RADIOLOGICAL MANAGEMENT OF HEPATOCELLULAR CARCINOMA

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Introduction

HCC is the fifth commonest cancer worldwide; with more than one million new cases diagnosed each year.[1] The incidence of HCC varies widely, being most common in Southeast Asia sub-Saharan Africa and much less in North America and Western Europe.[2] Annual incidence in Pakistan is 8/100,000.[3] Hepatitis C and B have been found to be the leading causes in Pakistan.[4,5,6] In developing countries, HCC is a leading cause of death and accounts for between 60% and 90% of all primary liver malignancies.[7]

Patient at risk of developing HCC i.e.chronic viral hepatitis commonly undergo surveillance with ultrasound due to the cost-effectiveness. However due to recent advances in imaging patients with a higher suspicion of HCC (such as rising alpha-fetoprotein), the best method of diagnosis involves a CT scan of the abdomen using intravenous contrast agent and three-phase scanning to increase the ability of the radiologist to detect small or subtle tumors.

A biopsy is not needed to confirm the diagnosis of HCC if certain imaging criteria are met.

The key characteristics on CT are hypervascularity in the arterial phase scans, washout or de-enhancement in the portal and delayed phase studies.[8] An alternative to a CT imaging study would be the MRI which is more sensitive and specific than CT.[9]

Patients at an early stage may achieve a 5-year survival rate above 50%, those at intermediate-advanced stage have 20-50% survival at 3 years and those at terminal stage die within six months.[10]

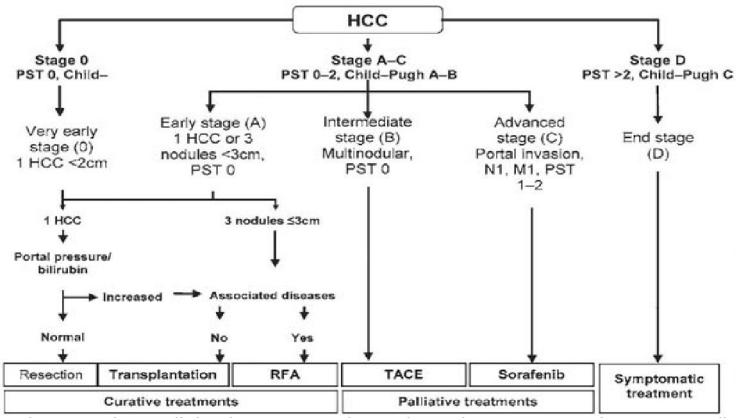

Figure 1: The Barcelona Clinic Liver Cancer (BCLC) staging system and treatment allocation.[11]

Treatment of HCC

Staging of HCC is important for selecting appropriate treatment choice.

There are many staging system for HCC. However the Barcelona Clinic Liver Cancer (BCLC) staging system has been widely and efficiently used in several major trials to define the patient population to be recruited and to stratify them into separate prognosis categories and therapies.[10,11,12]

According to BCLC staging system curative treatment which includes Surgical resection, Transplantation and Radiofrequency Ablation (RFA) is reserved currently only for the very early and early stage HCC. (Fig. 1).[11]

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Surgical resection involves removal of a tumor together with surrounding liver tissue while preserving enough liver remnants for normal body function. This treatment offers the best prognosis for long-term survival, but unfortunately only 10-35% of patients are suitable for surgical resection. In addition, the recurrence rate in the remnant liver after a hepatectomy is very high, ranging from 36% - 66%.[13]

The second curative option for early HCC is hepatic transplantation, whose long term survival is higher than resection. However, because of limited donor organ availability and also for cultural and economic reasons, surgical resection is still the mainstayof therapy worldwide for patients with liver-confined HCC.[14]

For selected patients with HCC confined to the liver whose disease is not amenable to resection or transplantation, locoregional therapies can be considered which include Percutaneous ethanol injection, cryotherapy, radiofrequency or microwave ablation (RFA), stereotactic radiation therapy, radio-active microspheres, transarterial (bland) embolization (TAE) and transarterial chemoembolization (TACE).

While nonresectional locoregional therapies are not curative, these approaches do produce tumor destruction while preserving nontumorous liver parenchyma and may serve as a bridge to more definitive therapy, such as liver transplantation or as salvage treatment for post resection recurrence.[15-19]

The breakdown of an initial treatment of HCC according to the Liver Cancer Study Group of Japan (LCSGJ) shows resection in 32%, local ablation including radiofrequency ablation, percutaneous ethanol injection and microwave coagulation in 31%, TACE in 32% and others. These proportions of treatment are almost similar during the 10-year period from 1996 to 2005.[21] For recurrent HCC, 58% of patients underwent TACE.

TRANSARTERIAL CHEMOEMBOLIZATION (TACE) FOR HEPATOCELLULAR CARCINOMA:

TACE is a locoregional therapy option that delivers chemotherapy and embolic materials via hepatic arterial infusion. TACE started in patients with unresectable HCC in the late 1970s in Japan[22] and lipiodol was introduced to enhance the therapeutic effect in the early 1980s.[23]

TACE involves gaining percutaneous access to the hepatic artery, usually by puncturing the common femoral artery in the right groin and passing a catheter through the abdominal aorta, through the celiac trunk and common hepatic artery, into the proper hepatic artery (which supplies the liver). Subsequently an arteriogram is performed to identify the branches of the hepatic artery supplying the tumor(s) and threads smaller catheters into these branches. This position is called a super-selective position. This is done to maximize the amount of the chemotherapeutic dose that is directed to the tumor and minimize the amount of the chemo-therapeutic agent that could damage the normal liver tissue.

When a blood vessel supplying tumor has been selected, alternating aliquots of the chemotherapy dose and of embolic particles, or particles containing the chemotherapy agent, are injected through the catheter.[24-28]

Chemotherapy has to be injected prior to arterial obstruction. It is usual to suspend chemotherapy in lipiodol, an oily contrast agent used for lympho-graphic studies. Lipiodol is selectively retained within the tumor and this expands the exposure of the neoplastic cells to chemotherapy. Several chemotherapeutic agents such as Cisplatinum, Doxorubicin, Epirubicin or Mitomycin C have been used for TACE, but the most common is to inject adriamycin or cisplatin.[29]

TACE derives its beneficial effect by two methods. Since most tumors are supplied by the hepatic artery, arterial embolization interrupts their blood supply and postpones growth until replaced by neovascularity. Secondly, focused administration of chemotherapy allows a higher dose to the tissue while simultaneously reducing systemic exposure, which is typically the dose limiting factor. This effect is potentiated by the fact that the chemotherapeutic drug is not washed out from the tumor bed after embolization. This way, in contrary with systemic chemotherapy, the therapeutic effect is focused in the liver, diminishing the systemic side effects of the agents.[24-28]

Acute hepatic arterial obstruction results in ischemic tumor necrosis as HCC nodules mainly have an arterial blood supply, in contrast to the background liver which is supplied by the portal vein.[30]

Different embolizing agents like Gelatinsponge, Steel coils, Degradable starch microspheres (DSM), Autologous blood clot, polyvinyl alcohol (PVA), Drug-eluting beads, Embospheres (100-700 lm) have been used.There is no consensus about which is the most effective embolizing agent however an ideal embolizing agent should have a standardized particle size, that can be delivered into smaller arteries and cause permanent thrombosis.[31-40] (Fig. 2 to 6) shows CT

and angiographic images of a TACE treated large hepatoma in right lobe of liver.

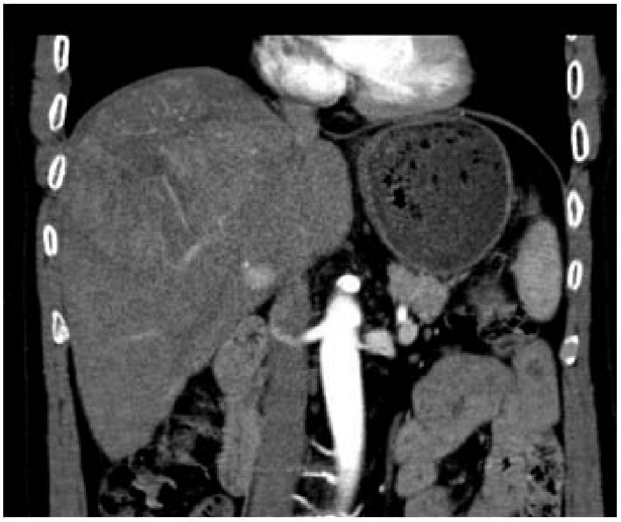


Figure 2: Coronal CT image early arterial phase showing a large enhancing mass lesion in right lobe of liver.

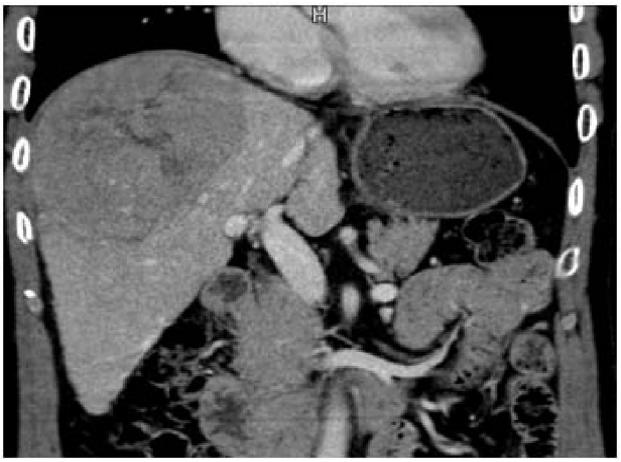
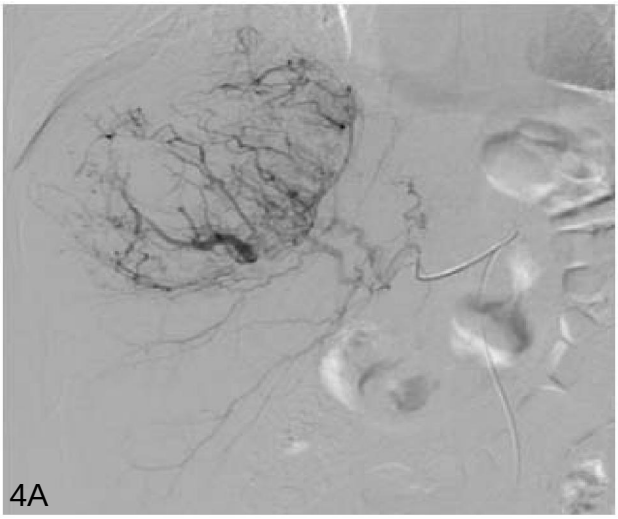


Figure 3: Coronal CT image Porto venous phase showing typical washout in mass lesion in right lobe of liver consistent with hepatoma.



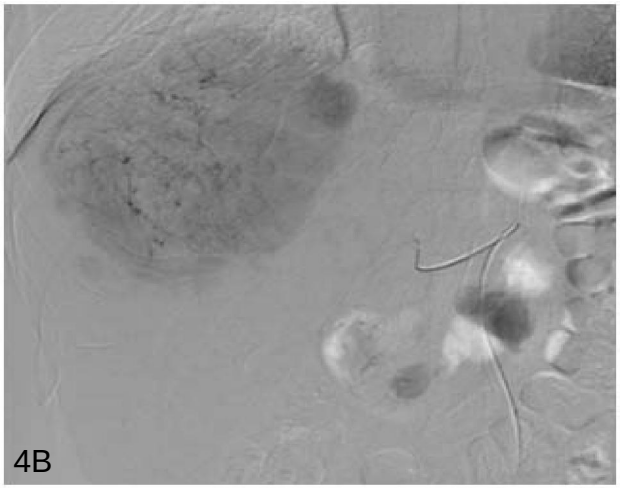


Figure 4 A, B: Preliminary angiogram showed tumor vascularity in the right lobe corresponding with lesions on CT scan.

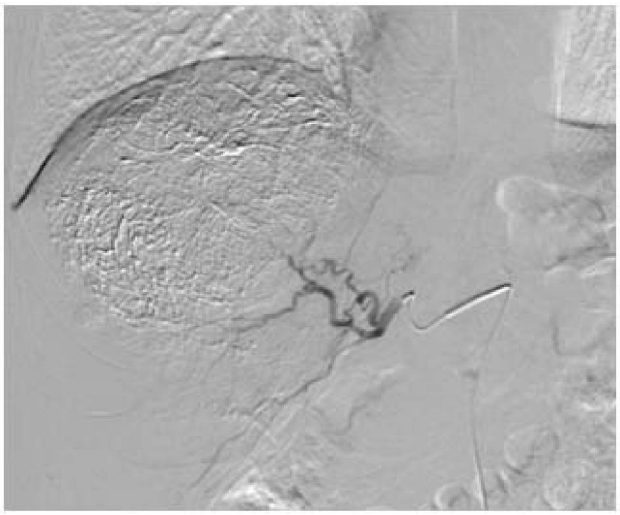


Figure 5: Post Chemoembolization angiogram revealed almost complete disappearance of previously seen tumor vascularity in right lobe of liver.

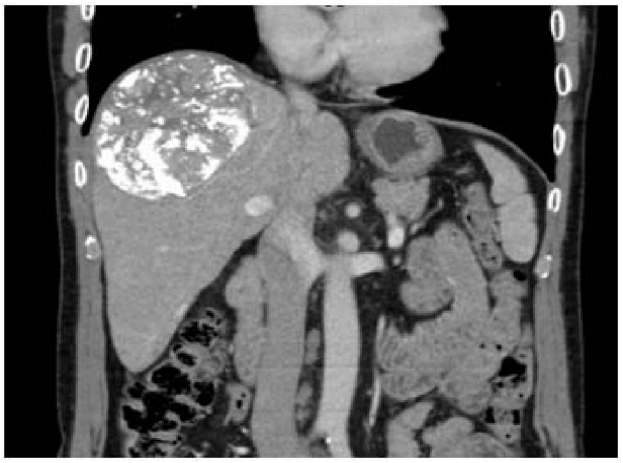


Figure 6: Post Chemoembolization CT after 7 weeks showed lipoid deposition in region of previously seen hepatoma in right lobe of liver. No evidence of abnormal enhancement to suggest residual or recurrence.

Efficacy of Tace

The efficacy of TACE can be assessed in different ways like imaging response (CT scan), biologic response (alpha-fetoprotein, AFP), degree of tumor necrosis, patient survival and also quality of life. The most effective index of TACE success is patient survival. A meta-analysis of five RCTs showed a significantly reduced 2 year mortality rate following chemo-embolization compared with non-active treatment.[41] A more recent meta-analysis involving six RCTs that compared 2 year survival with TACE/TAE versus conservative management (four RCTs) or suboptimal therapies (Two RCTs: oral tamoxifen and intravenous 5-fluorouracil)also showed that chemoembolization improved survival(OR 0.53; 95% CI 0.32–0.89; p = 0.017).[42]

Complications

During this procedure contrast media is utilized, which patients may develop an allergic reaction to. The procedure induces tumor necrosis in more than 50% of patients. The resulting necrotic material releases cytokines and other inflammatory chemicals into the blood stream. This can lead to post-embolisation syndrome. This is due to hepatic artery obstruction with an acute ischemia, characterized by fever, abdominal pain and ileus. The fever reflects the tumor necrosis. It is usually self-limiting (<48hrs). Treatment is by keeping the patient nil-by-mouth for 24 hours, with continued IV hydration. Prophylactic antibiotics are not routine.[43-47]

A minority develop severe infectious complications such as an abscess within the necrotic tissue. This is a potentially fatal event, although percutanous drainage can be utilized in order to prevent the septicemia and sepsis.

Other complications are Renal failure (2.4%), Liver abscess (1.8%), Liver infarction (0.17%), Acute hepatic failure (3%), bile duct injuries (2%) and Tumor rupture (0.04%).[48-56,57]

Prognostic Factor

As a prognostic factor of TACE for HCC, liver function, performance status, stage of cancer (number of tumor, tumor size, macroscopic vascular invasion and extra hepatic spread), AFP, des-gamma carboxy-prothrombin and skill of the operator have been given.[58,59,60] Based on common features shared by several staging systems, the following factors are given as the key factors impacting on HCC prognosis: solitary vs. multifocal tumors, presence of macro vascular invasion, extra hepatic spread, high serum AFP levels, patient performance status and degree of hepatic impairment.[61]

Other minimally invasive percutaneous therapies for Liver Tumours

CHEMICAL ABLATION:

The seminal technique used for chemical ablation of HCC has been percutaneous ethanol injection (PEI). Ethanol induces coagulation necrosis of the lesion as a result of cellular dehydration, protein denaturation,and chemical occlusion of small tumor vessels.

PEI is a well-established technique for the treatment of nodular-type HCC. HCC nodules have a soft consistency and are surrounded by a firm cirrhotic liver. Consequently, injected ethanol diffuses within them easily and selectively. The standard PEI protocol includes 4-6 sessions performed under ultrasound guidance by using fine noncutting needles.[62,63]

In patients with Child-Pugh class A cirrhosis and early stage tumors, treatment with PEI has been shown to result in 5-year survival rates of 47%-53%.[64,65]

The major limitation of PEI is the high local recurrence rate, which may reach 33% in lesions smaller than 3 cm and 43% in lesions exceeding 3 cm.[66,67]

THERMAL ABLATION:

The thermal ablative therapies involved in clinical practice can be classified as either hyperthermic treatments-including radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation-or cryoablation. Heating of tissue at 50°C - 55°C for 4-6 minutes produces irreversible cellular damage. At temperatures between 60°C and 100°C, near-immediate coagulation of tissue is induced with irreversible damage to mitochondrial and cytosolic enzymes of the cells. At more than 100°C - 110°C, tissue vaporizes and carbonizes.

On the other hand the freezing of tissue with temperatures between - 20°C and - 60°C followed by rapid

thawing results in cell membrane disruption and induces cell death.[68]

RADIOFREQUENCY ABLATION (RFA):

The goal of RFA is to induce thermal injury to the tissue through electromagnetic energy deposition. Several electrode types are available for clinical RFA, including internally cooled electrodes and multiple-tined expandable electrodes with or without perfusion. The needle electrode cost $500 to $1000, which can at least be reused on the same patient.

Lesions should be < 5 in number, 5 cm or smaller, primary or secondary. The procedure is done as an outpatient under US guidance.[68]

An important factor that affects the success of RFA is the ability to ablate all viable tumor tissue and possibly an adequate tumor-free margin. Ideally, a 360-degree, 0.5-cm-thick to 1-cm-thick ablative margin should be produced around the tumor. This cuff would ensure that the peripheral portion of the tumor as well as any microscopic invasions located in its close proximity has been eradicated.[69]

Recent reports on long-term outcomes of RFAtreated patients have shown that in patients with Child-Pugh class A and early-stage HCC, 5-year survival rates are as high as 51%-64%, and may reach 76% in patients who meet the BCLC criteria for surgical resection.

Ultrasound or CT can be used for guidance. While RFA can be quite painful, moderate sedation is usually adequate, often keeping this light until the needle is in position so the patient can follow breath holding instructions.

There is some limitation of percutaneous method in performance of ablation in critical regions like hepatomas close to Diaphragm, bowel or stomach. However newer techniques like hydrodissection have been advocated in performance in RFA to treat tumors in these difficult anatomical locations. In hydrodissection substance like sterile water, normal (0.9%) saline, 5% dextrose in water (D5W), and even 0.5% lidocaine is used to displace vital structures near the ablation area. When a hepatic tumor abuts the diaphragm, stomach, small bowel or large intestine, installation of water must be utilize to displace these vital structures in order to avoid injury.[70,71,72]

(Fig. 7 to 11) CT and ultrasound images of a RFA treated hepatoma in segment 4 of liver.

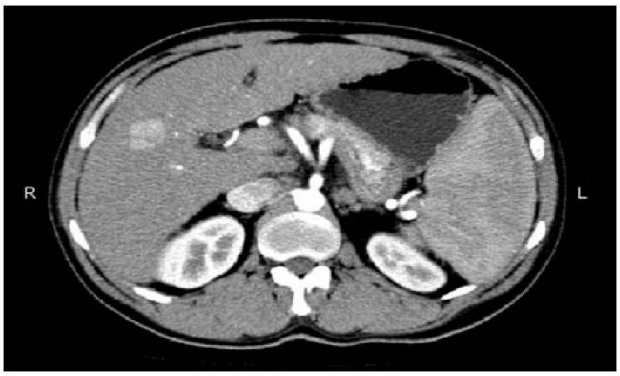


Figure 7: Early arterial phase image showing hepatocellular carcinoma of 2.5 cm in segment 4.

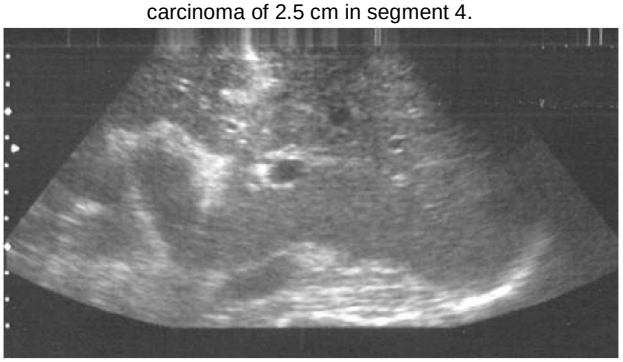


Figure 8:

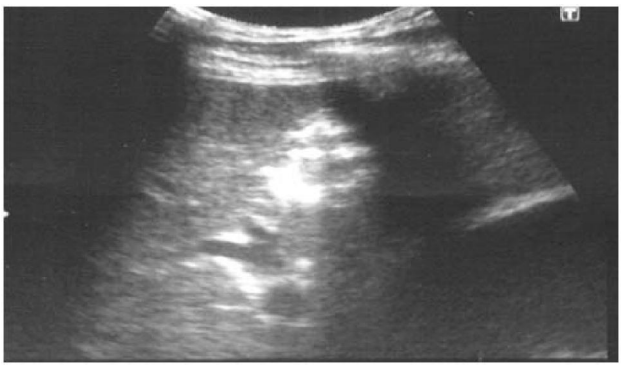


Figure 9: Figure 8 and 9: Ultrasound Image showing RFA needle in Segment IV lesion

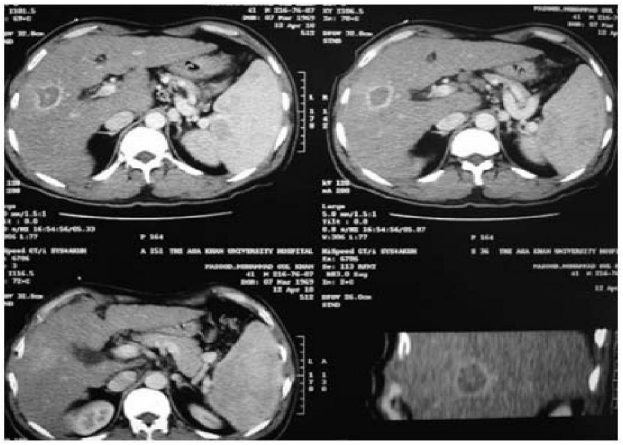


Figure 10: Immediate Post RFA CT segment IV lesion showing typical ring enhancement (inflammatory) and lesion is entirely avascular

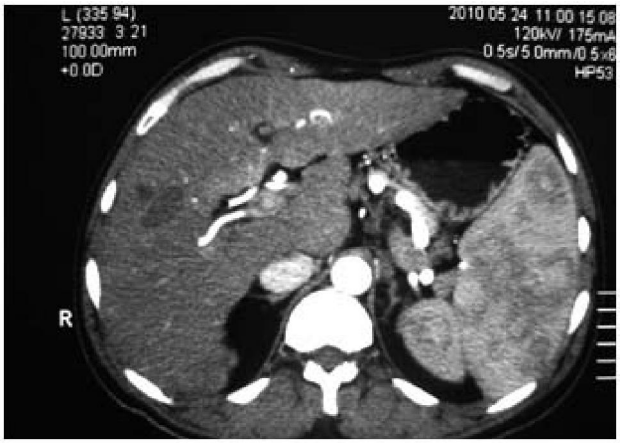


Figure 11 A: Arterial phase

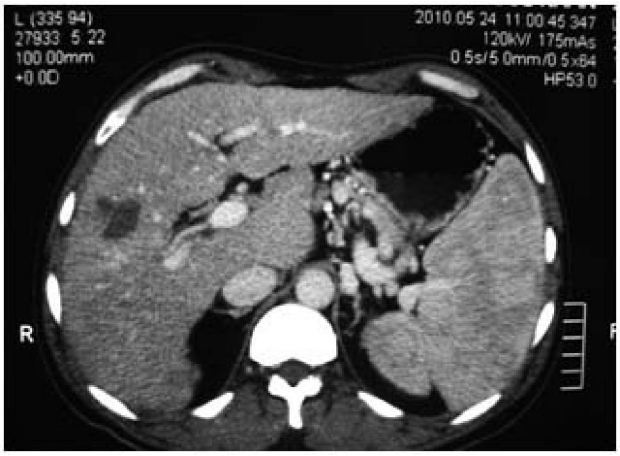


Figure 11 B: Portovenous phase

Figure 11 A, B: CT scan after 6 weeks show no enhancement in Segment IV RFA treated lesion.

Conclusion

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death. Early diagnosis of HCC can be achieved by surveillance of at-risk populations. A careful multi-disciplinary assessment of tumor characteristics, liver function, and physical status is required for proper therapeutic management even in patients with early-stage tumors.

When surgical options are precluded, Image-guided loco-regional therapies, including direct tumor ablation techniques and transcatheter treatments, play a major role in the clinical management of HCC in properly selected candidates.

Conflict of Interest: Authors declared no financial or institutional conflict of interest.

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