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OPINION ARTICLES

Transarterial Chemoembolization in Hepatocellular Carcinoma, Albanian Experience.

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Abstract

Liver cancer is the sixth most common cancer worldwide in terms of the number of cases (626,000 or 5.7% of new cancer cases) but due to the very poor prognosis, the number of deaths is nearly similar (598,000). The survival rate is 3% to 5% in cancer registries for the United States and developing countries. The modality of treatment in hepatocellular carcinoma (HCC) patients depends on the stage of the disease. The Barcelona Clinic Liver Cancer Classification (BCLC) is the favorite staging system. There are many patients who initially present with the intermediate-stage disease, and in this setting transarterial chemoembolization (TACE) is the treatment of choice.

The purpose of this article is to highlight and discuss the role of chemoembolization in the treatment of hepatocellular carcinoma, including the results of recent large studies, and the concept of combined therapies, illustrating our case.

The differences in individual factors that are not captured by the BCLC framework, such as the tumor growth pattern, degree of hypervascularity, and vascular supply, complicate the further evaluation of these patients. Because of these differences, not all patients benefit equally from TACE. Several tools have been devised to aid the decision-making process which have shown promising initial results but have failed external evaluation and have not been translated to the clinical aspects. Criteria for treatment decisions in daily clinical practice are needed in all stages of the disease.

Conclusion: TACE is a safe method for prolonging patients' survival with unresectable HCC. The correct treatment of HCC is concentrated in cancer centers, and cooperation between multiple specialists is necessary.

Keywords: hepatocellular carcinoma, chemoembolization, transcatheter therapy, TACE.

Introduction

Cancer ranks as a leading cause of death and an important barrier to increasing life expectancy in every country of the world. [1]

According to estimates from the World Health Organization (WHO) in 2019, cancer is the first or second leading cause of death before the age of 70 years in 112 of 183 countries and ranks third or fourth in a further 23 countries. [2]

Worldwide, there were 10.9 million new cases, 6.7 million deaths, and 24.6 million people alive with cancer (within three years of diagnosis). [3]

The most frequently diagnosed cancers are lung (1.35 million), breast (1.15 million), and colorectal (1 million); while the most common causes of cancer death are lung cancer (1.18 million deaths), stomach cancer (700,000 deaths), and liver cancer (598,000 deaths). [3]

Liver cancer is the sixth most common cancer worldwide in terms of the number of cases (626,000 or 5.7% of new cancer cases) but due to the very poor prognosis, the number of deaths is almost similar (598,000). The survival rate is 3% to 5% in cancer registries for the United States and developing countries. [4]

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82% of cases (and deaths) are in developing countries (55% in China alone). The overall sex ratio (male: female) is about 2.4, much greater in high-risk areas and less in low-risk areas. [4]

Primary liver cancer in terms of frequency is listed seventh in the world, and in terms of mortality, it ranks second. [1].

The regions with the highest incidence in the world are Asia and Africa [5] while Mongolia has the highest incidence at 93.7 per 100,000, but China has the highest number of new cases, due to an elevated rate (18.3 per 100,000) and the largest population in the world (1.4 billion people) [1].

Worldwide, hepatocellular carcinoma (HCC) is the main type of liver cancer, accounting for approximately 75% of the total [5].

In the interval between 1978 and 2012, the incidence of HCC decreased in many Asian countries and Italy but increased in other countries such as India, America, Oceania, and most European countries [6].

The prognosis of HCC is poor in all regions of the world [7], therefore the overall outcome, incidence, and mortality rates are approximately the same. According to literature data in 2018, the estimated global incidence rate of liver cancer per 100,000 person-years was 9.3 while the corresponding mortality rate reached 8.5 [1].

A number of risk factors for HCC can be mentioned as follows: Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Alcohol use, Non-Alcoholic Fatty Liver Disease (NAFLD), Aflatoxins (mycotoxins produced by fungi Aspergillus species), tobacco use, dietary factors, and genetic susceptibility. [8]

All this group of risk factors is related to the development of HCC, we can mention that the prevalence of cirrhosis in people with HCC is approximately 80% worldwide.[9]

HBV infection is unique in that it can lead to the development of HCC even in the absence of cirrhosis, and the annual incidence of HCC in HBV carriers was 0.5% to literature data.[10]

The synergy between alcohol intake and HCV/HBV infection has also been observed. The risk of liver cancer is increased approximately 2-4 times among people who drink more than 60 to 80 g of alcohol per day.[11] Suspicion of HCC should be raised in patients with previously compensated cirrhosis in whom decompensation develops, as this is often associated with tumor extension to the hepatic or portal vein or tumor-induced arteriovenous shunting.[12] Extrahepatic spread is present at the time of diagnosis in up to 15% of cases. The most common sites of spread, in order, are the lungs, intra-abdominal lymph nodes, bones, and adrenal glands.[13] In Albania, HCC mortality was comparable with other European countries with a low prevalence of hepatitis B virus. [14]

This paradox of low mortality rate in a hyperendemic country may be most plausibly explained by the employment of a Mediterranean diet—namely, low consumption of total energy, meat, and milk products, but the high consumption of fruit, vegetables, and carbohydrates. [14]

Previous studies have shown that closer adherence to the Mediterranean diet appears to be protective against HCC [15, 16].

As a matter of fact, our findings from Albania also point to the potential benefits of adhering to a Mediterranean dietary pattern among individuals infected with the hepatitis B virus. [15, 16].

Albania remains a high hepatitis B virus endemic country, despite the evident reduction of HBsAg in the general non-vaccinated population from 18% to 9.5% after the implementation of the hepatitis B vaccination program [14].

Also, chronic hepatitis B virus infection is recognized as the most common risk factor for hepatocellular carcinoma (HCC) which is the second cause of death from malignancy in the world [17].

HBV infection and heavy alcohol consumption significantly influenced the increased incidence of HCC in Albania.[18]

Surveillance is essential because high-risk patients who are screened for HCC receive a diagnosis at an earlier stage compared to those who are not screened. Patients who are diagnosed early have more treatment options and a better prognosis. In a series of studies, it was found that after a two-year follow-up, the mortality rate of HCC decreased by 37%.[19]

Modalities for timely diagnosis of HCC include both serological markers and radiographic tests. The most commonly used imaging tests for the diagnosis of HCC include ultrasonography (US), multiphase computed tomography (CT), and contrast-enhanced magnetic resonance imaging (MRI).[20] On CT and MRI, typical HCC lesions show increased arterialization as well as the decreased presence of contrast agents compared to the surrounding liver during portal vein and/or equilibrium phase imaging.[21] Imaging data to detect HCC demonstrated superior sensitivity with CT and MRI compared to the US, especially for small lesions. (Overall sensitivities of US, CT, and MRI were 46%, 65%, and 72%, respectively.) [22]

Treatment tactics for HCC include surgical resection or liver transplantation if diagnosed at an early stage; however, since most HCC patients present with advanced disease and underlying liver dysfunction, only 15% are amenable to curative treatments, [23] and they generally have a poor prognosis with a median survival time of less than 1 year. [24]

Several other treatment modalities exist, including radiofrequency ablation (RFA), microwave ablation, percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), radioembolization, cryoablation, radiation therapy, stereotactic radiotherapy, systemic chemotherapy and molecularly targeted therapies (e.g., sorafenib] [Bayer/Onyx]). [25] The BCLC staging classification provides stratification of Treatment tactics for HCC including surgical resection or liver transplantation if diagnosed at an early stage; however, since most HCC

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The problem is that, unlike most solid cancers, the incidence and mortality rate for HCC is expected to increase mainly in some regions in the next two decades as a consequence of hepatitis C virus infection. [26, 27]

Despite the implementation of detection, treatment, and surveillance programs for at-risk populations, the majority of patients with HCC are diagnosed late, and even when curative treatments cannot be applied, in a high percentage of cases the disease recurs even after attempts at curative or preventive therapy.[27]

The HCC treatment protocol is based on a series of techniques described in the table below:

In addition to liver transplantation, other treatments for HCC are classified into curative treatments such as; resection, percutaneous ablation, and palliative, all other treatments must match the higher rate of HCC recurrence. [28].

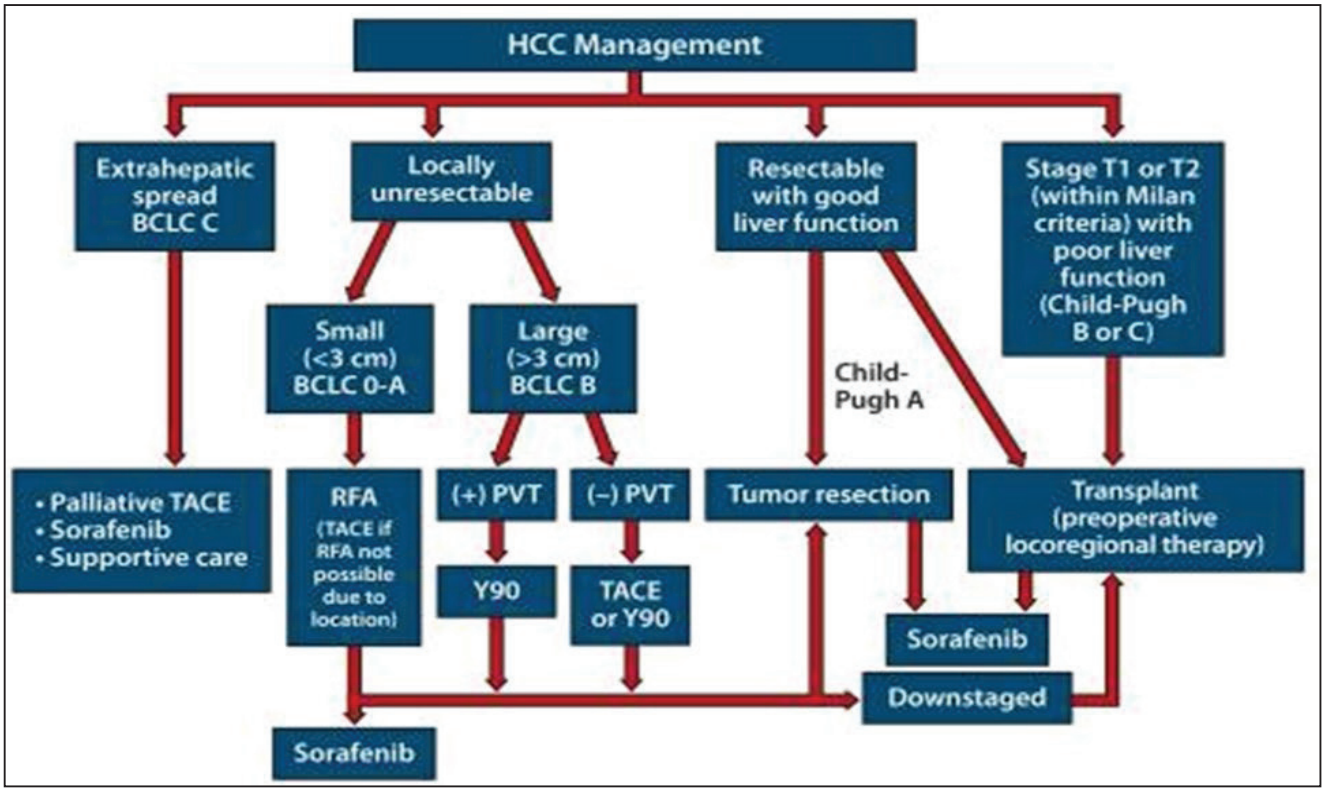
Percutaneous local ablation, namely radiofrequency ablation (RFA) and ethanol injection (EI) are the standard of care for BCLC O-A not suitable for surgery. [29]

Trans-arterial chemoembolization (TACE) is recommended for asymptomatic stage B multinodular tumors (according to BCLC classification) without the involvement of vascular structures or extrahepatic extension.

Drug-eluting beads have similar efficacy to gealfoam-lipiodol with probably fewer adverse events. Both should be discouraged in decompensated liver disease and in case of macroscopic vascular invasion or extrahepatic spread [30].

Transcatheter arterial chemoembolization (TACE) is now the current standard of care for patients with large or multinodular HCC and relatively preserved liver function, in the absence of cancer-related symptoms, and no evidence of vascular invasion and/or spread. extrahepatic (so they are classified as intermediate stage according to the Barcelona Clinic Liver Cancer staging system (BCLC).[30, 31]

Now known, the administration of an anticancer-in-oil emulsion followed by embolic agents has been the most popular TACE technique, the insertion of a drug-eluting



BCLC 0-A, Barcelona Clinic Liver Cancer stage 0 to early stage; BCLC B, Barcelona Clinic Liver Cancer immediate stage; BCLC C, Barcelona Clinic Liver Cancer advanced stage; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; Y90, yttrium-90.

Figure 1 Algorithm for the management of HCC.[20]

embolic bead. (DEB) has provided an interesting alternative to conventional protocols.[32]

Clinical studies have shown that doxorubicin-loaded DEB has a safer pharmacokinetic profile, with lower systemic drug exposure and significantly reduced liver toxicity compared to conventional TACE. [33- 35]

Procedure

The use of TACE has therapeutic effects only in the treated area; as a result, HCC in other regions of the liver, undetected at the time of the procedure, may progress or new tumors may develop.

By interrupting arterial vascularization in the tumor, TACE achieves necrosis at the site of disease but may create conditions that allow or even stimulate angiogenesis.[36]

In conventional TACE, an intra-arterial injection of a viscous emulsion, made of a chemotherapeutic drug such as doxorubicin or cisplatin mixed with iodized oil, is performed, providing embolization of the blood vessels with gelatin sponge particles or other embolic agents, which for consequently gives a strong cytotoxic effect enhanced by ischemia.[37]

There is very important computed tomography (CT) or magnetic resonance imaging (MRI) of the liver prior to the procedure of TACE to evaluate the tumor and local or peripheral spread.

Pain medication should be given according to protocols, and antibiotic prophylaxis and gastric protection are also given.

The most evaluated drug of the moment against HCC is doxorubicin, in conventional TACE, the dose of doxorubicin usually ranges from 30 to 75/m2, to a maximum of 150 mg.

As a general rule, every single treatment should include a planned dose of 50 to 75 mg of doxorubicin-loaded into a vial containing 2 ml.

In DEB-TACE, the use of 100 to 300 μm beads is recommended for a standard procedure. This choice is based on the demonstration that such small particles are distributed within the tumor or close to the tumor border, and thus they are ideal for drug delivery or precise embolization.[35]

Conventional transcatheter arterial chemoembolization.

After super-selective catheterization of the hepatic arterial branch feeding the tumor. An angiographic image obtained after the procedure shows the absence of residual tumor vascularity. The injection should be very slow.

Many authors recommend an injection rate of 1 ml of contrast medium/DC Bead suspension per minute.

Care should be taken to avoid the sedimentation of the beads in the syringe by swirling the syringes or using a three-way stand to gently suspend the beads in the solution. [38] DEB injection is continued until near stasis is observed in the artery directly feeding the tumor. [38]

Experience

The patient is a 70-year-old male, without a prior history of any disease. Under random ultrasound, he was diagnosed with large liver tumor 80mm in right lobe of the liver (Fig. 2).

The MRI confirmed the same tumor 80mm diameter. All the examinations seemed in normal value. However, the general surgeon could not operate the patients. Therefore, we did biopsy under ultrasound guidance (CNB) 16 G needle, which approved hepatocellular carcinoma (HCC). (Fig. 3).

In these conditions the patient is in the group who can treated with transcatheter arterial chemo-embolization (TACE) (Fig 5, 6) based on Barcelona Clinic Liver Cancer classification (BCLC). (Fig.4)

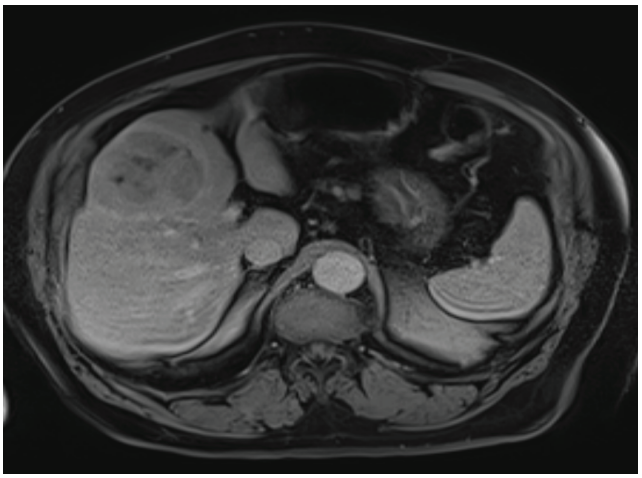


Figure 2 -MRI before Transcatheter arterial chemoembolization (TACE)

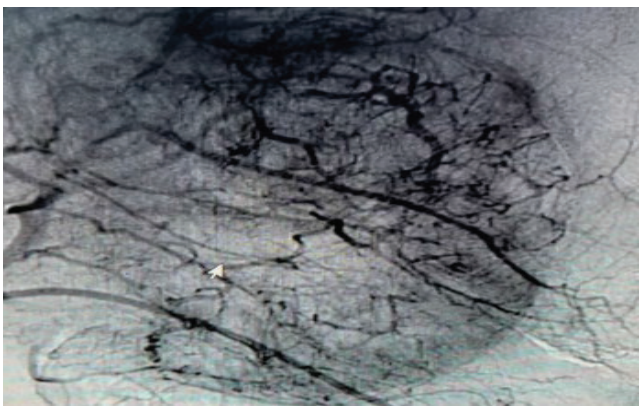
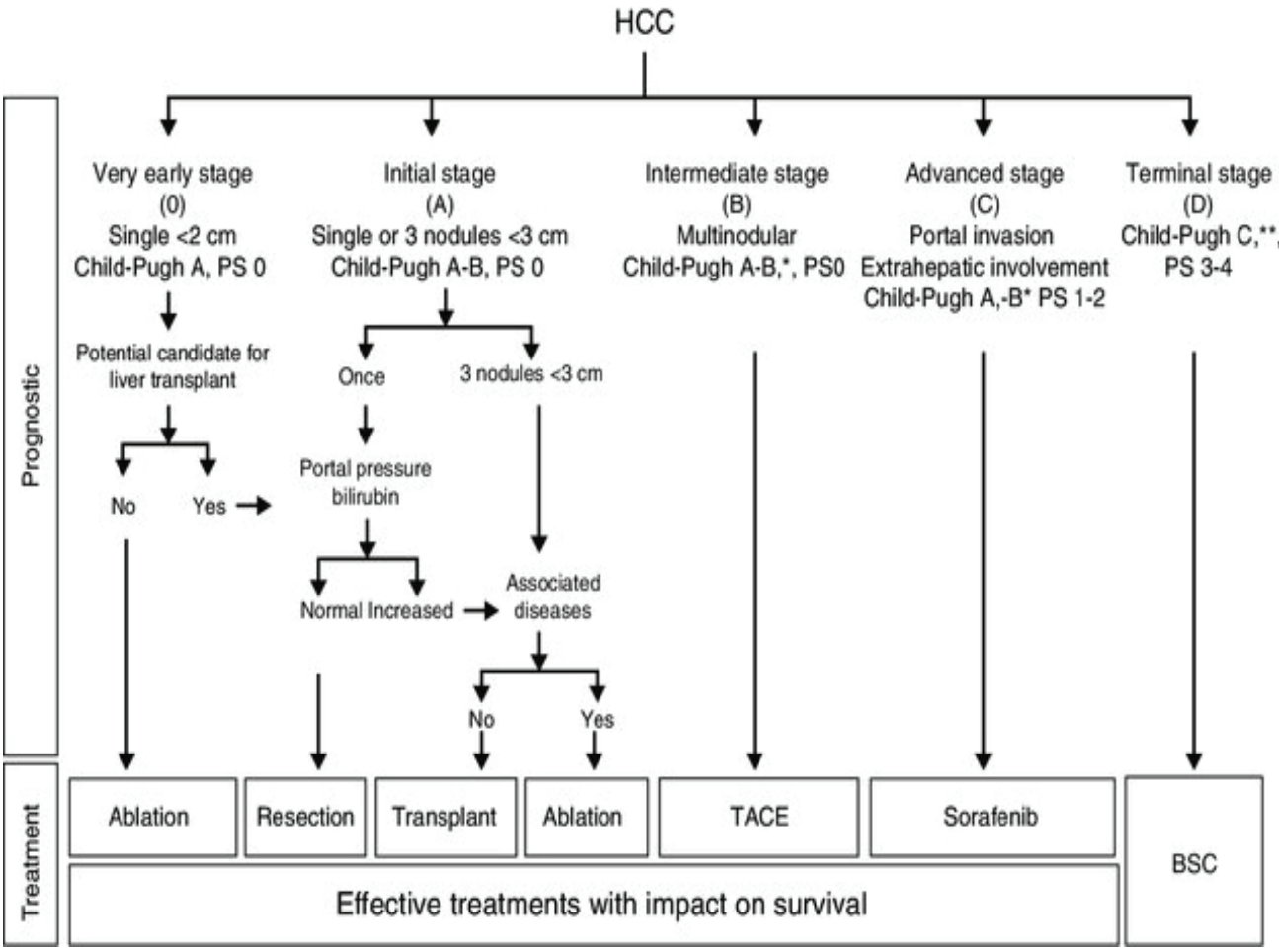


Figure 3 - Diagnostic angiography.



BSC - best supportive care; HCC - hepatocellular carcinoma; PS - performance status.

*The Child-Pugh classification does not identify all patients with severe hepatic dysfunction requiring to be considered for liver transplantation.

** Patients with end-stage cirrhosis due to severe hepatic impairment (Child-Pugh C or earlier stages with episodes predicting poor prognosis, high MELD score) should be considered for liver transplantation. In these patients, the presence of HCC can be a contraindication for liver transplantation if it exceeds the inclusion criteria. Adapted from Bruix et al. [39]

Figure 4 - Barcelona-Clinic Liver-Cancer (BCLC) Staging System.

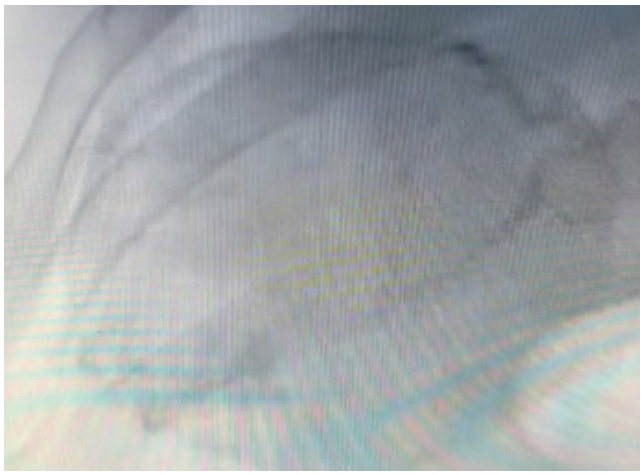


Figure 5 - Injection of (DEB-TACE) 50 mg of doxorubicin loaded into one vial containing and 100- to 300-µm beads.

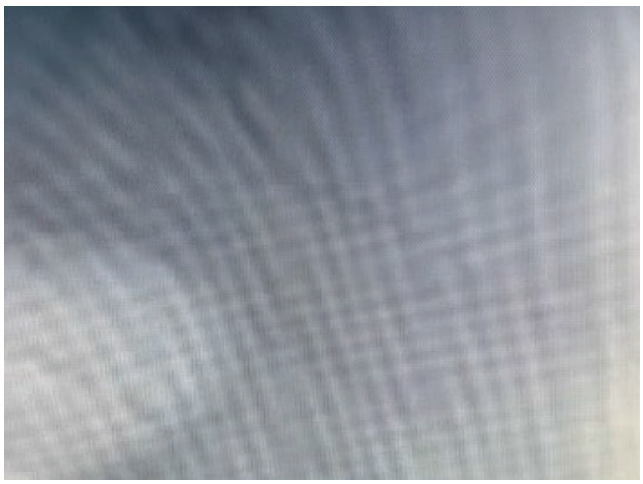


Figure 6 -After treatment we did not see vascularity of the tumor.

MRI 3 month after the procedure follow up (Fig 7). Tumor had not enhanced further, due to necrosis. There are only two small lesions in anterolateral wall (less than 10mm) and posterior less than 15mm) which may treat with MWA (microwave ablation) or surgery. We see very good response from treatment of this patient.

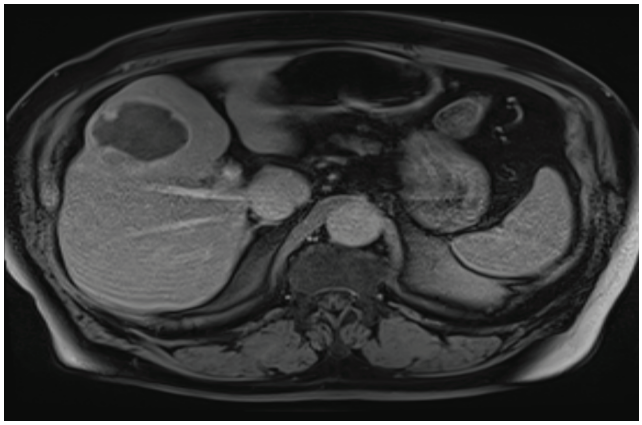


Figure 7 - MRI 3 month after the procedure follow up

The patient stayed in hospital only one night. Drug used 2 g cephazolin iv, pantoprazole iv. Next day patient went home without any complain. This modest experience in transcatheter arterial chemoembolization (TACE) treatment in a patient with hepatocellular carcinoma (HCC) inoperable is hoped to make this way of treatment more common to help this patient.

Not all patients with intermediate HCC may benefit from TACE [40].

Patients with intermediate-stage HCC present a wide range of tumor burden, tumor biology, liver function, and comorbidities.

Adequate patient selection for TACE is essential to maximize therapeutic effect. Therefore, in addition to staging systems for HCC, other selection criteria have been developed to predict treatment response after TACE to aid decision making.

Discussion.

The only treatment that has shown a survival benefit for patients with intermediate-stage HCC (BCLC stage B) is TACE.

This treatment is mainly at the level of arterial vascularization of HCC, which includes selective catheterization of the hepatic artery and supra selective of the arteries feeding the tumor, and injection of a chemotherapeutic agent along with blood flow through an embolizing substance. [41]

The TACE technique is contraindicated in patients with decompensated cirrhosis (such as after the Child-Pugh B ≥ 8 classifications, which include jaundice, encephalopathy, refractory ascites), in cases with the involvement of two lobes, when we have reduced portal vein flow (thrombosis or hepatofugal leakage), intractable arteriovenous fistulas, or biliary stenting, and creatinine clearance <30 ml/min. [41]

In these cases, there is a high risk of disease decompensation, and although an objective tumor response may be achieved, the survival benefit is limited. [41]

The survival benefit of TACE is based on some randomized controlled trials [42, 43] and subsequent meta-analysis of pooled data,[44] which show that TACE is better than placebo in patients with HCC intermediate, obtaining a median survival with the treatment of approximately 20 months. [44]

Conclusion:

TACE is a safe method for prolonging patients' survival with unresectable HCC. The correct treatment of HCC is concentrated in cancer centers, and cooperation between multiple specialists is necessary.

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