2(12%), liver cell failure in 6% (1), puncture site hematoma in 1 (6%) patients. The liver cell failure patient died in 35 days after TACE from intractable gastrointestinal hemorrhage. Proportion of major complications (were higher in our study than Sakamoto et al study (5%) probably because of small study group and inclusion of main portal vein thrombosis in our study.**

**Partial response as indicated by the size of the tumor reduction by more than 20% was noted in (6) 38% patients. Stable disease indicated by no change in size of the tumor was noted in 7(44%) patients. Progressive disease indicated by increase in size of tumor of at least 20% was noted in 3 (18 %) patients in TACE group. While in symptomatic treatment group, none of the patients showed reduction in the size of the tumor, 8 (35%) patients showed no change in size (stable disease), and 15 (65%) patients showed increase in the size of the tumor. TACE of unresectable HCC produced significant reduction in size of tumor than symptomatic management with statistical significance. ($p < 0.05$)**

**Analysis showed significant reduction of VAS score in TACE group when compared with symptomatic management group. The mean VAS score, pre &post treatment in TACE and symptomatic group are 5.8, 3.8 and 5.3, 6.2 respectively. In TACE group reduction of pain was more in Child Pugh A than B with statistical significance ($p<0.01$).**

**Performance status scale showed mild improvement in TACE group than symptomatic group. The mean PSS score in pre & post treatment group being 2 &1.94 in TACE group, 2.5 &2.8 in symptomatic management group which is statistically significant with p value < 0.001. So TACE showed mild improvement of the performance status of the advanced hepatocellular carcinoma patients.**

**In TACE group 14 out of 16 patients survived beyond 6 months. Whereas in symptomatic therapy group only 9 out of 26 patients survived beyond 6 months. 6 months survival rate was**

**87.5% in TACE group. 6 month survival rate of TACE patients with Child Pugh A & B criteria were 90%& 83% respectively. In symptomatic therapy 6 months survival rate was 60% &18% in Child Pugh A &B criteria patients respectively.**

**In TACE group, 9 out of 16 patients survived beyond 12 months with 12 month survival rate of 56%. All survived patients belonged to Child Pugh A. None of the Child Pugh B patients survived beyond 10 months. In symptomatic therapy group only 2 patients out of 26 survived beyond 12 months with survival rate of 7%.**

***Solomon et al*, in their study of 38 patients with Okuda stage 2 who underwent chemoembolization noted that the one year and two year survival rate as 60 % and 41% respectively. In our study one year survival rate was 56%.**

***In Brown et al*, study of 81 patients, chemoembolization produced one year and two year survival rates of 61% and 42%. Our study produced similar one year survival results.**

***Lo et al*, compared survival outcomes of chemoembolization versus symptomatic management, with 40 patients per group. One, 2-, and 3-year survival rates in the study group were 57%, 31%, and 26% compared with 32%, 11%, and 3% in the control. 1 year survival rates were comparable with our study.**

**In patients without portal vein involvement, 6 &12 month survival rates were 83% &55% respectively, whereas in portal vein branch involvement patients 6&12 month survival rates were 46%&7% respectively. In main portal vein thrombosis 6&12 month survival rates were 18% &0. Our study showed portal vein status was one of the main prognostic factors in HCC management.**

**Further analysis showed 6 month survival rate in patent portal vein patients , branch vein involved patients, main portal vein involved patients being 100%,100%,33% and 88%,22%,12% in TACE and symptomatic therapy patients respectively. 12month survival rate in patent portal**

**vein patients, branch vein involved patients, main portal vein involved patients were 88%, 25%, 0%and 25%, 0%, 0% in TACE and symptomatic therapy patients respectively.**

**Even though statistical analysis showed no significant association, median survival rate of 9 months in portal vein involved patients treated with TACE group was noted, whereas it was 3 months in symptomatically treated patients group. In Child Pugh A group patients treated with TACE the median survival rate was more than 12months, whereas in symptomatically treated patients it was 7.5 months. In Child Pugh B group patients treated with TACE and symptomatic management, the median survival rates were 7 and 2 months respectively.**

**This median survival rates were compared with *Georgiades et al* study in John Hopkins University. They studied 31 patients with unresectable HCC with portal vein thrombosis patients. They did TACE using Cisplatin , Mitomycin, Doxorubicin, Lipiodol and PVA. They found median survival rate of 5.1 months for TACE group as compared to 3.7 months in symptomatically treated group. They observed median survival rate in Child Pugh class A & B as 12 and 5 months respectively. In our study median survival rate was slightly more in all groups except in symptomatically treated portal vein involved patients.**

# SUMMARY

**In our study of 42 unresectable HCC patients TACE was done in 16 patients, remaining 26 patients treated with symptomatic therapy.**

**Of these 16 TACE patients 10 patients belonged to Child Pugh A remaining 6 patients belonged to Child Pugh B and 7 patients had portal vein involvement.**

**TACE was done using cisplatin, adriamyin ,lipiodol, gelfoam .Remaining 26 patients treated symptomatic therapy.**

**Significant reduction of VAS score in the TACE group of patients improved symptomatically treated patients ($p<0.05$).**

**TACE group patients showed significant improvement in performance status than symptomatically treated patient ($p <0.01$).**

**In our series liver cell failure was noted in one patient in TACE group immediately after embolization & died in 30 days after the procedure.**

**6 month survived rate, increased from 60% in symptomatically treated patients to 87.5% in TACE group patients.**

**One year survival rate, increased from 7 % in symptomatically treated patient to 50% in TACE group of patients. All survived patients belonged to Child Pugh A criteria with statistical significance.**

**Median survival rate in Child Pugh A criteria patients were higher in TACE group (>12 months) than symptomatically treated patients (7 months). In Child Pugh "B" criteria TACE produced same results.**

**Even though there was no statistical significance portal vein involved patients showed prolongation of median survival rate in TACE group (9months) than symptomatically treated patients (3 months).**

# CONCLUSION

**Transarterial Chemoembolization of unresectable hepatocellular carcinoma (n=16) is useful in palliative care as indicated by improvement in performance status score and visual analogue pain scale when compared to symptomatic management (n=26).**

**Transarterial chemoembolization prolongs the survival of the patients with unresectable hepatocellular carcinoma when compared to symptomatic management.**

**Selective embolization of advanced hepatocellular carcinoma proves safe in the presence of portal vein thrombosis.**

**So in the present scenario where our patients present in late stage of HCC, TACE should be offered as a palliative procedure to relieve pain and also to improve the general well being and survival of the patient.**

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# KEY TO MASTER CHART

**1. Sex** Male- 1 Female - 2

**2. CF-Clinical Features**

| | | |
|---|---|---|
| Pain | - | 1 |
| Constitutional Symptoms | - | 2 |
| Palpable Mass | - | 3 |
| Ascites | - | 4 |
| Jaundice | - | 5 |

**3. Child Pugh Criteria**

| | | |
|---|---|---|
| A | - | 1 |
| B | - | 2 |

**4. Portal vein status**

| | | |
|---|---|---|
| Patent | - | 1 |
| Right branch involvement | - | 2 |
| Left branch involvement | - | 3 |
| Main Portal involvement | - | 4 |

**5. Treatment**

| | | |
|---|---|---|
| TACE | - | 1 |
| Symptomatic management | - | 2 |

**6. Pre VAS**

Pre Treatment Visual Analogue Scale

**7. Post Vas**

Post Treatment Visual Analogue Scale

**8. Pre Performance status scale**

**Pre Treatment PSS**

**9. Post PSS**

**Post Treatment PSS**

**10. Size Change after 1 month**

| | | |
|---|---|---|
| **No Change** | **-** | **1** |
| **Reduction more than 20%** | **-** | **2** |
| **Increase more than 20%** | **-** | **3** |

**11. 6 months Follow up**

| | | |
|---|---|---|
| **Survived** | **-** | **1** |
| **Died** | **-** | **2** |

**12. 12 months Follow up**

| | | |
|---|---|---|
| **Survived** | **-** | **1** |
| **Died** | **-** | **2** |

**13. Complications**

| | | |
|---|---|---|
| **Nil** | **-** | **0** |
| **Post embolization Symptoms** | **-** | **1** |
| **Liver Abscess** | **-** | **2** |
| **Liver Cell Failure** | **-** | **3** |
| **Catheter related complication** | **-** | **4** |

**14. Repeat TACE**

| | | |
|---|---|---|
| **Nil** | **-** | **0** |
| **Present** | **-** | **1** |

**15. Died At (in months)**

# ABBREVIATIONS

| | | |
|---|---|---|
| **AFP** | **-** | **Alpha Feto Protein** |
| **CTA** | **-** | **CT Arteriography** |
| **CTAP** | **-** | **CT Arterial Portography** |
| **HCC** | **-** | **Hepatocellular Carcinoma** |
| **PEI** | **-** | **Percutaneous Ethanol Injection** |
| **PSS** | **-** | **Performance Status Scale** |
| **RFA** | **-** | **Radio Frequency Ablation** |
| **TACE** | **-** | **Transarterial Chemo Embolization** |
| **USG** | **-** | **Ultrasonogram** |
| **VAS** | **-** | **Visual Analog Scale** |

# PROFORMA

**Name:** **Age :**

**Occupation :** **IP NO :**

**Presenting complaints**

**Constitutional symptoms** **yes/ no**

**Abdominal pain** **yes/ no**

**Palpable liver mass** **yes/ no**

**Ascites** **yes/ no**

**Jaundice** **yes/ no**

**Past history:**

**Cirrhosis** **HBV** **HCV** **H/O primary**

**Surgery** **H/o Blood transfusion**

**Personal history:**

**Smoker** **yes/ no**

**Alcoholic** **yes/ no**

**Allergic History:** **yes/ no**

**General examination:**

**Anaemia**

**Jaundice**

**Lymphadenopathy**

**Systemic examination:**

**CVS :**

**RS :**

**Abdomen:**

**Hepatomegaly**

**Splenomegaly**

**Ascites**

**CLINICAL DIAGNOSIS:**

**INVESTIGATION:**

**Hemoglobin**

**Bleeding time, Clotting time**

**PT, APTT**

**Bilirubin**

**Serum albumin**

**Urea, creatinine**

**AFP**

**CHILD PUGH SCORE A / B:**

**ULTRASONOGRAM / CT:**

**Lesion size**

**Number**

**Location**

**Echogenicity / Density**

**Portal vein involvement**

**Bile duct dilatation**

**Regional lymphadenopathy**

**Ascites**

**Color Duplex**

**Intra lesional flow pattern**

**Portal vein involvement**

**Histopathology**

**TREATMENT:**

**TACE / SYMPTOMATIC**

**COMPLICATIONS:**

**POST TREATMENT FOLLOW UP:**

**At 1 month:**

**Pre treatment visual analogue scale Post treatment visual analogue scale**

**Pre treatment performance status scale Post treatment performance status scale**

**Tumor size change: --- decreased/ increased / static**

**Repeat TACE : yes / no**

**At 6 month:**

**Survival yes / no**

**At 12 month:**

**Survival yes / no**

# PERFORMANCE STATUS SCALES
# ECOG (Eastern Cooperative Oncology Group)

| | | | |
|---|---|---|---|
| 1. | Asymptomatic; Normal Activity | = | 0 |
| 2. | Symptomatic; ambulatory; able to carry out activities of daily living | = | 1 |
| 3. | Symptomatic; in bed less than 50% of the day; occasionally needs nursing care | = | 2 |
| 4. | Symptomatic; in bed more than 50% of the day; needs nursing care | = | 3 |
| 5. | Bedridden; may need hospitalization | = | 4 |