Y-90 PERSONALISED DOSIMETRY TARE VERSUS DEB-TACE IN THE TREATMENT OF BCLC B HEPATOCELLULAR CARCINOMA

A MULTICENTRE, RANDOMISED, OPEN-LABEL CLINICAL TRIAL

FINAL DEGREE PROJECT

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1. ABREVIATIONS

HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
DNA	Deoxyribonucleic acid
HCV	Hepatitis C virus
NAFLD	Non-alcoholic fatty liver disease
PBC	Primary biliary cirrhosis
HH	Hereditary haemochromatosis
AAT	Antitrypsin-α 1 deficiency
BCLC	Barcelona clinic liver cancer
TACE	Transarterial chemoembolization
MRI	Magnetic resonance imaging
CT	Computed tomography
RE	Radioembolization
TARE	Transarterial radioembolization
SIRT	Selective Internal Radiotherapy
mCRC	Metastatic colorectal carcinoma
BSA	Body surface area
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SPECT	Single photon emission computed tomography
PVT	Portal vein thrombosis
LSF	Lung shunt fraction
ECOG	Eastern Cooperative Oncology Group
DEBs	Drug-Eluting Beads
RFA	Radiofrequency ablation
PS	Performance status
TIPS	Transjugular intrahepatic portosystemic shunt
NASH	Non-Alcoholic SteatoHepatitis
MRI	Magnetic resonance imaging
HUDJT	Hospital Universitari Doctor Josep Trueta
MMA	Macroaggregated albumin
RILD	Radiation induced liver disease
LRT	Locoregional treatment
OS	Overall survival
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
CEIC	Comitè d'Ètica d'investigació Clínica

2. ABSTRACT

BACKGROUND: Liver tumours are a major health problem worldwide with a rising incidence and increasing prevalence of intermediate and advanced stages with a poor prognosis. This has led to the development and use of new therapeutic procedures, including various minimally invasive intra-arterial local treatments, such as TARE. Transarterial Radioembolisation (TARE) is presented as a promising therapeutic alternative to the loco-regional treatments accepted in clinical practice, but until now, it has not been able to show a significant increase in terms of survival in intermediate HCC. Due to that, it has not replaced TACE as a gold-standard treatment for Intermediate Stage disease according to the BCLC system (BCLC B). The role of radioembolisation is still to be defined and further trials are necessary to delineate which group of patients could benefit from this therapy. Scientific evidence supports that personalised dosimetry will improve outcomes in clinical practice and future clinical trials must be conducted using this approach. If we demonstrate that personalised dosimetry improves the outcomes of this technique, it would be the beginning of a paradigm shift and would justify the lack of increased survival in all current evidence where personalised dosimetry has not been used.

OBJECTIVE: The aim of this study is to demonstrate that personalised dosimetry TARE offers better outcomes than DEB-TACE in patients diagnosed with BCLC B Hepatocellular Carcinoma.

DESING: This study will be carried out through a multicentric, prospective, randomised, open-label clinical trial performed among fifteen hospitals belonging to the National Health System from January 2022 until December 2026.

PARTICIPANTS: Study subjects will consist of 18 years or older reference population of each of the hospitals participating in this clinical trial, that are diagnosed of an intermediate stage hepatocellular carcinoma BCLC class B.

METHODS: A non-probabilistic consecutive method will be used. Patients treated in the hospitals included in the study who meet the inclusion and exclusion criteria will be requested to participate. 756 patients will be assigned randomly to one of the two intervention groups on a 1:1 ratio: Control group TACE n=378 and Intervention group TARE n=378. A two-year follow-up will be carried out.

KEYWORDS: Clinical Trial, Prospective, Liver Cancer, Hepatocellular carcinoma, HCC, BCLC B, Intermediate Stage, Radioembolization, TARE, Y-90, Personalized dosimetry, Selective internal radiation therapy, TACE, DEB-TACE, Locoregional treatment, Overall survival.

3. INTRODUCTION

3.1. HEPATOCELLULAR CARCINOMA (HCC)

3.1.1. DEFINITION

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver composed of epithelial cells showing hepatocellular differentiation (1).

Table 1: ICO-3 Topography Liver Code (2).

ICO-3 Topography Codes	
Code	Description
C22.0	Liver

Table 2: WHO Hepatocellular Carcinoma Classification (2).

WHO Classification of Tumours	
Code	Description
8170	Hepatocellular carcinoma
8171	Fibrolamellar carcinoma
8172	Scirrhous hepatocellular carcinoma
8173	Sarcomatoid hepatocellular carcinoma

3.1.2. EPIDEMIOLOGY

Hepatocellular carcinoma (HCC) accounts for 80-90 % of primary malignant liver tumours (3). It is currently the sixth most frequent neoplasia in the world and the third most common cause of cancer death (4). It accounts for approximately 5.4 % of all cancers worldwide and it is one of the most common cancers in geographic areas with high rates of Hepatitis B (5). Worldwide distribution is very heterogeneous and is related to the prevalence of the different risk factors for this disease. It represents more than 1 million new cases annually around the world (4).

According to the International Agency for Research on Cancer (IARC) the age-specific incidence rate of this type of tumour in Southern Europe is 6.8 x 100,000 inhabitants, in Western Europe 5.3 x 100,000 inhabitants and in North America 6.6 x 100,000 inhabitants

(4). Spain belongs to an area of intermediate incidence and mortality. Sub-Saharan Africa and Southeast Asia are areas of high incidence. The cause of these geographical differences is based on the exposure to certain oncogenic factors that favour HCC development (3).

In developed countries, hepatocellular carcinoma is present in liver cirrhosis in more than 90 % of cases. Cirrhosis associated with viral infection, alcoholism and haemochromatosis has a greater oncogenic capacity. The probability of developing HCC at five years in cirrhotic patients may exceed 15-20 % (3).

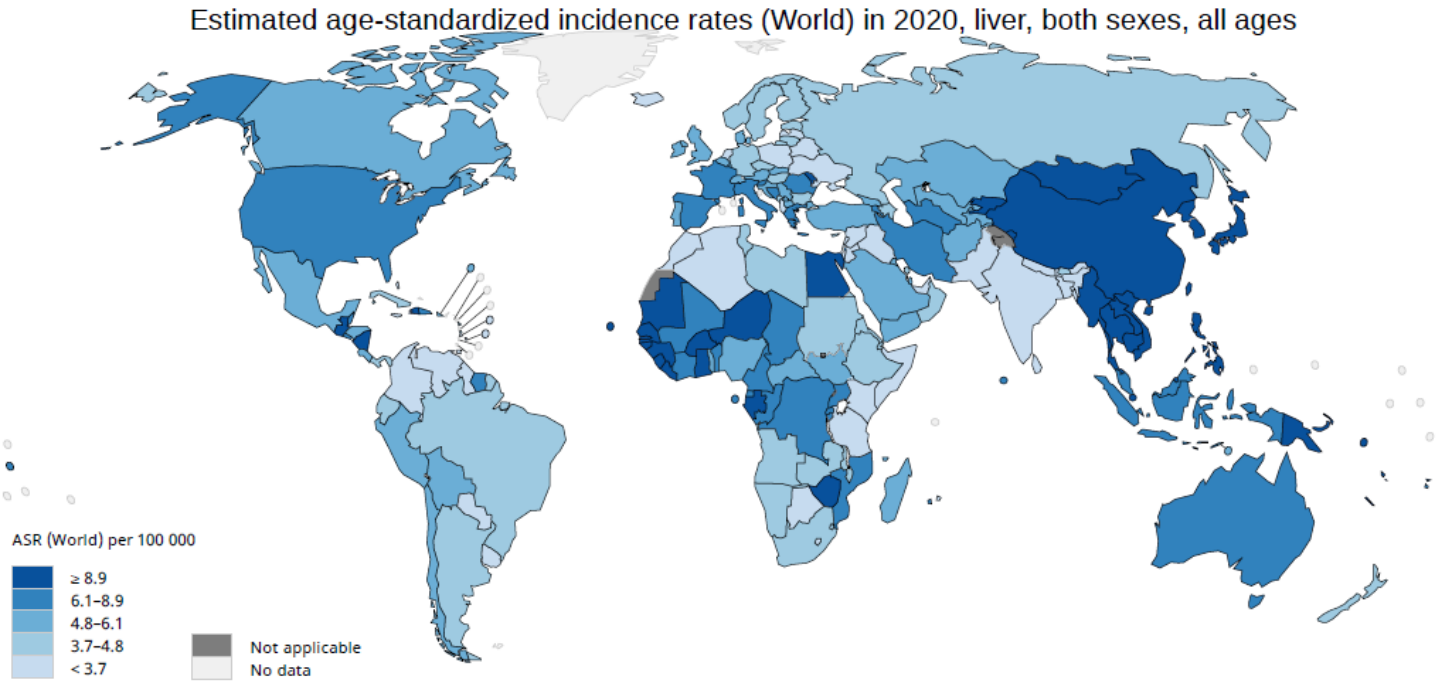

Figure 1: Estimated age-standardised incidence rates (World) in 2020, liver, both sexes, all ages. GLOBOCAN 2020.

In Spain, the *Red Española de Registros de Cáncer* estimated that there were 6.499 new cases of liver cancer in 2019, of which 4.869 were men and 1.630 were women (4).

CAN GIR number six of September 2021 establishes that this group of tumours has an average annual incidence in both sexes of 97 cases in our environment. It is the seventh most common tumour in men and is not in the top ten most common tumours in women (6).

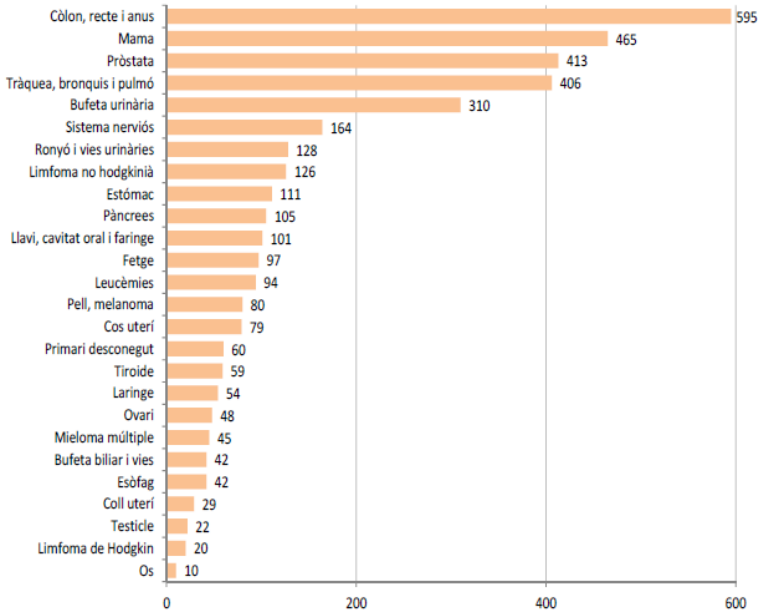

Figure 2: Annual average number of incident cases in both sexes. Period 2013 - 2017 (6).

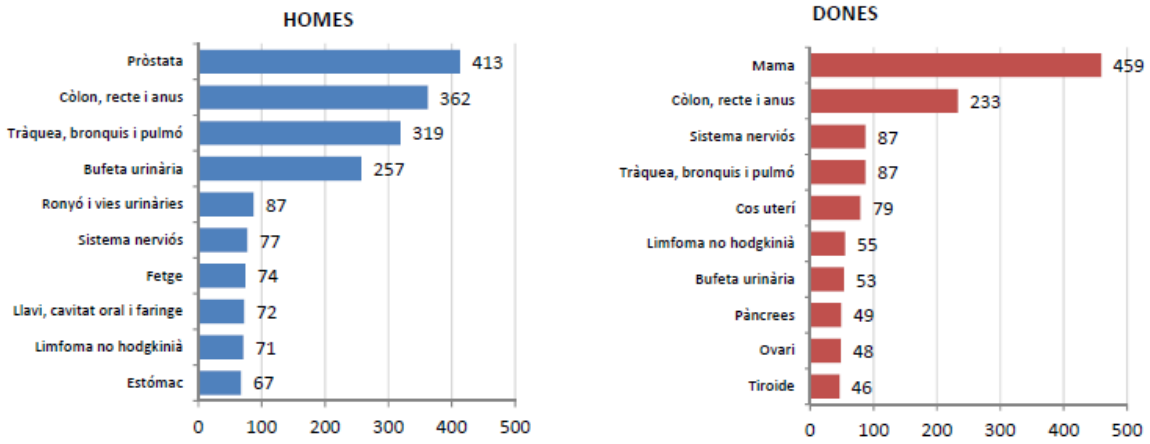

Figure 3: Average annual number of incidents by sex. Period 2013 - 2017 (6).

The average annual number of deaths from this type of tumour are 67 cases, making it the eighth most common neoplasm in terms of deaths. In our population, it is the fifth cancer with the highest mortality in men, not appearing in the ten most frequent causes of death in women (6).

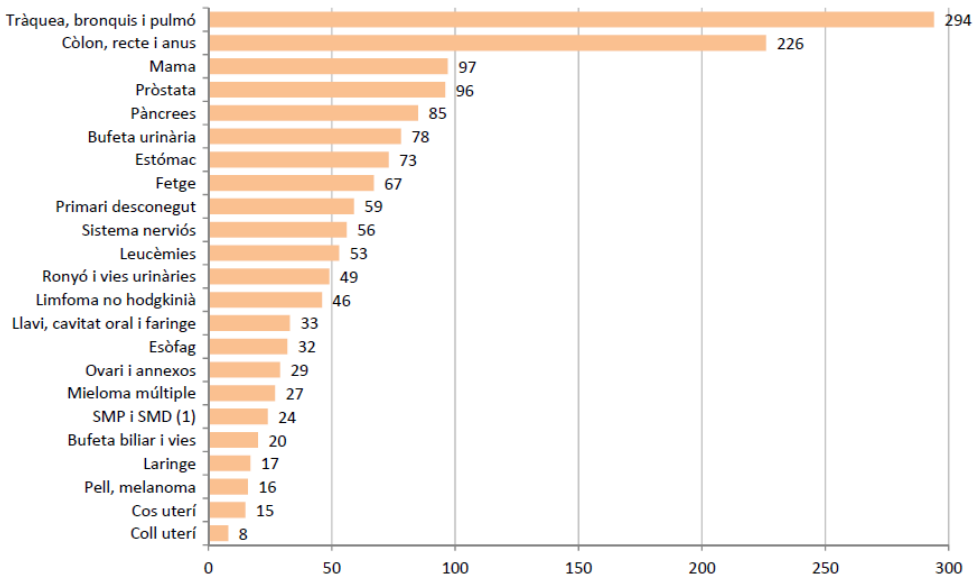

Figure 4: Average annual number of deaths from cancer in both sexes. Period 2013- 2017 (6).

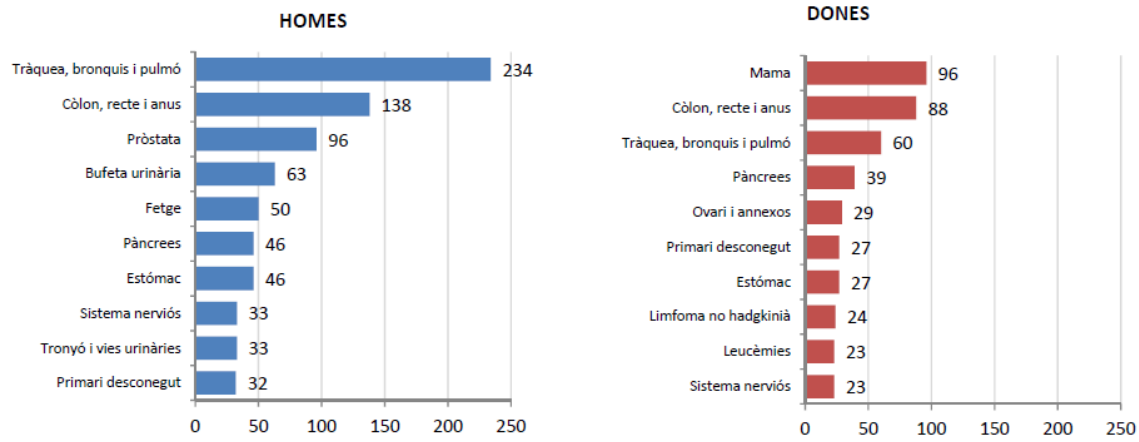

Figure 5: Average annual number of deaths from cancer by sex. Period 2013 - 2017 (6).

3.1.3. RISK FACTORS

In all populations, the risk of HCC depends on the degree of liver fibrosis, being less than 1 % per year in patients without liver fibrosis and increasing to 3-7 % per year in patients who have developed cirrhosis, therefore, the relevant risk is acquired with its establishment. The intensity of the hepatic inflammation is the responsible of the chronic

process of necrosis/regeneration that progresses to cirrhosis (4). Cirrhosis, regardless of its cause, predisposes patients to HCC and It is present in 70-90 % of HCC patients at diagnosis (7).

Chronic HBV infection affects 380 million individuals worldwide. There is a geographical overlap between areas with a high incidence of HCC and areas with a high HBV penetration rate. In Asia and Africa, chronic HBV infection is the leading cause of HCC (7). Chronic HBV infection has been shown to increase the risk of developing HCC (8), while implementation of HBV vaccination campaigns against HBV decreases the incidence of HCC. It should be noted that current HBV antivirals do not completely eliminate the risk of HCC, especially in patients with cirrhosis, in whom even very low viral means an increased risk of HCC compared to patients with undetected HBV DNA (9). Its oncogenic mechanism is thought to be related to the integration of viral DNA into the hepatocyte genome (3).

Currently, around 170 million individuals are infected with HCV worldwide and, as with HBV, there are significant geographic differences in prevalence. Chronic C hepatitis infection is the leading cause of HCC in North America, Europe and Japan (7). In Spain more than 70 % of patients with HCC have antibodies to HCV. The development of a prophylactic vaccine as primary prevention is still a challenge due to the high variability of viral genetics, although much progress is being made (10). Therefore, prevention is primarily based on the avoidance of transmission, in particular through the transfusion of blood products or contaminated needles (4). Its oncogenic action would be achieved by the binding of viral proteins to transcription factors and/or by oxidative DNA damage due to the chronic inflammation process of liver inflammation/repair (3).

Excessive alcohol intake induces liver damage that can lead to cirrhosis. In this circumstance, an elevated risk of HCC is acquired, as is the case with any aetiology of cirrhosis: hereditary haemochromatosis, primary biliary cirrhosis, etc. Alcohol excessive intake is the most important cause of HCC in Spain (11). A meta-analysis of cohort studies showed that abstinence reduced the risk of HCC by 6-7 % per year. The patients with alcohol HCC are most often diagnosed at an advanced stage, within decompensated cirrhosis, and

less frequently in surveillance programmes, compared to those with viral aetiology (12). The combination of alcohol intake with viral infection exerts a synergistic oncogenic action (3).

Non-alcoholic fatty liver disease (NAFLD) is an entity of increasing incidence and carries a risk of progression to cirrhosis and liver cancer. About 25 % of the of the world's population has NAFLD (4,13).

Aflatoxin B1 is a potent hepatocarcinogen produced by *Aspergillus flavus* and *A. parasiticus*, fungi that require humidity and heat for growth and often contaminate food stored under these conditions like cassava, corn, and peanuts. In some countries where the incidence of HCC is high, high rates of aflatoxin B1 have been found. Its mechanism of action is not known. It should be noted that in countries with high aflatoxin contamination, there is also a high prevalence of viral infection, and therefore it is not possible to delimit the importance of each of these factors. The recognition of aflatoxin-specific alterations of P53 and the implementation of HBV vaccination programmes should clarify the importance of each of them (3,7).

Based on reasonable evidence, cigarette smoking increases the risk of HCC. In the absence of viral infection, it is associated with up to a two-fold increase in HCC risk. People who have quit smoking have a lower risk than current smokers, although both groups have a higher risk than people who have never smoked.

Some types of autoimmune diseases that affect the liver can also cause cirrhosis. For example, in primary biliary cirrhosis (PBC), the bile ducts in the liver are affected and even destroyed, which can lead to cirrhosis. People with advanced PBC have a high risk of liver cancer.

Based on solid evidence, untreated hereditary haemochromatosis (HH), antitrypsin-α 1 deficiency (AAT), glycogenosis, porphyria cutanea tarda and Wilson's disease increase the risk of HCC but cause very few cases.

Obesity increases the risk of liver cancer. This is probably because it can lead to fatty liver disease and cirrhosis.

Diagnosis of metabolic syndrome (MS) is associated with an increased risk of HCC.

Type 2 diabetes has been associated with an increased risk of liver cancer, usually in patients who also have other risk factors, such as heavy alcohol consumption, chronic viral hepatitis, or both. This risk may also be increased because people with type 2 diabetes are often overweight or obese, which in turn can cause liver problems (7).

3.1.4. ANATOMOPATHOLOGICAL CHARACTERISTICS

In the macro description it presents as a single mass, multiple nodules, or as diffuse liver involvement simulating cirrhosis. The lesions may be poorly circumscribed or even have a thick capsule surrounding them. In some cases, the tumour may also be pedunculated. The size of the tumour varies greatly between cases. Portal thrombosis (including thrombosis with tumour) occurs in many advanced cases.

Microscopically, HCC can have a trabecular, solid, or pseudo-glandular growth pattern. Multiple growth patterns are often present in the same tumour. A few histological variants have also been described, most of which, have no clinical implications.

In 80 % of cases, the portal venous system is affected, which can lead to the inferior cava or even the right atrium. Involvement of the biliary tree is less common but can occur. The most common sites of extrahepatic dissemination are lungs, bone, and abdominal lymph nodes. Other less common sites of dissemination are brain, adrenal, and head and neck (14).

3.1.5. DIAGNOSTIC (ANNEX 1)

Ultrasound follow-up plays a key role in the diagnosis of hepatocellular carcinoma in the vast majority of cases. In a cirrhotic liver, the likelihood that a newly ultrasound-detected nodule will be HCC is very high, especially if its diameter exceeds 10 mm. Because of that,

if the detected nodule reaches or exceeds this limit, it is advisable to continue studies to reach a definitive diagnosis.

HCC has a predominantly arterial vascularisation due to neovascularisation with a progressive decrease in portal radicals as the process of hepatocarcinogenesis progresses. This differentiates it from the liver parenchyma where the vascularisation is mixed with an arterial and portal supply. The characteristic vascular pattern of HCC is characterised by intense contrast uptake in the late arterial phase, followed by washout of the lesion in the venous phases.

This is manifested in the imaging techniques by a higher density/intensity signal of the lesion in the late arterial dynamic phase of the study (washin) and a lower density/intensity signal of the lesion with respect to the neighbouring liver parenchyma in the portal and/or late phase (washout). This characteristic pattern Washin-Washout has shown a specificity of close to 100 % for the diagnosis of HCC, favoured by the high pre-test probability of HCC in patients with chronic liver disease (4).

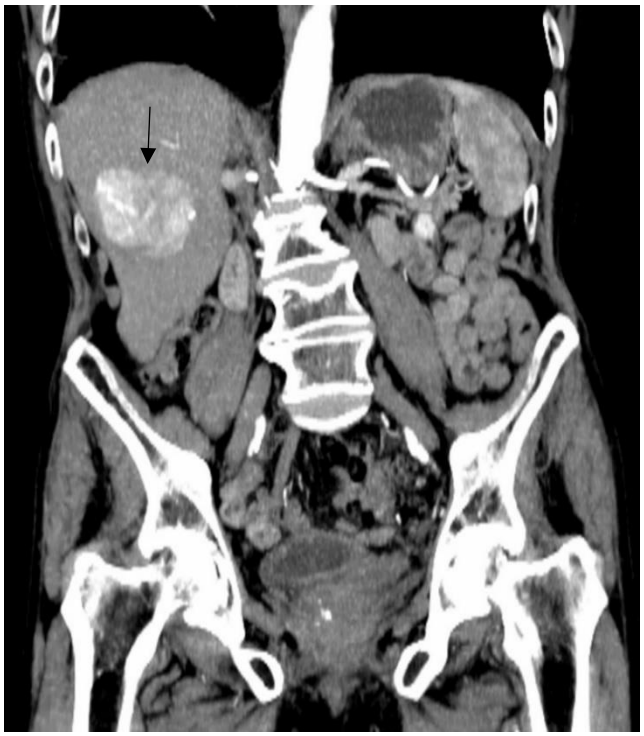

Figure 6: Basal Coronal CT-scan. From HUDJT.

3.1.6. BCLC PRONOSTIC CALSSIFICATION AND TREATMENTS (ANNEX 2)

The most used staging system for HCC in Western countries is Barcelona Clinic Liver Cancer (BCLC). Due to the BCLC system, prognosis is based on factors related to tumour stage (lesion number and size, the presence of vascular invasion, and extrahepatic spread), on liver function (Child-Pugh status), and on the presence of cancer-related symptoms (ECOG-performance status) (15). It establishes prognosis according to five stages that are related to the possible indication of treatment (4).

The Very Early Stage (Stage 0) is a group with a particularly good prognosis, which includes patients with compensated cirrhosis of the liver (Child-Pugh A), totally asymptomatic, with single tumours smaller than or equal to 2 cm without vascular invasion or spread. This very early stage corresponds to the concept of carcinoma in situ. Percutaneous ablation, in these cases, offers a high chance of cure, with similar survival with to those obtained with surgical resection, but with lower cost and morbidity. Because of this, it is considered the first therapeutic option, especially for those patients who have no options for a future liver transplant.

The Early Stage (Stage A) includes asymptomatic patients with preserved liver function (Child-Pugh A and B without liver function criteria for liver transplant) with solitary HCC or a maximum of three nodules up to 3 cm in diameter. These patients can be treated with curative intent by surgical resection, percutaneous ablation, and liver transplantation. They have an expected five-year survival between 50-75 %.

The Intermediate Stage (Stage B) consists in patients with multinodular tumours exceeding the criteria described above, without vascular or extrahepatic invasion, with liver function and general condition preserved. The expected treatment-free survival in this group of patients is 49.6 % (95 % CI 32-75 %) at one year. Transarterial Chemoembolisation of the liver (TACE) is the only treatment that has demonstrated efficacy in terms of survival (4,15).

Patients with preserved liver function, but with HCC with vascular and/or extra-hepatic invasion or mild general condition are classified as Advanced Stage (stage C). In this group

of patients, median treatment-free survival is 4-8 months, and they are candidates for systemic treatment.

Finally, patients who present with severe impairment of general condition and/or compromised liver function (Child-Pugh C or Child-Pugh B cirrhosis with decompensation associated with poor prognosis such as refractory ascites, chronic/recurrent hepatic encephalopathy, or spontaneous bacterial peritonitis) and who are not candidates for liver transplantation are Stage D or End-stage. Their median survival is less than three months and only symptomatic treatment should be indicated (4).

3.1.7. HEPATIC ANATOMY

Normal liver is brown in colour and has a smooth external surface. It weighs about 1400 g in women and 1800 g in men, which is about 2 % of the weight of an adult person (16). It´s located on the right upper quadrant of the abdomen, where it is protected by the rib cage and diaphragm. It occupies most of the right hypochondrium and the upper epigastrium and it extends into the left hypochondrium (17).

ANATOMICAL DIVISION

Externally, the liver is divided into two anatomical lobes and two accessory lobes. The plane formed by the intersection of the falciform ligament, and the left sagittal fissure separates the large right lobe from the left lobe, which is smaller. On the inclined visceral side, the umbilical and main portal fissures are located on either side of the two accessory lobes, which are part of the anatomical right lobe. These are separated by the hepatic portal and are the square lobe, which is located anteriorly and inferiorly; and the caudate, located posteriorly and superiorly. Both lobes are connected by a caudate process (18).

FUNCTIONAL DIVISION

The functional anatomy of the liver is fundamental for radiologists and surgeons. At the functional level, the Couinaud classification differentiates eight segments in the liver (18–20).

In the hepatic hilum, the hepatic proper hepatic artery, the hepatic portal vein, and the common hepatic duct penetrate the liver forming the portal triad of vessels. The central branch divides into two major branches (primary division of the portal triad) and subdivides the liver functionally. This forms a left hepatic portion, the right hepatic portion, and the caudate lobe (segment I), which functions independently from these two and may be considered a third portion. Between right and left portions, an imaginary line is established that joins the inferior vena cava bed with that of the gallbladder (18).

In this way the liver can be subdivided in four divisions, and these, in eight hepatic segments being each one of them irrigated independently by a secondary or tertiary branch, respectively, of the portal triad. Each hepatic portion has its own branches of the hepatic artery, the hepatic portal vein, and its own biliary drainage. In addition, each liver segment has a hepatic venous branch that carries the outflow of blood (16). Caudate lobe has to be considered an exception due to the fact that it receives vessels from the left and right bundles and drains through one or two hepatic veins that go directly to the inferior vena cava (18).

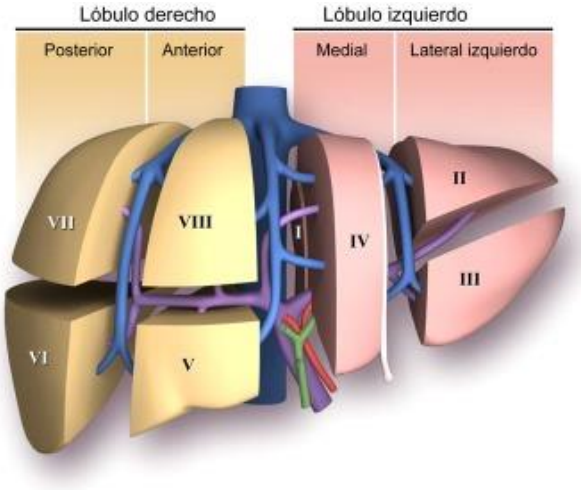

Figure 7: Segmental anatomy of the liver (16).

Therefore, we can differentiate seven segments in the main part of the liver (segments II-VIII) numbered clockwise, and the caudate lobe, which represents segment number I. In relation to the aforementioned division, on the left side of the liver we will place the numbers II, III and IV, and on the right side the numbers V, VI, VII and VIII (18).

Although the segmentation pattern we have described is the most frequent, the segments may vary in shape and size due to anatomical variations of the hepatic and portal vessels and are related to embryological development (18).

Due to this, in radioembolization and in other surgical and non-surgical techniques, we can intervene in segments without affecting the totality of the liver (18).

The regional lymph nodes are the hepatoduodenal ligament, hilar, inferior phrenic, and caval lymph nodes. Within the latter, the most prominent are those of the portal vein and hepatic artery (21).

ARTERIAL ANATHOMY

Celiac artery is the first branch of the three odd-numbered arteries originating from the abdominal aorta, usually at the level of the T12-L1 vertebra (22,23).

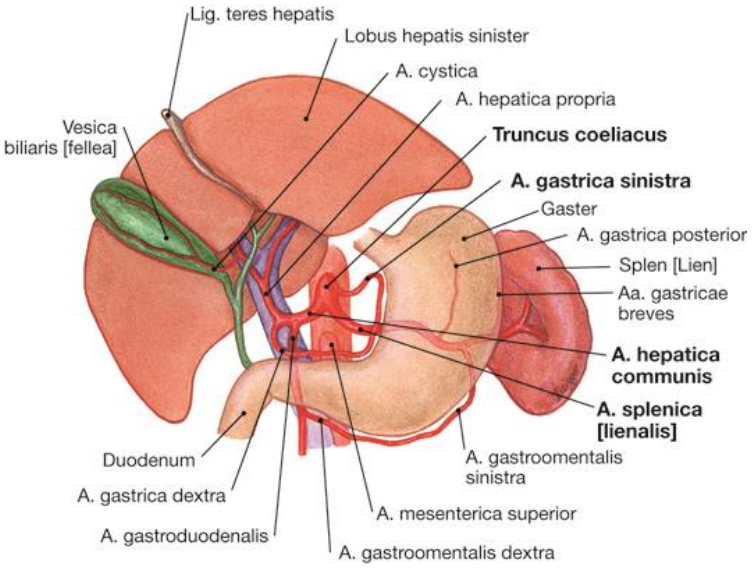

Figure 8: Celiac trunk arterial anatomy (24).

It will give rise to the common hepatic artery, the splenic artery, and the left gastric artery. The common hepatic artery, after giving rise to two branches, the right gastric artery, and the gastroduodenal artery, will form the proper hepatic artery. This will divide to form the right hepatic artery and the left hepatic artery (17,23).

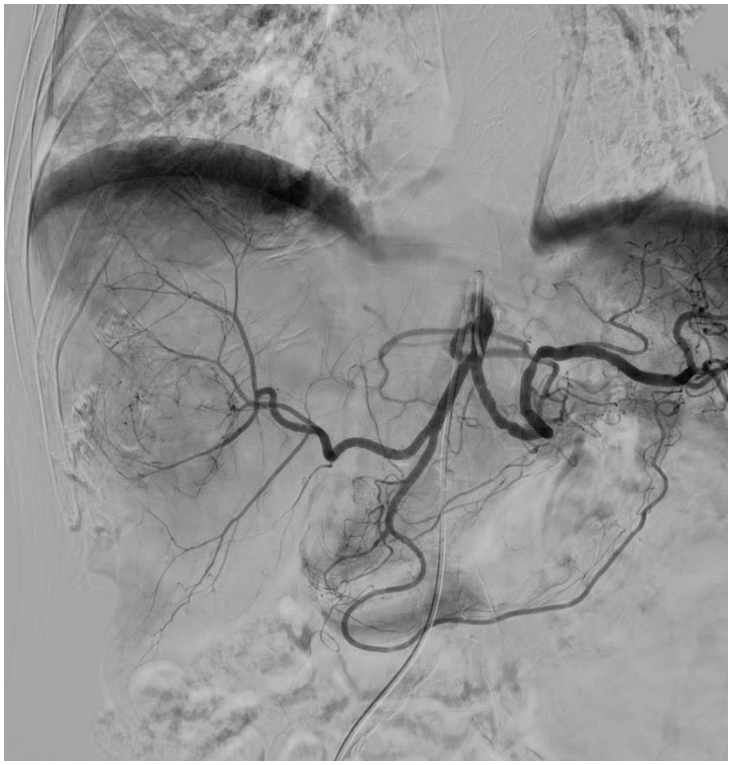

Figure 9: Celiac trunk arteriography. From HUDJT.

3.2. INTERVENTIONAL RADIOLOGY

Interventional radiology is a subspecialty of radiology that focuses on the diagnosis and/or treatment of a wide range of diseases in a minimally invasive manner.

Procedures are carried out using imaging techniques, including X-rays, ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT).

Interventional radiology has gained a lot of importance in recent years as an important alternative to surgical treatment. Its treatments involve, in most cases, shorter hospital

stances, do not require general anaesthesia and have lower risks, less pain and less convalescence compared to traditional surgery (25).

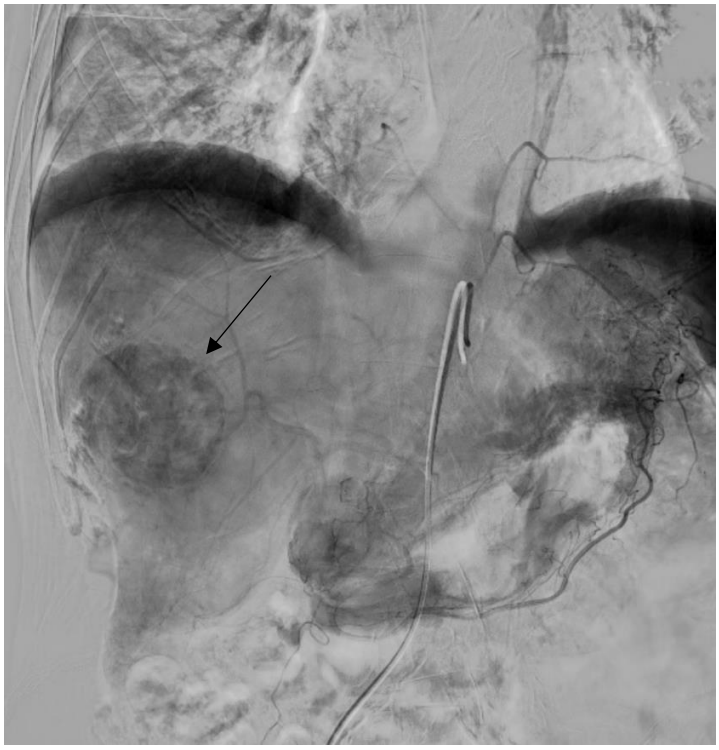

Figure 10: Enhancement of a hepatic nodule during the catheterisation. From HUDJT.

Table 3: Angiographic Appearance of HCC (26).

HCC	**Vascuarity**	Vascular
	Angiographic Findings	Solitary or multifocal; neovascularity, parenchymal stain, arteriovenous shunting; hepatic and portal thrombus

3.3. RADIOEMBOLISATION

Radioembolisation (RE) also known as Transarterial Radioembolisation (TARE) or Selective Internal Radiotherapy (SIRT) is a therapeutic technique based on the intra-arterial injection of a high-energy radioisotope in the form of microspheres, which aims to selectively

irradiate a tumour. This technique is based on the use of radioactive microspheres labelled with Yttrium-90 (Y-90) through the hepatic artery. Y-90 is a high-energy beta emitter with a half-life of 64 hours and a tissue penetration of 2.5 mm that decays to stable Zirconium-90.

TARE is being used basically in the treatment of malignant liver tumours and in some liver metastases from other tumours, when other therapeutic options (surgery, chemotherapy, radiotherapy, radiofrequency, chemoembolisation...) have been discarded or have proved ineffective. In Europe, the most common indication for radioembolisation is HCC, followed by metastatic colorectal carcinoma (mCRC).

Radioembolisation in Hepatocellular carcinoma (HCC) is possible thanks to the hypervascularisation of the tumour, more than 80 % of which comes from the hepatic artery. Vascularisation of healthy liver tissue comes from the portal vein. Therefore, we can understand that the radiation will have a highly selective effect on the tumour. In relation to hepatic metastases, vascularisation is very variable. Some are very poorly vascularised, as in the case of those from colon or pancreatic tumours; and others, are highly vascularised, as in the case of those secondary to neuroendocrine, breast, renal or thyroid tumours. Even so, thanks to the small size of the particles used in RE we can overcome the limitation caused by hypovascularisation and affirm that the radiation will selectively reach the tumour tissue.

Although it is not a curative technique, TARE improves the quality of life of patients with inoperable liver tumours. In some cases, it will reduce the tumour stage or induce hypertrophy, opening the possibility of surgery or other therapeutic procedures that were initially ruled out. The patient is usually discharged in less than 24 hours and will not require hospitalisation in a specially designed radiation protection room. It is recommended, however, that the patient be in a room for individual use.

This is a technique that will normally be demanded by liver surgeons, hepatologists or oncologists in the case of a multidisciplinary committee, and its performance will require

interventional radiologists, physicians specialising in nuclear medicine, radiophysicists, radiopharmacists and other professionals involved in the different phases of the process: angiography, pre- and post-therapeutic scans, dose calculation, radiopharmac preparation, and clinical management of the patient (27–30).

3.3.1. HISTORICAL CONTEXT

Y-90 use in the treatment of liver tumours dates to 1960s. Nolan and Grady described the use of Yttrium-90 oxide (Y-$90_2 0_3$) to treat histologically proven cancer in humans. From that time on, a very small number of countries began to develop and improve the protocols for this technology. The results were very promising, but due to the collateral damage to both healthy non-tumorous hepatic and extrahepatic tissue, this technique had a very limited use until the 1980s. It was at this time when SIR-Spheres ® and TheraSphere™ began to be commercialized. In addition to the improvement in their technology, a substantial improvement in all aspects related to computed tomography took place. During these years, CT spread throughout the world and the clinical use of radioembolization with Y-90 began to be resumed (31).

3.3.2. MICROSPHERES AVAILABLE FOR TARE

We currently have 3 radiopharmaceuticals marketed in Spain with the approved indication to perform TARE. They differ in the type of radioisotope they use and the type of material they are made of. Two of the types contain the Y-90 isotope. 90-Y is a pure beta emitter with a physical half-life of 64.1 hours which decays to stable zirconium-90 (22). One is made of resin (SIR-Spheres®, Sirtex Medical Ltd, Woburn, MA, United States) and the other of glass (TheraSphere™, Boston Scientific, Marlborough, MA, United States). There are other Poly-L-

lactic acid microspheres labelled with Holmium-116 (QuiremSpheres®, Quirem Medical B.V., Deventer, the Netherlands) (27).

Technical characteristics of the microspheres are summarised in Table 4 (27).

Table 4: Technical characteristics of the microspheres.

Features	SIR-Spheres®	TheraSphere™	QuiremSpheres®
Radioisotope	Yttrium-90	Yttrium-90	Holmium-166
Half-life (h)	64.1h	64.1h	26.8 h
Main emitted radiation	Beta	Beta	Beta and gamma
Mean (maximum) tissue penetration (mm)	2.5 (11)	2.5 (11)	2.5 (8.4)
Visualisation method	Bremsstrahlung-SPECT Yttrium-90 PET	Bremsstrahlung-SPECT Yttrium-90 PET	MRI SPECT
Material	Resin	Glass	Poly-L-lactic acid
Microsphere size (mm; range)	32.5 (20e60)	25 (20e30)	30 (25e35)
Specific activity per sphere (Bq)	40-70	4354*, 1539**, 544***	200-400
Millions of spheres in a typical administration	20-40	1.7** 4.8***	12-24
Embolic effect	Moderate	Low	Moderate
Treatment planning method indicated in product leaflet.	BSA (two compartment)	Mono-compartment	Mono-compartment

BSA: body surface area; **MRI**: magnetic resonance imaging; **PET**: positron emission tomography; **SPECT**: single photon emission computed tomography.

* Measured, at the reference date.
** Four days after the reference time.
*** Eight days after the reference time.

Current evidence seems that the three products have a very similar clinical impact, with differences in terms of procedure, radiopharmaceutical characteristics, marking, dispensing

formats, dosing, and emission energies. That make necessary to evaluate individually which option is the most optimal in each case (32).

3.3.3. INDICATIONS, ABSOLUTE CONTRAINDICATIONS AND RELATIVE CONTRAINDICATIONS OF THERASPHERE™ AND SIR-SPHERES® FOR TARE (22)

TARE will be **indicated** in the following clinical situations:

1. Glass microspheres
   a) TheraSphere™ was approved by the U.S. Food and Drug Administration (FDA) in 1999 under a humanitarian device exemption, defined as safe and probably beneficial for the treatment of unresectable hepatocellular carcinoma (HCC) with or without portal vein thrombosis (PVT), or as a bridge to transplantation in patients who could have appropriately positioned catheters. This device is also approved for the treatment of liver neoplasia in Europe and Canada.
2. Resin microspheres
   a) SIR-Spheres® were granted premarket approval by the FDA in 2002, defined as safe and effective for the treatment of metastatic colorectal cancer to the liver with concomitant use of floxuridine. This device is also approved in Europe, Australia, and various Asian countries for the treatment of liver neoplasia.

As **absolute contraindications** of TARE we would have:

1. Contraindications to angiography:
   a) Uncorrectable coagulopathy.
   b) Severe renal insufficiency.
   c) Severe anaphylactoid reaction to iodinated contrast agents.
   d) Severe peripheral vascular disease precluding arterial access.
2. Immediate life-threatening extrahepatic disease.
3. Inability to prevent ^{90}Y delivery to the gastrointestinal (GI) tract.
4. Hepatopulmonary lung shunting:

a) For TheraSphere™, the limitation of what can be administered to the lungs is based on the lung dose, not lung shunt fraction (LSF) (30 Gy per infusion, 50 Gy cumulative).
b) For SIR-Spheres®, infusion is limited by the LSF (20%).

As **relative contraindications** we would have:

1. PVT:
   a) Patients with main PVT have poor prognosis; Child-Pugh A patients with main PVT may be safely treated.
   b) Radioembolization is not contraindicated in lobar or segmental PVT.
2. Poor hepatic reserve:
   a) Total bilirubin >2 mg per dL.
   b) Risks may be mitigated by selective radioembolization.
3. Poor performance status:
   a) Eastern Cooperative Oncology Group (ECOG) >2.
4. Biliary obstruction:
   a) Risks of infectious complications significantly higher in the setting of compromised sphincter of Oddi.

3.3.4. COMPLICATIONS OF RADIOEMBOLISATION

Table 5: Complications of Radioembolisation for Hepatoma (32).

Radiation hepatitis	0%-4%
Cholecystitis	1%
Gastrointestinal ulceration	<5%
Postembolization syndrome requiring extended stay or readmission	<1%
Pain, fatigue, nausea	20%
Biliary (focal dilation, biloma)	10%

3.3.5. CURRENT CONTEXT IN THE CATALAN AND SPANISH HOSPITAL NETWORK

Today, this technique is already being performed routinely in some of the hospitals of the ICS network (Vall d'Hebron, Bellvitge and Germans Trias i Pujol de Badalona). There is also experience in assistance at Hospital Clínic de Barcelona, Hospital de Sant Pau, and Hospital Parc Taulí de Sabadell.

In Spain, this procedure has been performed for several years in multiple hospitals in the Autonomous Communities of:

- Madrid: La Paz, Gregorio Marañón, Puerta de Hierro, Ramon y Cajal, Fundación Jiménez Díaz, Doce de Octubre and La Princesa.
- Valencia: La FE, Hospital Clínico, Hospital del Vinalopo.
- Navarra: Clínica Universitària, Hospital de Navarra.
- Castilla León: Hospital de Burgos, Hospital de Valladolid and Hospital de Salamanca.
- Galicia: Santiago de Compostela, Hospital Álvaro Cunqueiro de Vigo and Hospital Lucus Augusti de Lugo.
- Andalucía: Virgen del Rocío de Sevilla and Virgen de las Nieves de Granada.
- Canary Islands: Virgen Candelaria and Hospiten Rambla de Tenerife.
- Islas Baleares: Clínica Rotger.
- Extremadura: Infanta Cristina.
- Murcia: Virgen de la Arrixaca.
- Aragón: Hospital Clínico de Zaragoza.
- Asturias: Hospital General de Asturias.

3.4. CHEMOEMBOLISATION

TACE is the treatment of choice in patients with intermediate HCC, stage B of the BCLC classification due to clinical guidelines. It consists of selective catheterisation of the hepatic

artery, supraselective catheterisation of the of tumour nutritional arteries, and injection of a chemotherapeutic agent with occlusion of arterial flow by means of an embolising substance (33). TACE has robustly demonstrated benefit in terms of survival (34–36).

TACE is indicated in patients with compensated liver disease with multifocal tumours without vascular invasion or extrahepatic dissemination. It is considered contraindicated in patients with decompensated cirrhosis and/or multicentric involvement of both hepatic lobes that preclude a selective intervention, absence of portal flow (thrombosis or hepatofugal flow), untreatable arteriovenous fistula, biliary-enteric anastomosis or biliary stent and a creatinine clearance <30 mL/min. In these cases, there is a high risk of decompensation of the liver disease, and although an objective tumour response can be achieved, the survival benefit is marginal (37).

There are available microspheres that can be loaded or coated with chemotherapeutic agents and provide more controlled drug delivery to the liver than conventional TACE. It´s known as Drug-Eluting Beads TACE (DEB-TACE). The administration of DEBs follows the same principles as TACE. Lobar or selective treatment is preferred to whole liver embolisation. Cost of DEBs is higher than that of inert spheres or lipiodol, but much lower than that of Y-90-loaded spheres (26).

3.4.1. INDICATIONS (22)

1. The primary indication for TACE is treatment of unresectable HCC, specifically those with intermediate stage (Barcelona Clinic Liver Cancer [BCLC] stage B) according to the Barcelona Clinic Liver Cancer staging system.
2. Secondary indications include:
    a. Bridge to transplant, especially for patients at risk of exceeding the Milan liver transplantation criteria (one tumour less than 5 cm, or up to three tumours, each less than 3 cm).

b. Downstage to resection or transplantation size criteria. Data are strong but not conclusive.

c. Aid surgery by shrinking a tumour abutting a major resection plane (i.e., right or left portal vein). Weak supportive data and mainly surgeon's preference.

d. Palliate patients with advanced stage HCC (BCLC stage C) which includes patients with macrovascular invasion and a weakened performance status.

3.4.2. CONTRAINDICATIONS (22)

Absolute

1. Poorly compensated advanced liver disease. Occasionally, patients with well-compensated Child-Pugh C disease can be treated with TACE if it can be performed selectively.
2. Encephalopathy, refractory to medical management, unless TACE can be performed selectively.
3. Poor performance status. Generally, patients with Eastern Cooperative Oncology Group (ECOG) >2 or Karnofsky Index <70 do not benefit from TACE.
4. Uncorrectable bleeding diathesis.
5. Large burden extrahepatic metastatic disease. If the patient's HCC is not thought to be the life-limiting factor, then TACE will not benefit the patient.
6. Active infection.

Relative

1. Total bilirubin >4. If hyperbilirubinemia is due to biliary obstruction and can be reversed with drainage, TACE can be considered. Drainage should be external to avoid crossing the sphincter of Oddi. Violation of the ampulla of Vater may result in

bacterial colonization of the intrahepatic bile ducts which can contribute to post-TACE intrahepatic abscess formation and/or cholangitis as a result of the profound ischemia to the peribiliary plexus caused by TACE.

2. Anaphylactic reaction to contrast. Gadolinium can be substituted in the absence of renal failure or CO_2, if the vascular target is mapped a priori.
3. Anaphylactic reaction to chemotherapy drugs. Embolization alone may confer a benefit.
4. Portal vein occlusion. Studies have demonstrated that portal vein occlusion does not increase the risk of complications, as long as liver reserve is within criteria (Child-Pugh A or B) and/or collateral flow to the liver exist.

3.4.3. COMPLICATIONS OF CHEMOEMBOLIZATION

Table 6: Complications of Chemoembolization (32).

Specific Major Complication	Reported Rate (%)
Liver failure	2.3
Abscess with functional sphincter of Oddi	<1
Abscess with biliary-enteric anastomosis/biliary stent/sphincterotomy	25
Postembolization syndrome requiring extended stay or readmission	4.6
Surgical cholecystitis	<1
Biloma requiring percutaneous drainage	<1
Pulmonary arterial oil embolus	<1
Gastrointestinal hemorrhage/ulceration	<1
Iatrogenic dissection preventing treatment	<1
Death within 30 days	1

4. JUSTIFICATION

Liver tumours, both primary and metastatic, are a major health problem worldwide with a rising incidence and increasing prevalence of intermediate and advanced stages with a poor prognosis. This has led to the development and use of new therapeutic procedures including various minimally invasive intra-arterial local treatments such as Y-90 TARE (28).

Although in general, surgical resection, liver transplantation and radiofrequency ablation (RFA), are considered curative treatments, it is estimated that more than 80% of cases are not candidates for them and require palliative treatment with other therapeutic procedures and/or maintenance care (28).

Currently, Transarterial Chemoembolisation (TACE) is the first line treatment for Intermediate Stage disease (BCLC B) according to the BCLC system, which includes asymptomatic patients with limited unresectable multinodular lesions, without vascular invasion or extrahepatic spread and who have well preserved liver function (4). TACE can be repeated at regular intervals or depending on tumour response, but should be discontinued in case of intractable progression (38).

Yttrium-90 Transarterial Radioembolisation (Y-90 TARE) is presented as a promising therapeutic alternative to the Gold Standard loco-regional treatments indicated by clinical guidelines. The individualised therapy that TARE allows, together with the emergence of very promising results, has greatly increased the literature studying TARE. This technique has been introduced in the treatment of HCC for more than 10 years. It has demonstrated its safety, anti-tumour effect (30) and have been included in the therapeutic algorithm of clinical guidelines within intra-arterial techniques but not as Gold Standard (39,40).

Numerous results support the use of RE-Y90 in patients with liver tumours that are not candidates for curative treatment, but the absence of data from prospective, randomised trials and comparative trials with other forms of therapy maintains uncertainty about its effectiveness. The efficacy of TARE in settings such as intermediate-stage HCC compared to

TACE as a salvage element in patients for surgical resection or as a bridge to transplantation, is based on cohort studies and the occasional clinical trial involving a limited number of cases. Most of the literature is retrospective. Therefore, its use and evaluation in the context of clinical trials is advised (4,28).

Y-90 TARE is a safe and well-tolerated treatment for patients with primary or metastatic liver tumours. RE-Y90 delivers high doses of radiation to malignant lesions while sparing normal liver tissue. RE-Y90 had similar efficacy to TACE in patients with HCC and can be used to shrink liver tumours, making the patient a potential candidate for curative treatments (28).

The evidence allows us to know that TARE decreases tumour size (41–43), promotes hypertrophy (44,45), increases resectability and transplantation options (43,46,47), allows safe resection (48), increases liver-specific progression-free survival (46,49,50) and have shown similar survival outcomes that TACE. Currently, TARE can be offered for the treatment of patients with intermediate HCC with level 2 evidence (51). TARE has efficacy in terms of radiological response and adequate safety profile but has not been able to show a significant increase in terms of survival in advanced HCC and has therefore not replaced TACE as a gold-standard treatment (4).

The role of radioembolisation is still to be defined and further trials are necessary to delineate which group of patients could benefit from this therapy (51). There is increasing evidence that the efficacy of TARE depends on the radiation dose delivered to the tumour as measured by dosimetry. Future studies should be performed in experienced centres, with an appropriate group of patients, with an adequate technique and according to microsphere planning, and delivery protocols to maximise the risk/benefit ratio (4,28). In line with the DOSISPHERE-01 study, scientific evidence supports that personalised dosimetry is likely to improve outcomes in clinical practice and future clinical trials should be conducted using this approach. If we demonstrate that personalised dosimetry improves the outcomes of this technique, it would be the beginning of a paradigm shift and would

justify the lack of increased survival in all current evidence where personalised dosimetry has not been used (39).

Due to the above, we feel the obligation to create this protocol for future development in our environment to draw conclusions that will allow us to improve both the benefits and the safety of this technique in our National Health System.

5. HYPOTESIS

In the treatment of hepatocellular carcinoma BCLC stage B, Y-90 personalised dosimetry TARE has better outcomes after intervention compared to DEB-TACE.

6. OBJECTIVES

6.1. PRIMARY OBJECTIVE

To evaluate the Overall Survival of patients treated with Y-90 personalised dosimetry TARE and to demonstrate that it is longer than in those treated with DEB-TACE in individuals diagnosed with hepatocellular carcinoma BCLC stage B.

6.2. SECONDARY OBJECTIVES

1. To compare Time to Progression (TTP) evaluated by mRECIST in patients treated with Y-90 personalised dosimetry TARE and in those treated with DEB-TACE in individuals diagnosed with hepatocellular carcinoma BCLC stage B.
2. To determine Adverse Events in patients treated with Y-90 personalised dosimetry TARE and in those treated with DEB-TACE in individuals diagnosed with hepatocellular carcinoma BCLC stage B.
3. To determine Overall Response to Therapy according to mRECIST in patients treated with Y-90 personalised dosimetry TARE and in those treated with DEB-TACE in individuals diagnosed with hepatocellular carcinoma BCLC stage B.
4. To analyse Quality of Life evaluated with FACT-Hep in patients treated with Y-90 personalised dosimetry TARE and in those treated with DEB-TACE in individuals diagnosed with hepatocellular carcinoma BCLC stage B.

7. MATERIAL AND METHODS

7.1. STUDY DESING

This study will be carried out through a multicentric, prospective, randomized, open-label clinical trial.

Our patients will be randomized assigned into two groups ratio 1:1:

- Group A: The patient will be treated with DEB-TACE.
- Group B: The patient will be treated with personalised dosimetry TARE.

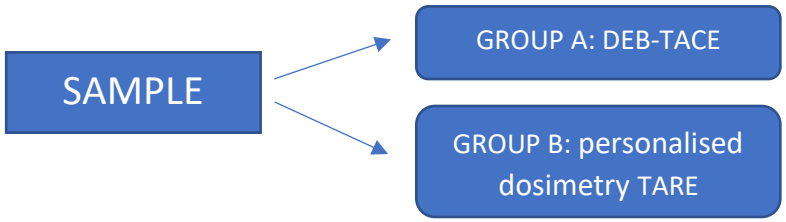

Figure 11: Study Design.

All our patients will be followed up for 2 years since the intervention (Day 1).

7.2. STUDY SETTING

Study setting will consist of fifteen hospitals:

- *Hospital Universitari Doctor Josep Trueta*, Girona.
- *Hospital Vall d'Hebron*, Barcelona.
- *Hospital Clínic*, Barcelona.
- *Hospital de la Santa Creu i Sant Pau*, Barcelona.
- *Hospital de Bellvitge,* L´Hospitalet de Llobregat.
- *Hospital Germans Trias i Pujol*, Badalona.
- *Hospital Parc Taulí*, Sabadell.

- *Hospital Universitario La Paz*, Madrid.
- *Hospital Universitario Doce de Octubre*, Madrid.
- *Hospital Universitario y Politécnico La Fe*, Valencia.
- *Complejo Hospitalario de Navarra*, Pamplona.
- *Hospital Álvaro Cunqueiro*, Vigo.
- *Hospital Universitario Virgen del Rocío*, Sevilla.
- *Hospital Clínico Universitario Miguel Servet*, Zaragoza.
- *Hospital General de Asturias*, Oviedo.

Hospital Universitario Doctor Josep Trueta will be the reference hospital. A clinical trial main coordinator (He or She will be a physician) and a main research assistant (He or She will not be a physician) will be assigned to this hospital.

In each of the other hospitals participating in the study, another head researcher and a research assistant will be appointed as at HUDJT.

The clinical trial main coordinator assigned to HUDJT, and each head researcher of the other hospitals will form the study coordination group. Periodic meetings will be held.

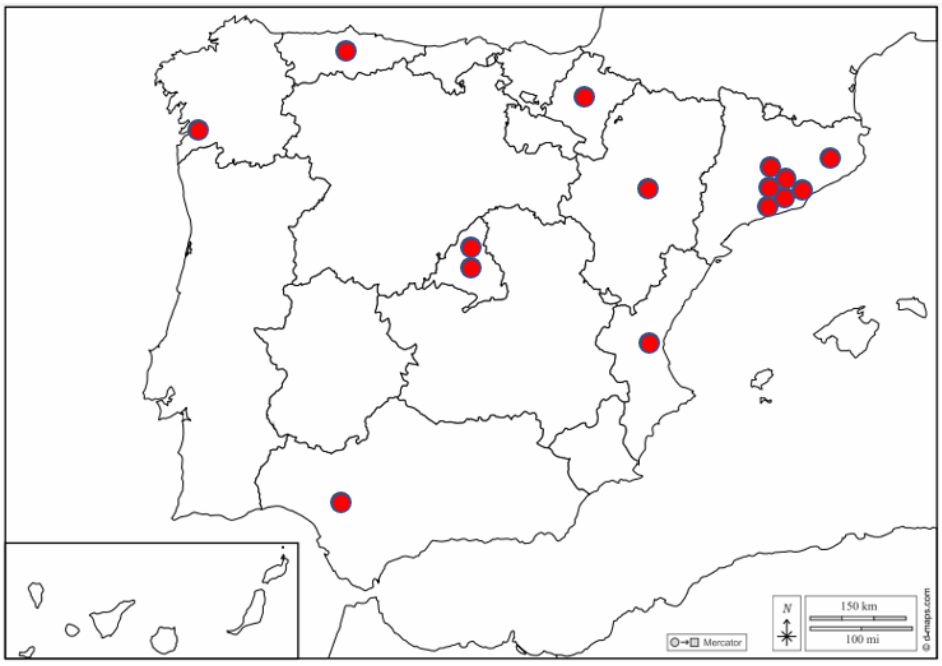

Figure 12: Study setting.

7.3. STUDY POPULATION

The study population of this clinical trial will consist of the fifteen participating hospitals reference population. It is estimated to be approximately 7.700.000 people.

- *Hospital Universitari Doctor Josep Trueta*, Girona. 839.960 inhabitants of reference.
- *Hospital Vall d'Hebron*, Barcelona. 430.000 inhabitants of reference.
- *Hospital Clínic*, Barcelona. 540.000 inhabitants of reference.
- *Hospital de la Santa Creu i Sant Pau*, Barcelona. 450.000 inhabitants of reference.
- *Hospital de Bellvitge,* L´Hospitalet de Llobregat. 201.192 inhabitants of reference.
- *Hospital Germans Trias i Pujol*, Badalona. 800.000 inhabitants of reference.
- *Hospital Parc Taulí*, Sabadell. 494.600 inhabitants of reference.
- *Hospital Universitario La Paz*, Madrid. 530.000 inhabitants of reference.
- *Hospital Universitario Doce de Octubre*, Madrid. 500.000 inhabitants of reference.
- *Hospital Universitario y Politécnico La Fe*, Valencia. 300.000 inhabitants of reference.
- *Complejo Hospitalario de Navarra*, Pamplona. 489.568 inhabitants of reference.
- *Hospital Álvaro Cunqueiro*, Vigo. 600.000 inhabitants of reference.
- *Hospital Universitario Virgen del Rocío*, Sevilla. 550.000 inhabitants of reference.
- *Hospital Clínico Universitario Miguel Servet*, Zaragoza. 700.000 inhabitants of reference.
- *Hospital General de Asturias*, Oviedo. 300.000 inhabitants of reference.

7.4. STUDY SUBJECTS

The study subjects will consist of 18 years or older reference population of each of the hospitals participating in this clinical trial, that are diagnosed of an intermediate stage hepatocellular carcinoma: BCLC class B, locally advanced, liver restricted disease, non-candidate for curative treatment.

All patients must meet the following inclusion and exclusion criteria.

7.4.1. INCLUSION CRITERIA

- Patients diagnosed of intermediate stage hepatocellular carcinoma (BCLC class B, locally advanced, liver restricted disease, non-candidate for curative treatment).
- Patients with unilobar involvement and affecting a maximum of 50% of this area.
- Patients with preserved liver function Child-Pugh A to B.
- Patients with Eastern Cooperative Oncology Group (ECOG) performance status 0.
- Patients ≥ 18 years old.
- Patients of either gender.
- Patients with criteria of DEB-TACE and personalised dosimetry TARE.
- Patients able to answer and understand the questionnaires by themselves.
- Patients who have signed the informed consent form.

7.4.2. EXCLUSION CRITERIA

- Patients for whom personalised dosimetry Y-90 TARE and DEB-TACE is not indicated or feasible.
- Patients with extrahepatic disease.
- Patients with ECOG performance score ≥ 1.
- Patients with a life expectancy of < 3 months.
- Patients ≥ 70 years old.
- Patients who are candidates for curative treatment (Resection, transplant, or ablation).
- Patients with Child-Pugh C.
- Patients with contraindications against angiography (uncorrectable coagulopathy, severe renal insufficiency, severe anaphylactoid reaction to iodinated contrast agents, severe peripheral vascular disease precluding arterial access).
- Patients with previous TACE or TARE whatever their technical characteristics.
- Patients with transjugular intrahepatic portosystemic shunt (TIPS).
- Patient with infiltration or occlusion of the portal vein.

- Patients with por family and psychosocial support, not able to answer and understand the questionnaires by themselves, with any psychiatric or cognitive disorder that would limit the compromise compliance with the requirements of this protocol or with possible great difficulty in attending the clinical controls.

7.4.3. PARTICIPANT WITHDRAWAL OR TERMINATION

- Patients who ask to withdraw from the study.
- Patients for whom we lose follow-up.
- Patients with severe complications that justify the patient not continuing in the clinical trial (SAFETY).
- Patients suffering from COVID-19 during study follow-up.

7.5. SAMPLE

7.5.1. SAMPLE SIZE

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, are necessary 756 patients, 378 subjects in the first group and 378 in the second, to detect as statistically significant the difference between two proportions, which is expected to be 0.63 for group 1 and 0.73 for group 2. A follow-up loss rate of 10% has been estimated.

Patients will be distributed in these two groups a 1:1 ratio.

7.5.2. SAMPLE SELECTION AND ESTIMATED TIME OF RECRUTIMENT

A non-probabilistic consecutive method will be used. Patients treated in the hospitals included in the study who meet the inclusion and exclusion criteria may be requested to participate in the clinical trial.

Based on the reference population of the study, the epidemiological characteristics of the disease and the paradigm shift that TARE will bring, we estimate that the recruitment time for the 756 patients will be about two years.

7.5.3. RANDOMIZATION METHODS

Once the patient is entered into the study database, after review of the inclusion and exclusion criteria and the patient has agreed to participate, he/she will be assigned to one of the two intervention groups on a 1:1 ratio.

To carry out the randomisation, nQuery Advisor 7 (Statistical Solutions Ltd., Cork, Ireland) will be used by the statistician in charge. Thanks to the randomisation programme, each participant will be assigned a number that will identify him or her throughout the process. In this way, the personal data of each participant will be kept confidential.

Patients will be able to find out which group they have been assigned to.

7.5.4. MASKING TECHNIQUES

As we are assessing interventional radiology procedures, patient and the interventional radiologists can know which procedure will be performed and they will not be blinded.

Radiologists in charge of analysing the medical images will be blinded because both techniques are not identifiable in the images analysis. The statistical evaluator will also be blinded. These measures will minimise the possibility of bias.

7.6. DATA COLLECTION

All information collected from each patient's medical record and during the two-year follow-up will be included in the database by the physician responsible for each intervention.

7.6.1. TRIAL ENTRY

A non-probabilistic consecutive sample method will be used. When the tumour committee meets, and a decision is made to perform TACE because the patient is diagnosed with stage B Hepatocellular carcinoma BCLC, interventional radiology team must assess whether he/she is a candidate to participate in the study. Then when the patient will be summoned in person to HUDJT to be informed of the decision of tumour committee he or she will be informed about the clinical trial.

If the patient agrees to participate in the study, he/she must sign the informed consent for the study after reading the information sheet.

During this visit, the medical history will be reviewed, a physical examination will be performed, and the functional status will be assessed. At the laboratory level, a complete blood count, coagulation study, urea, creatinine, ions, liver function test, albumin, LDH, PT and tumour markers (CEA, AFP) will be requested.

Four weeks prior to the intervention a diagnostic imaging of the liver will be done to assess tumour and non-tumour volume, portal vein patency and to ensure that there is no extrahepatic extension of the disease. An MRI will be performed on a 1.5-T MRI using a T1-weighted sequence with spoiled gradient echo and T2-weighted sequence with fat suppression. A dynamic multiphase contrast-enhanced, spoiled gradient echo and T1-weighted sequence with arterial, portal, equilibrium and delayed phase will be performed.

7.6.2. INTERVENTION

Randomisation will be performed 14 days before each intervention. TACE and TARE will be carried out as defined in the INTERVENTION section.

7.6.3. CLINICAL FOLLOW-UP

Patients will be evaluated every 6 weeks during two years after the treatment (Day 1). All interventional radiology teams in each of the hospitals participating in the study will be fully informed about how they will obtain the information that they will enter into the database.

Post-treatment evaluation will be performed the day of intervention (Day 1) and every 6 weeks. A laboratory examination will be performed: complete blood count, electrolytes, renal function tests, liver function tests, albumin, prothrombin time/INR, and alpha-fetoprotein. Patients will be asked to complete the FACT-Hep quality of life (QoL) questionnaires on Day 1 post-procedure at each follow-up visit (every 6 weeks).

An MRI will be performed the day of the intervention and on months 3, 6, 12 and 24 of the entire follow-up period on a 1.5-T MRI using a T1-weighted sequence with spoiled gradient echo and T2-weighted sequence with fat suppression. A dynamic multiphase contrast-enhanced, spoiled gradient echo and T1-weighted sequence with arterial, portal, equilibrium and delayed phase will be performed.

Adverse events will be recorded within 6 months of the TARE treatment and within 6 weeks of any TACE via a 24-hour contact telephone number. They will be coded using NCI-CTCAE version 3.

Patients who switch to other treatments will be registered as such and overall survival will be monitored.

All information will be collected and entered into the online database by each physician responsible for each intervention.

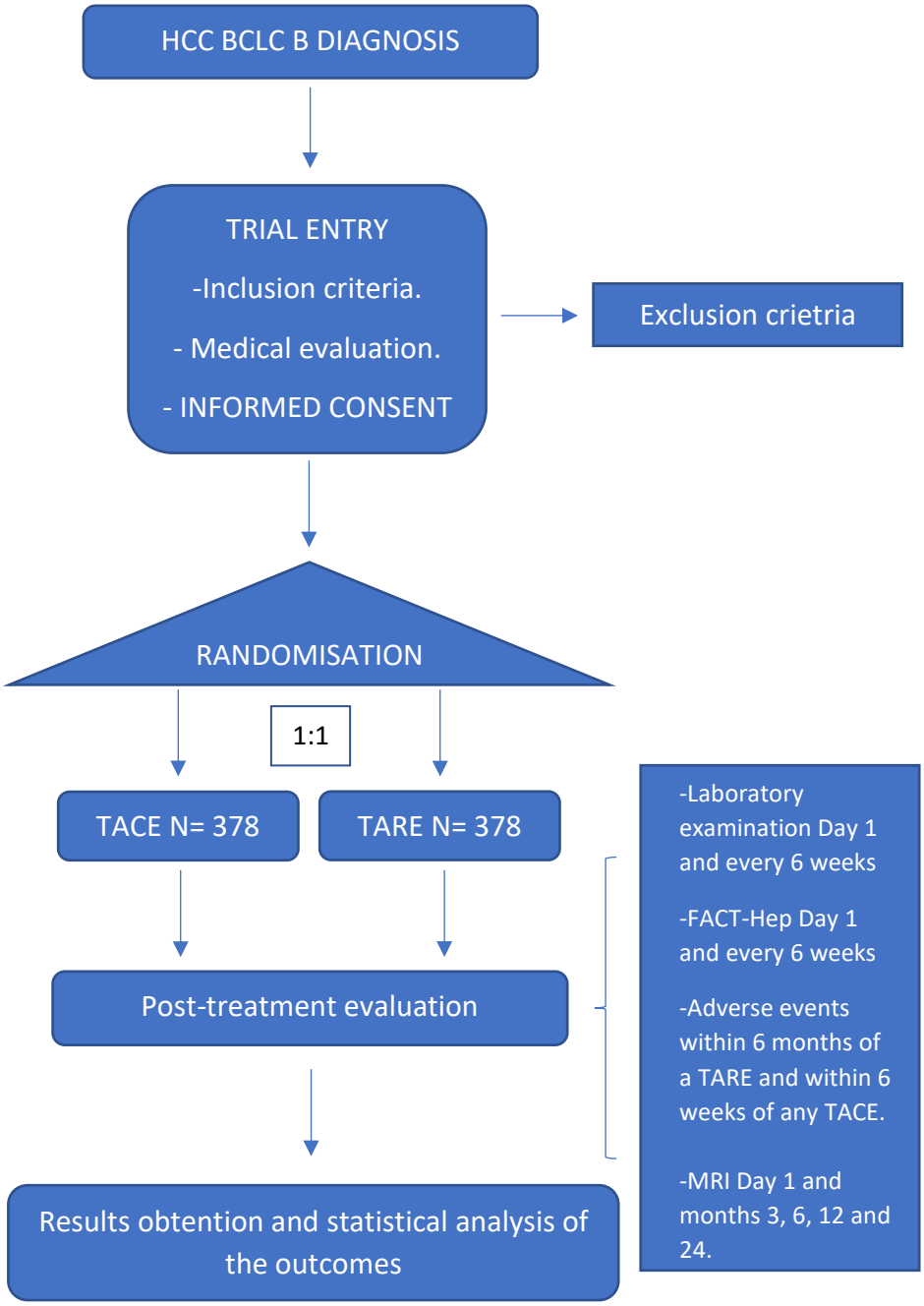

Figure 13: Data collection flow diagram.

7.7. INTERVENTION

Once HCC stage BCLC B has been diagnosed and patients accept to participate in the study, our 756 participants will receive one of the two following treatments randomised on a 1:1 ratio:

- TACE n= 378
- TARE n= 378

7.7.1. DEB-TACE WITH HepaSphere™

TACE will be carried out with drug-eluting beads (DEBs) (HepaSphere™, Merit Medical Systems, South Jordan, Utah, USA) microspheres with a size range of 30-60 µm and expanding range 120-240 µm loaded with doxorubicin. A maximum dose of 150 mg will be received in each session. A super-selective injection of the lesion will be performed in this clinical trial.

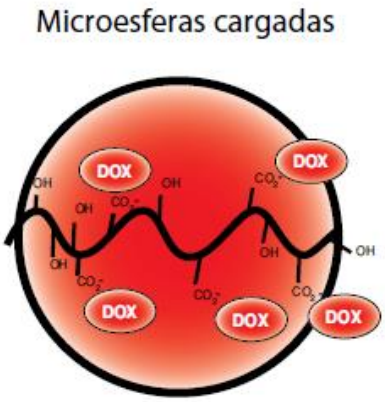

Figure 14: Microspheres loaded with Doxorubicin (51).

For each administration, the dose injected must be recorded. The end point of administration will be when the entire dose is administered, or when the flow is observed to stop (this will avoid embolisation of non-target areas).

Retreatment TACE will be repeated whenever indicated until tumour progression or progression of cirrhosis contraindicates continuation of treatment and with a minimum interval of six weeks between them.

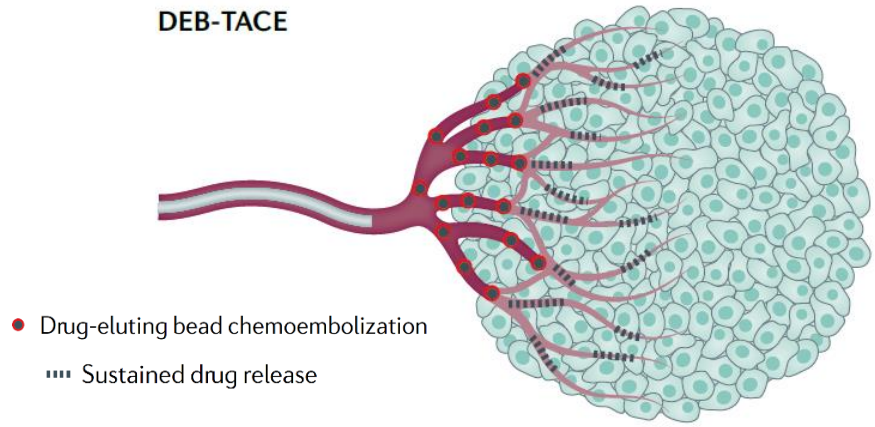

Figure 15: Drug-eluting bead chemoembolization (51).

7.7.2. TARE WITH TheraSphere™

Radioembolisation will be carried out using glass Yttrium-90 microspheres from TheraSphere™ (Boston Scientific, Marlborough, MA, United States). A super-selective approach will be used in this clinical trial.

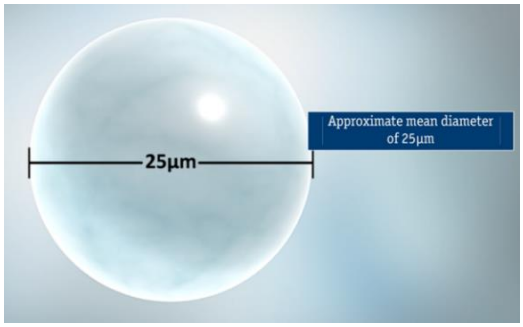

Figure 16: TheraSphere glass spheres labelled with Y-90 (52).

This technique will be divided in two sessions, a work-up session, and a treatment session:

WORK UP SESSION

Angiography with selective visceral catheterisation and simulated therapy with 99Tc-labelled macro albumin aggregates

An angiographic assessment will be performed as a first step, as the anatomy of the mesenteric system and the hepatic arterial bed varies considerably. To prevent dystopic spread, embolisation of arteries such as the gastroduodenal, right hepatic, pancreatic duodenal and cystic branches, if appropriate, will be done.

Angiography should be performed with 99Tc-labelled albumin macroaggregates injected into the hepatic artery in a manner similar to its application during future microsphere therapy. A super-selective approach will be used. After placement of the hepatic catheter, 150 MBq of Tc-99m MAA will be administered into the hepatic artery to determine the magnitude of the A-V shunt to the lungs and to confirm the absence of gastric and duodenal flow.

In patients with two arteries requiring treatment (those with an anatomical variant or a central lesion vascularised by two arteries) two albumin assessments will be performed in two separate angiographic procedures, with an interval of at least 24 hours between them.

The SPECT-CT should be performed within one hour after injection of the albumin macroaggregates to prevent false positives in extrahepatic activity due to the release of technetium.

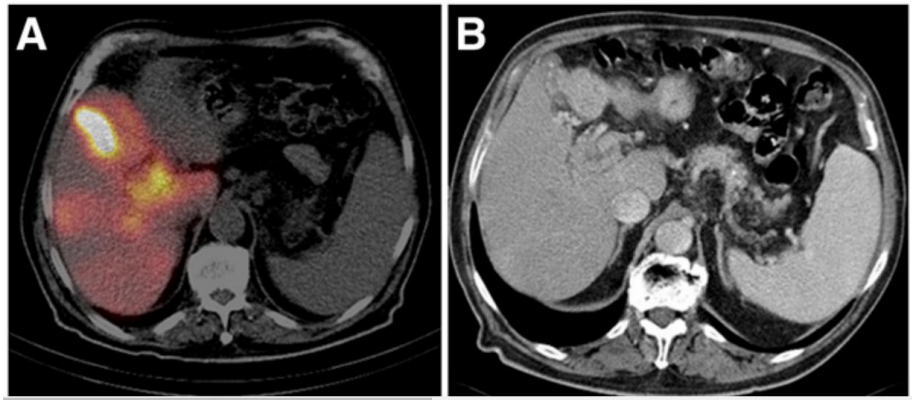

Figure 17: A: SPECT/CT with99mTc-MAA; B: triple-phase diagnostic CT (53).

Dosimetry calculation

Dosimetry calculation will be performed using Simplicity^{90}Y software (Mirada Medical, Oxford, UK). The dosimetry personalised target for patients will be defined as at least 205 Gy to the tumour (tumour dose), and more than 250 Gy, if possible; a dose of 120 Gy or less to the healthy perfused liver tissue; and a dose of 30 Gy or less to the lungs (39).

The activity of the ^{90}Y-loaded glass microspheres required to achieve the dosimetry objective will be calculated by using the following formula:

$$D_{VOI} = \frac{A_{VOI} \times 50}{W_{VOI}}$$

- D_{VOI} is the mean absorbed dose (measured in Gy) in the volume of interest (ie, the perfused liver, tumour, or healthy perfused liver tissue).
- A_{VOI} is the activity of ^{90}Y-loaded microspheres (measured in GBq) in the volume of interest.
- W_{VOI} is the weight of the volume of interest (measured in kg), with the weight equal to the volume (measured in L) multiplied by 1·03. Volume of interest was evaluated by use of macroaggregated albumin SPECT/CT scan images.

The Y-90 Physical Decay Table (ANNEX 6) is necessary to determine the appropriate injection time.

TREATMENT SESSION

TARE will be performed 14 days before of the hepatic arteriography with 99Tc-labelled macro albumin aggregates.

Patient catheterisation and TheraSphere™ administration

The calculated activity is injected after confirming that no new vessels are connected to the gastrointestinal tract. This confirmation is done by fluoroscopy, performed by the interventional radiologist in the angiography suite, where the therapeutic infusion will also

be performed. The catheter should be placed in basically the same position as used in the planning arteriography, when the macroaggregates were injected.

During the infusion of the glass beads, direct tracking of the distribution of the glass beads is not possible and is normally not necessary.

A catheter with an internal diameter of ≥ 0.5 mm (0.020 inches) must be used to deliver TheraSphere™ to the liver. Use of a smaller catheter diameter will cause excessive resistance to flow in the delivery system, which could cause the microspheres to be system, which may cause the microspheres to become entrapped in the TheraSphere™ delivery set and catheter. This could lead to infradosification.

As the delivery of TheraSphere™ is dependent on blood flow through the hepatic vasculature distal to the catheter tip, it is important that the catheter does not occlude the vessel in which it is placed in order to perform the administration.

Post-treatment imaging

After the infusion of microspheres, a PET-TC will be performed during the first 24 hours after application to document their distribution within the liver and to be sure that no extrahepatic uptake occurs. We will use Simplicity^{90}Y software (Mirada Medical, Oxford, UK) to verify the administered dose.

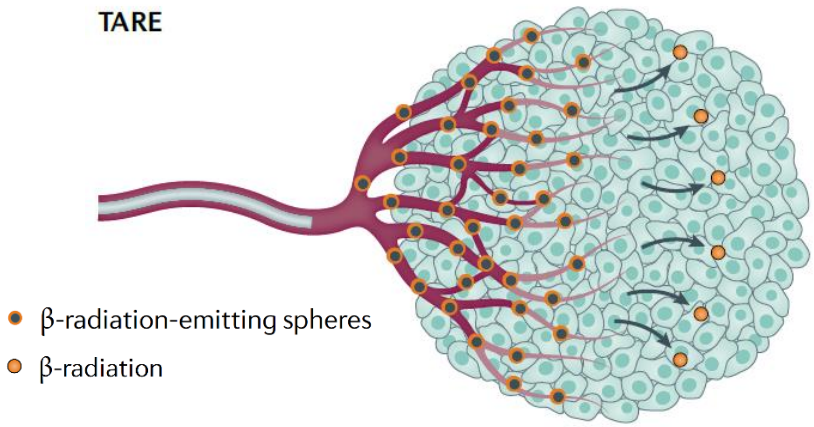

Figure 18: TARE (51).

The steering committee in agreement with the hepatobiliary tumour committees of each study hospital will review the evolution of the patients and assess whether there are better therapeutic alternatives according to the evolution of the disease. In this case, the patient will be treated with the best available treatment and will be followed up to assess overall survival.

7.8. VARIABLES

7.8.1. INDEPENDENT VARIABLE

The independent variable in this study is the intervention performed to treat intermediate stage BCLC B hepatocellular carcinoma: DEB-TACE (control group) or Personalised dosimetry TARE (intervention group).

This variable will be divided into two categories according to the technique that has been made: TACE/TARE. It´s is a qualitative nominal dichotomous variable.

They have been previously defined in the INTERVENTION section.

7.8.2. PRINCIPAL DEPENDENT VARIABLE

Overall survival (OS): Will be defined in days. It will be assessed as the interval between the day when the first TACE or TARE is performed (Day 1) and the day of death from any cause, opposition to data collection, or study termination (up to year 2), whichever occurs first.

7.8.3. SECONDARY DEPENDENT VARIABLES

Time to Progression (TTP): It will be defined in days. It will be assessed between day 1 and month 24 or until death from any cause, opposition to data collection, whichever occurs first. It will be evaluated with mRECIST. It will be defined as the time between the start of treatment (day on which TARE or first TACE is performed) until tumour progression. Tumour progression will be tracked by the mRECIST criteria and Progressive disease will be defined

as an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded. Starviewer software will be used to make the necessary measurements and calculations according to mRECIST indications.

Adverse events: It will be assessed within 6 months of the TARE treatment and within 6 weeks of any TACE or until death from any cause, opposition to data collection, study withdrawal due to adverse effects, whichever occurs first. An AE is any adverse medical event or undesirable event experienced by a participant that begins or worsens after administration of TheraSphere™or HepaSphere™. We will use Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (NCI-CTCAE v5). They will be assessed dichotomously: Do not appear/appear. An external committee will be in charge of monitoring and evaluating the occurrence of adverse events in the set of patients participating in this study.

Overall response to therapy: It will be assessed six months after the day of the first intervention in the MRI control with mRECIST. Starviewer software will be used to make the necessary measurements and calculations. It will be categorized as:

- Complete response: the disappearance of any intratumoral arterial enhancement in all target lesions.
- Partial response: at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
- Progressive disease: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions re- corded since the treatment started.
- Stable disease: any cases that do not qualify for either partial response or progressive disease.

Quality life QoL: It will be evaluated with FACT-Hep (ANNEX 7, ANNEX 8) after treatment on day 1 and every 6 weeks after the first treatment, participant's death, opposition to data collection or study withdraw for any cause, whichever occurs first. The higher the score, the better the QoL, with a range 0-180.

7.8.4. COVARIATES

Age: It´s a continuous quantitative variable. It will be measured in years. It will be defined based on the information in the medical record by each physician responsible for the patient.

Sex: Qualitative nominal dichotomous: Female / Male. It will be defined based on the information in the medical record by each physician responsible for the patient.

Ethnicity: Qualitative nominal polychotomous: Caucasian, Asian, African, Latin-American, Other. Self-referred for each patient.

Lobe location of tumour(s) Qualitative nominal dichotomous: Left / Right. It will be defined in the MRI scan that will be performed on the patient 4 weeks prior to the procedure by each physician responsible for the patient.

Number of nodules: It´s a discret quantitative variable. It will be defined in the MRI scan that will be performed on the patient 4 weeks prior to the procedure by each physician responsible for the patient. Starviewer software will be used to determine the value.

Tumoral volume: It´s a continuous quantitative variable. Measured in mL. It will be defined in the MRI scan that will be performed on the patient 4 weeks prior to the procedure by each physician responsible for the patient. The tumour volume will be assessed by measuring the largest and smallest diameter of each lesion with the help of Starviewer software.

Child-Pug Class: Qualitative nominal dichotomous: A / B. It will be defined based on the information in the medical record by each physician responsible for the patient.

HCC Etiology: Qualitative nominal polychotomous: Alcohol / HCV / HBV / NASH / Autoinmune disease / other / multiple / unknown. It will be defined based on the information in the medical record by each physician who treat the patient.

7.9. SAFETY

Y-90 TARE is a safe and well-tolerated treatment for patients with primary or metastatic liver tumours. RE-Y90 delivers high doses of radiation to malignant lesions while sparing normal liver tissue (28).

All techniques used in this study are safe and approved by the relevant authorities in the indication used. All possible complications that may arise in these interventions have been considered in the design of this protocol. During all the procedure an external committee will be in charge of monitoring and evaluating the occurrence of adverse events in the set of patients participating in this study and may stop the trial due to the occurrence of disproportionate adverse effects or death. The principal investigator will be notified.

The steering committee in agreement with the hepatobiliary tumour committees of each study hospital will review the evolution of the patients and assess whether there are better therapeutic alternatives according to the evolution of the disease. In this case, the patient will be treated with the best available treatment and will be followed up to assess overall survival.

In TACE, level 1 evidence is available to support this procedure thanks to two randomised trials by Llovet et al. (34) and Lo et al. (35) and a meta-analysis by Cammà (54) in 2002. As a result, TACE has become the standard of care for patients with unresectable hepatocellular carcinoma (HCC) and has been included in all HCC treatment guidelines (American Association for the Study of Liver Diseases, National Comprehensive Cancer Network, European Association for the Study of the Liver) (4,22).

Even so, it is not a risk-free technique. The most common side effect of TACE is post-chemoembolisation syndrome which is seen in up to 80% of patients. It is composed of a triad of abdominal pain, nausea and fever and is not indicative of a true complication. The most serious complications related to TACE are liver failure, non-target embolisation and liver abscess (22). Complications of TACE are described in the INTRODUCTION section.

Radioembolisation (TARE) is a technique that has already demonstrated safety in a large number of studies. It is an approved technique that has been used for many decades. Some groups have already made the decision to adopt TARE as first-line transarterial LRT for liver-limited HCC (55). In addition, TARE can be offered as a treatment for patients with an BCLC intermediate stage HCC (BCLC B) with level 2 evidence (51). Up to now, TARE has efficacy in terms of radiological response and adequate safety profile but has not been able to show a significant increase in terms of survival in advanced HCC (4). Furthermore, there are many studies that defend the safety of this process and conclude that treatment of primary HCC with ablative radioembolisation using 90Y-containing glass microspheres is generally well tolerated and results in low levels of AE (56). Complications of TARE are described in the INTRODUCTION section.

This is not a risk-free technique either. It can lead to post-radioembolization syndrome and present symptoms as fatigue, abdominal pain, nausea, anorexia, or fevers. Another complication could be idiosyncratic reaction and during the immediate postprocedural time following radioembolization, patients experience a rare and unusual reaction, nearly identical to that obtained in patients receiving urokinase, with clinical symptoms of rigors and alterations in hemodynamics. Other complications are: abscess, biloma, gastritis/ulceration and radiation cholecystitis (22).

7.10. STATISTICAL ANALYSIS

The statistician responsible for the evaluation of the results will be blinded to the study groups. The IBM Statistical Package for Social Sciences (SPSS) version 25 for Windows® will be used to carry out the statistical analysis of the data.

We will establish a value of $p<0.05$ as statistically significant, defining a confidence interval of 95% for all analyses.

All variables have been described in the STUDY VARIABLES.

7.10.1. UNIVARIANT ANALYSIS

Qualitative variables will be expressed as percentages with a 95% confidence interval.

Quantitative variables with normal distribution will be expressed by the mean as a measure of central trend, with standard deviation as a measure of dispersion with a 95% confidence interval. In the case of a quantitative variable that does not flow normal distribution, the median is used as a measure of central tendency with interquartile ranges as a measure of dispersion.

7.10.2. BIVARIATE ANALYSIS

To compare the means of the quantitative dependent variables between control group and intervention group we will use a Student´s t-test

To compare percentages of the qualitative dependent variables between control group and intervention group we will use a $\chi 2$ test (Chi-Square).

Survival curves will be estimated using the Kaplan-Meier estimator and plotted stratifying between control and intervention groups.

Differences between the survival curves of the two groups will be tested by means of the long-rank test.

To analyse the differences in patients' quality of life between the control group and the intervention group, the ANOVA test will be used as data will be obtained from the FACT-Hep questionnaire every 6 weeks throughout the study. In case that the requisites for the application of ANOVA will not fulfilled we will use the Kruskal-Wallis' test.

7.10.3. MULTIVARIATE ANALYSIS

Multivariate analysis will be performed to adjust variables for covariates to avoid potential confounding factors that may modify the results. Covariates considered in this study are age, sex, ethnicity, lobe location of tumour(s), number of nodules, tumoral volume, Child-Pug class and etiology.

For Overall Survival, Time to Progression (TTP), and adverse events the effect of the intervention will be adjusted by Cox regression controlling for all covariates.

I will assess the association between the 'overall response therapy' variable and the independent variable using multinomial regression adjusting for covariates.

Quality of life will be adjusted by General Linear Model (GLM) with a Poisson link (i.e. a Poisson regression) for repeated measurements to find out if there are differences between the two groups.

8. WORK PLAN AND CHRONOGRAM

The duration of the study will be 5 years. It will be divided into the following phases:

STAGE 0: STUDY DESIGN (January 2022- February 2022)

- **Activity 1 (January 2022):** Bibliographic research about TARE and its current application in clinical. Designation of the clinical trial main coordinator from HUDJT (he or she must be a physician) and the main research assistant (he or she can not

be a physician) assigned to this hospital who will be the responsible of the coordination of hospitals.

- **Activity 2 (February 2022):** Study design by the clinical trial main coordinator from HUDJT. A detailed explanation of the hypothesis, objectives, variables, and methodology will be provided and shared with other hospitals. All the participating hospitals should, in case of disagreement, propose any modifications to the study.

The research assistant assigned to the HUDJT will be responsible for this phase.

STAGE I: ETHICAL EVALUATION AND APPROBATION (March 2022- May 2022)

- **Activity 3:** Presentation of the protocol to the CEIC (Clinical Research Ethics Committee) of the Hospital Universitari Doctor Josep Trueta de Girona. Once the protocol will be accepted at the referral hospital, it will be shared with the other hospitals and the approval process will be set in motion. Online database will be created.
- **Activity 4:** After ethical approval, one research assistant will be assigned to each hospital except for HUDJS in which it will already be designated. They can´t be physicians. A meeting will be held at the HUDJT with all research assistants from each of the participating hospitals and the clinical trial main coordinator assigned to the HUDJT. At this meeting, a detailed explanation of all the characteristics of the study will be given, as well as the necessary training for all the research assistants for the proper implementation of the study.
- **Activity 5:** Insurance contract.

The research assistant assigned to the HUDJT will be responsible for this phase.

STAGE II: COORDINATION (May 2022- June 2022)

- **Activity 6:** Selection of the head researcher of each of the hospitals who must be physicians. Together with the trial main coordinator assigned to the HUDJT will form the study coordination group.

- **Activity 7:** The first meeting of the study coordination group will be held, made up of all those head researchers for each hospital. All issues related to the organisation of the clinical trial will be discussed and resolved.
- **Activity 8:** A training session will be held at *Hospital Universitari Doctor Josep Trueta* for the interventional radiology teams participating in the study.

The research assistant assigned to the HUDJT supported by the research assistants of each hospital will be responsible for this phase.

STAGE III: DATA COLLECTION AND FOLLOW-UP VISITS (48 months: June 2022- June 2026)

- **Activity 9 (June 2022-June 2024):** Patient recruitment will be carried out in the fifteen hospitals participating in the study. Inclusion and exclusion criteria must be met in all patients. A non-probabilistic consecutive method will be used to form the sample. They will be assigned to each of the two intervention groups on a 1:1 ratio.

- **Activity 10 (June 2022-June 2026**): Periodically follow-up visits will be performed. Investigators should complete the database with all variables studied in the clinical trial.

The study coordination group will be responsible for this phase. Periodic visits will be held every 6 months to assess the evolution and problems that may arise in the clinical trial. Research assistants will have the task of supporting the members of the coordination group in order to ensure that the study is carried out correctly.

STAGE IV: DATA ANALYSIS AND INTERPRETATION (June 2026- July 2026)

- **Activity 11:** A statistician will be hired and blinded for the intervention groups. He or she will carry out the analysis of the data once the database has been completed.
- **Activity 12:** A meeting will be set up where the data will be evaluated and discussed by the study coordination group. After this, they will elaborate the discussion and conclusion of the study.

The study coordination group together with the statistician will be responsible for this phase. Research assistants will have the task of supporting the members of the coordination group in order to ensure that the study is carried out correctly.

STAGE V: RESULTS PUBLICATION AND DISSEMINATION OF THE RESEARCH RESULTS (July 2026-December 2026)

- **Activity 13:** The study coordination group will prepare the final article to show the results and conclusions of the study.
- **Activity 14:** Presentation of the results to the *Sociedad Española De Radiología Vascular e Intervencionista (SERVEI).*
- **Activity 15:** Share the results of the clinical trial in scientific publications. Results will be presented at national and international specialist conferences.

The clinical trial coordinator assigned to the HUDJT will be responsible for this phase.

Table 7: Chronogram.

TASKS		2022					2023	2024		2025		2026		
		Jan	Feb	Mar-May	May-Jun	Jun-Dec	Jan-Dec	Jan-Jun	Jul-Dec	Jan-May	Jul-Dec	Jan-Jun	Jun-Jul	Jul-Dec
STAGE 0	A1: Bibliographic research.													
	A2: Study design													
STAGE 1	A3: CEIC													
	A4: Meeting research assistants in HUDJT.													
	A5: Insurance contract													
STAGE 2	A6: Selection the head researchers.													
	A7: First meeting of the coordination group.													
	A8: training session													
STAGE 3	A9: Patient recruitment													
	A10: Periodically follow-up visits													
STAGE 4	A11: statistics contracting													
	A12: data discussion													
STAGE 5	A13: prepare the final article													
	A14: Presentation of Results													
	A15: Share the results													

9. LEGAL AND ETHICAL CONSIDERATIONS

This study respects the four principles of bioethics postulated in *Principles of Biomedical Ethics* by Tom L. Beauchamp y James F. Childress: non-maleficence, beneficence, autonomy, and justice.

Before starting the study, the project will be presented and entered into the European Clinical Trials Database where it is given a registration number. In accordance with current legislation, before putting the protocol into practice, it should be evaluated by the Clinical Research Ethical Committe ("Comitè d'Ètica d'investigació Clínica" CEIC) of Hospital Universitario Doctor Josep Trueta who coordinates this study. Once approved by the Ethics Committee and implemented, and although not required, it will also be submitted to the Ethics Committees of all participating hospitals. Any modifications deemed necessary by these CEIC will be carried out.

This study has been designed respecting *"The World Medical Association Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects (1964, Last actualization October 2013)".* In this way, human rights and ethical considerations are guaranteed.

To respect the law on patient autonomy *"Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y derechos y obligaciones en materia de información y documentación clínica",* all the patients must be informed of the details of the study and will be provided with the clinical trial inform sheet (ANNEXES 9-10), where they will be informed of the procedures as well as the risks and benefits of participating in the protocol. They will then have to sign the informed consent form (ANNEXES 11-12) and will have another document at their disposal in order to withdrawal of the study (ANNEXES 13-14). The researchers will ensure that the participants have understood all the information and are responsible for answering any questions the patient may have.

Patients must voluntarily read and sign the informed consent form to participate in the study. They have the right to withdraw from the study and revoke informed consent at any time, thus respecting the principle of autonomy throughout the process.

Confidentiality will be respected in accordance with *the "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales (LOPD-GDD)*", in particular in its Additional Provision 17.2 and "*Regulation (EU) 2016/679 of parliament and the European Council, April 27, 2016, concerning the protection of natural people with regard to the processing of personal data"*. Information may only be used for research purposes. In relation to the collection of all information, it must be treated in a uniform manner without any exceptions.

Since this is a project involving medical interventions in the field of interventional radiology, the following law will be taken into account *"Ley 14/2007, de 3 de julio de investigación biomédica", "Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos."*

As this is a clinical trial considered as high interventional, an insurance will be taken out to cover any problems arising from participation in the study.

A steering committee in agreement with the hepatobiliary tumour committees of each study hospital will review the evolution of the patients and assess whether there are better therapeutic alternatives according to the evolution of the disease. In this case, the patient will be treated with the best available treatment and will be followed up to assess overall survival.

There will be an adverse events committee consisting of experts who are independent of the study that will assess the occurrence of complications and will withdraw from the study patients with disproportionate adverse events.

All data will be published with full transparency.

Investigators will declare they don´t have conflicts of interest.

10. STRENGTHS AND LIMITATIONS

Analysing this study, some limitations have been detected that may interfere with the research. All these elements must be considered.

We may have a selection bias that does not allow us to obtain a representative sample due to the non-probabilistic consecutive recruitment that we have carried out in this clinical trial. In addition, there is a higher prevalence of BCLC B patients in older adult men, therefore, the sample may be biased due to the smaller number of younger and female patients we will obtain. Even so, the inclusion and exclusion criteria for our study are like the baseline criteria for both techniques and are almost perfectly like the definition of BCLC B stage, which will make the sample more representative.

The assignment of the intervention to each patient will be randomised. Thus, the two treatment groups will be equivalent, and the covariates will be symmetrically distributed. As a result, the groups will be similar and comparable to each other allowing a future generalisation to the whole population. In addition, the study we will carry out is defined as multicentric. We will include fifteen hospitals of National Health System and the results should be applicable to clinical practice, so it is a strength of the study.

Another limitation of this study is the open-label design. As we are performing an interventional radiology procedure, we will not be able to blind either the physician performing the technique or the patient. To try to minimise this bias, we will blind the radiologist who will analyse radiology test and the statistical expert who will perform the data analysis, thus avoiding a detection bias.

As this is a multi-centre trial involving fifteen teams of interventional radiologists and invasive techniques, there may be a certain degree of variability in how they are performed and could be a limitation of our study. Interventions depend on the radiologist, his or her experience and learning curve. To minimise this, all teams will undertake a training day at the HUDJT prior to the start of the study. Furthermore, although the embolization technique and spheres used will be similar in both groups, the catheters may be different due to the different suppliers owned by each of the hospitals. Although this should not be a problem, it may be a limitation of our study.

Losses and withdrawals could lead to a selection bias, which we have minimised, as a 10% drop-out rate has been considered when calculating the sample. As our sampling is consecutive will allow us to replace losses arising during the recruitment period. In addition, we must consider that drop-outs may occur being a limitation of the study.

The calculation of the dose administered will be done on an individual basis as each patient's tumour volume and distribution will be different. Although it will be done in a very rigorous manner as described in the INTERVENTION section, this could be another limitation of our study as it may increase the heterogeneity of the data.

A strength of the study is that most of the data collected from the patient is always provided to the database by the physician in charge of the intervention apart from ethnicity, which is self-referred. This avoids information bias due to erroneous data that a patient may provide.

Another limitation of our study is the cost involved. Even so, we consider that the change in patient care and the new paradigm it can open is a strength for the study.

Another limitation in all clinical trials is external validity. More multicentre studies should be conducted in the future to reduce this limitation. All covariates will be controlled during the statistical analysis to achieve internal validity of the clinical trial.

11. FEASIBILITY

We consider this study to be feasible. Hospitals that will participate in this study have extensive experience in performing these types of procedures. According to the protocol design, the interventional radiology teams will undergo an adequate training for the correct performance of the entire procedure. In addition, all participating teams will be thoroughly trained in the procedures and steps of the study.

As the inter-hospital organisation has been designed, the research assistants of all hospitals will be in charge of the coordination in the early stages of the trial. They will be trained and coached. This will free up the physicians who will be able to devote their time to their medical work, at the same time as participation and organization of the study will be regular and possible. Later, when the doctors take more responsibility, the research assistants will have the task of supporting the members of the coordination group in order to ensure that the study is carried out correctly.

Both procedures are included in the health care system, so the coverage of both TARE and successive TACE and the follow-ups of the study are similar as those routinely performed in all hospitals participating in the study. All material requirements (radiology equipment, interventional rooms, radiological protection equipment…) for the implementation of the protocol are available now.

The number of patients participating in the study is manageable (756 patients in 15 hospitals recruited over two years). The next few years we will see a major revolution in the number of TARE procedures. Even so, the actual volume of TARE and TACE will allow the sample to be completed despite the inclusion and exclusion criteria.

Data collection will be easy to perform because a well-structured online database will be created where all clinical information will be uploaded and organised. All interventional radiology teams will have access to it. This will facilitate the inter-hospital organisation, as well as the organisation and sharing of all data.

We anticipate that the main obstacle in the execution of this protocol is its duration and costs. We believe in its technical feasibility, so we will seek funding to carry out the protocol and will apply for research grants.

12. BUDGET

PERSONNEL EXPENSES

All medical staff participating in the study will be physicians employed by the hospitals participating in the study, so there will be no cost to the study.

One research assistants will be recruited for each hospital to assist coordination of the study. Their work will take about 60 hours per each, so paying €20 per hour will make a total of €18.000.

A statistician will be recruited, as this is necessary for the randomisation of patients into the two intervention groups, for the creation of the database and for the analysis of the data. The salary is stipulated at €35/hour, at an estimated cost of €1.400 (estimating 40 hours of work).

LIABILITY INSURANCE

As we are performing invasive interventional radiology procedures, it will be necessary to take out insurance to cover any adverse effects that the patient may suffer due to participation in the clinical trial. The estimated cost for each patient is €100, so it will amount to €75.600.

As this is an independent (non-commercial) study, and both techniques are approved for the indication used in the study, there is no need to pay study fees.

EXECUTION EXPENSES

The literature review will be free of charge for the study.

Both TACE and TARE are already approved techniques in the hospitals that participate in the study. There will be no additional cost for the application of these techniques. Radiological imaging will be provided the National Health System (NHS).

The follow-up of patients after the intervention will be similar as for patients treated with these techniques, so there will be no extra cost. All Radiological imaging that we will carry out are available in the National Health System and will therefore not entail a cost.

The implementation costs shall be as follows:

- The licence for the use of the FACT-Hep questionnaire must be requested at a price of €500.
- The licence for use nQuery Advisor 7 wich will cost €450.
- The licence for the use for one year of the IBM Statistical Package for Social Sciences (SPSS) version 25 for Windows® which will cost €200.

TRAVEL AND COORDINATION EXPENSES

The coordination group meetings will be face-to-face. A travel allowance of €80 will be paid to each hospital manager for each meeting.

The costs are estimated at €16.000, calculating the meetings of the coordination group throughout the duration of the study, as well as the practical training workshop for the interventional radiology groups of the hospitals. All will be held at the HUDJT.

CONFERENCE EXPENSES

To publish the results to the scientific community, we will participate in national and international congresses.

The principal investigator of HUDJT and another physician will participate as speakers at the national congress of the "*Sociedad Española de Radiología Vascular e Intervencionista (SERVEI)*" with the final conclusions of the study.

The admission fee is approximately €500 per person and the accommodation and travel costs are stipulated at €500 per physician per day, so that €3,000 is budgeted for this congress.

Two physicians will participate in the European Congress of Radiology (ECR). The admission fee is approximately €1000 per person and the accommodation and travel costs are stipulated at €1000 per physician per day, so that €7,000 is budgeted for this congress.

PUBLICATION EXPENSES

After evaluation of the information and interpretation of the results, the article will be published. €500 will be reserved for the correction of the English and €2000 for the preparation of the open access.

The value of the publication is estimated to be around €2500.

The total costs are summarised in the following table:

Table 8: Budget summary.

ITEM	QUANTITY	COST	SUBTOTAL
PERSONNEL COSTS			
Research assistants	60 hours/pp	€20/hour	€18.000
Statistician	40 hours	€35/hour	€1.400
INSURANCE COSTS			
Insurance	756	€100 pp	€75.600
MATERIAL AND EXECUTION			
TACE procedure	378 patients	Provided by the NHS	
TARE procedure	378 patients	Provided by the NHS	
Radiological imaging	756 patients	Provided by the NHS	
Follow-up costs	756 patients	Provided by the NHS	
FACT-Hep Licence	1 year	€500	€500
nQuery Advisor 7 Licence	1 year	€450	€450
SPSS Licence	1 year	€200	€200
TRAVELS AND COORDINATION			
Meetings face-to-face	15 people	€80 p x11 meeting	€13.200
Practical training workshop	35 people	€80 pp	€2.800
PUBLISHING EXPENSES AND DISSEMINATION OF RESULTS			
National congress	2 inscriptions fees	€500 pp	€3,000.
	2 travels and accommodations	€500 pp per day	
International Congress	2 inscriptions fees	€1000 pp	€7,000
	2 travels and accommodations	€1000 pp per day	
Article publication expenses	English correction	€500	€2.500
	Open Access	€2000	
TOTAL: 124.650€			

13. IMPACT ON THE NATIONAL HEALTH SYSTEM

We believe that this clinical trial will have a great impact on the National Health System and worldwide, since if our hypothesis is confirmed, it will be the first step towards TARE replacing TACE, becoming the Gold Standard treatment for patients with BCLC B hepatocellular carcinoma.

Hepatocellular carcinoma accounts for 80-90 % of malignant liver tumours and it is currently the sixth most frequent neoplasm in the world and the third most common cause of cancer death. 1 million cases are diagnosed worldwide each year.

As mentioned in the justification section, this study represents one of the first prospective, randomised clinical trials to be conducted in our population and worldwide, and is the first step towards the paradigm shift that TARE is expected to undergo in the coming years. In addition, the use of personalised dosimetry makes this study unique, so we consider the study to be very innovative.

If we confirm our hypothesis and demonstrate that personalized dosimetry TARE, in our environment, improves survival, this study will change the prognosis of a large number of patients and will represent a major paradigm shift. This change would lead to fewer interventions than currently occur with TACE and if it happens as in other populations, the occurrence of adverse effects would be lower than at present, improving the quality of life of our patients.

If we demonstrate the outcomes of the study, the indication of TARE as a first line of treatment in BCLC B patients would be a substantial improvement over the current situation. The increased demand would allow for competition between commercial companies and a reduction in the cost of TARE, leading to an improvement in terms of cost-effectiveness for the National Health System making more patients benefit from this technique than ever before.

Currently, TACE makes the patient highly dependent on the system, as although the initial procedure is cheaper than TARE, it carries a higher rate of side effects.

Because of all this, we believe that all these advantages would mean a change in the treatment of hepatocellular carcinoma. Our national healthcare system would pioneer in the use of personalised dosimetry TARE for the treatment of HCC BCLC B, thus enabling a paradigm shift and changing the prognosis of a large number of patients worldwide.

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15. ANNEXES

15.1. ANNEX 1: ALGORITHM FOR THE DIAGNOSIS OF HEPATOCELLULAR CARCINOMA (4)

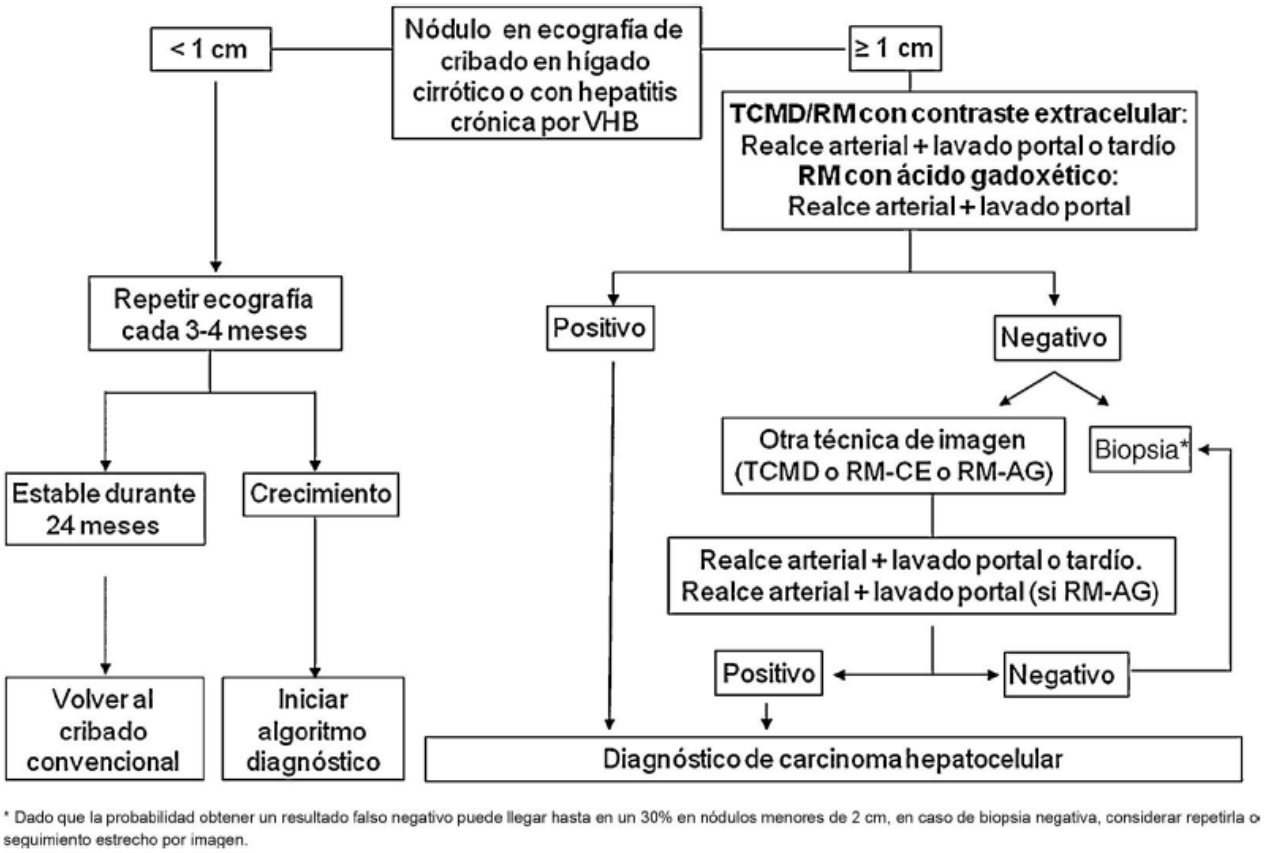

Figure 19: Algorithm for the diagnosis of hepatocellular carcinoma (4).

TCMD: TC multidetector, **RM-CE**: Resonancia magnética con contraste extracelular, **RM-AG**: Resonancia magnética con ácido gadoxético.

15.2. ANNEX 2: BCLC STAGING SYSTEM (BARCELONA-CLINIC-LIVER-CANCER)

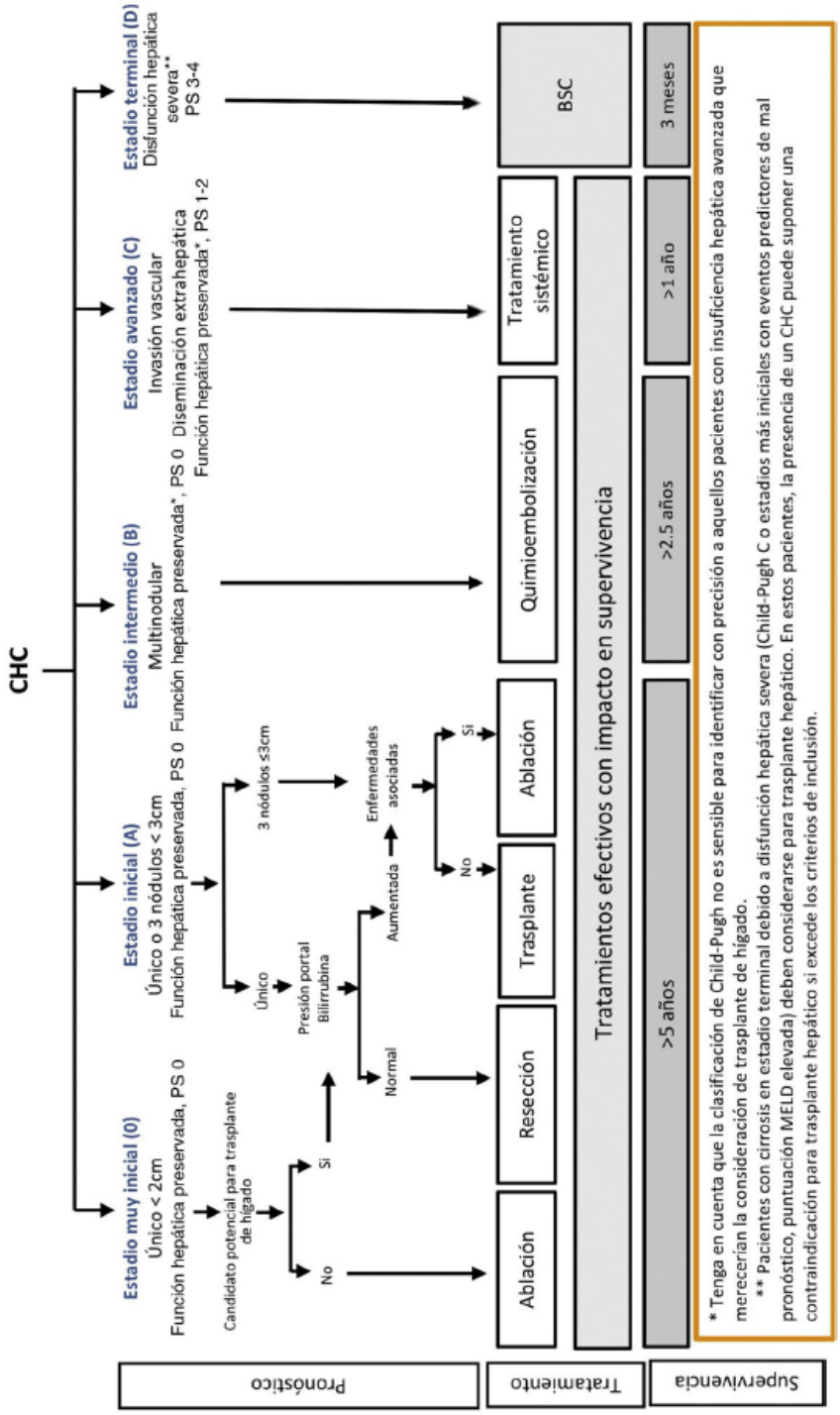

Figure 20: BCLC staging system (Barcelona-Clinic-Liver-Cancer) (4).

PS: Performance status; **BSC**: Best supportive care.

15.3. ANNEX 3: ECOG (Eastern Cooperative Oncology Group Performance Scale) (26)

Table 9: Eastern Cooperative Oncology Group Performance Scale.

PERFORMANCE STATUS	DEFINITION
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

15.4. ANNEX 4: CHILD-PUGH CLASSIFICATION (21)

Table 10: Child-Pugh Classification.

PARAMETER	POINTS ASSIGNED		
	1	2	3
Ascites	None	Moderate	Severe
Bilirrubin	<2 mg/dL	2 to 3 mg/dL	>3 mg/dL
Albumin	>3.5 g/dL	2.8 to 3.5 g/dL	<2.8 g/dL
Prothrombin time (seconds over control) or INR	1-4 <1.7	4 - 6 1.7 - 2.3	>6 >2.3
Encephalopathy	None	Grade I - II	Grade III - IV

INR: international normalized ratio.

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy.

Table 11: Child-Pugh Classification Annex.

PUNTOS	CLASE	SUPERVIVENCIA AL AÑO	SUPERVIVENCIA A LOS DOS AÑOS
5-6	A	100%	85%
7-9	B	80%	60%
10-15	C	45%	35%

- A score of 5 to 6 is considered Child-Pugh class A (well-compensated disease).

- A score of 7 to 9 is class B (significant functional compromise).

- A score of 10 to 15 is class C (decompensated disease).

15.5. ANNEX 5: MODIFIED mRECIST ASSESMENT FOR HEPATOCELLULAR CARCINOMA (57)

Table 12: mRECIST assesment for hepatocellular carcinoma (57).

mRECIST for HCC	
CR	Disappearance of any intratumoral arterial enhancement in all target lesions.
PR	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.
SD	Any cases that do not qualify for either partial response or progressive disease.
PD	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

HCC: hepatocellular carcinoma; **mRECIST**: modified Response Evaluation Criteria in Solid Tumors; **CR**: complete response; **PR**: partial response; **SD**: stable disease; **PD**: progressive disease.

15.6. ANNEX 6: Y-90 PHYSICAL DECAY TABLE

Table 13: Y-90 physical decay table (58).

Tabla de desintegración física del Itrio-90
Semivida de 64,1 horas

Horas	Fracción restante	Horas	Fracción restante	Horas	Fracción restante
-4	1,044	30	0,723	64	0,501
-2	1,022	32	0,707	66	0,490
0*	1,000	34	0,692	68	0,479
2	0,979	36	0,678	70	0,469
4	0,958	38	0,663	72 (Día 3)	0,459
6	0,937	40	0,649	96 (Día 4)	0,354
8	0,917	42	0,635	120 (Día 5)	0,273
10	0,898	44	0,621	144 (Día 6)	0,211
12	0,878	46	0,608	168 (Día 7)	0,163
14	0,860	48 (Día 2)	0,595	192 (Día 8)	0,125
16	0,841	50	0,582	216 (Día 9)	0,097
18	0,823	52	0,570	240 (Día 10)	0,075
20	0,806	54	0,558	264 (Día 11)	0,058
22	0,788	56	0,546	288 (Día 12)	0,044
24 (Día 1)	0,771	58	0,534		
26	0,755	60	0,523		
28	0,739	62	0,511		

*Tiempo de calibración

15.7. ANNEX 7: FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Ver mu**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Ver mu**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Ver mu**
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

15.8. ANNEX 8: FACT-Hep SCORING GUIDELINES (Version 4)

Instructions:*
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-Hep).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL WELL-BEING (PWB)	GP1	4	-	_____	=_____
	GP2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

Subscale	Item Code	Reverse item?		Item response	Item Score
HEPATOBILIARY	C1	4	-	_____	=_____
CANCER	C2	4	-	_____	=_____
SUBSCALE	C3	0	+	_____	=_____
(HCS)	C4	0	+	_____	=_____
	C5	4	-	_____	=_____
Score range: 0-72	C6	0	+	_____	=_____
	Hep1	4	-	_____	=_____
	Cns7	4	-	_____	=_____
	Cx6	4	-	_____	=_____
	HI7	4	-	_____	=_____
	An7	0	+	_____	=_____
	Hep2	4	-	_____	=_____
	Hep3	4	-	_____	=_____
	Hep4	4	-	_____	=_____
	Hep5	4	-	_____	=_____
	Hep6	4	-	_____	=_____
	HN2	4	-	_____	=_____
	Hep8	4	-	_____	=_____

Sum individual item scores:_____
Multiply by 18: _____
Divide by number of items answered: _____=**HC Subscale score**

To derive a FACT-Hep Trial Outcome Index (TOI):
Score range: 0-128

_____ + _____ + _____ =_____=**FACT-Hep TOI**
(**PWB** score) (**FWB** score) (**HCS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-Hep total score:
Score range: 0-180

_____ + _____ + _____ + _____ + _____ =_____=**FACT-Hep Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**HCS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

15.9. ANNEX 9: CLINICAL TRIAL INFORM SHEET (Catalan Version)

Hospital Universitari de Girona Doctor Josep Trueta

Av. França s/n 17007 Girona

FULLA D'INFORMACIÓ Al PACIENT

Y-90 PERSONALISED DOSIMETRY TARE VERSUS DEB-TACE IN THE TREATMENT OF BCLC B HEPATOCELLULAR CARCINOMA

INTRODUCCIÓ

Ens dirigim a vostè per a convidar-ho a participar en un estudi de recerca que s'està duent a terme en el servei de Radiologia Intervencionista de l'Hospital Doctor Josep Trueta de Girona.

Mitjançant aquest document volem facilitar-li tota la informació necessària perquè pugui avaluar si vol participar o no en l'estudi. Abans d'acceptar o denegar la participació, li demanem que llegeixi detingudament aquest document.

No dubti a formular totes les preguntes necessàries i sol·licitar qualsevol informació extra. Pot consultar la decisió amb qui consideri oportú.

PARTICIPACIÓ VOLUNTÀRIA

La seva participació en l'estudi és totalment voluntària. Pot decidir no participar, canviar la seva decisió i retirar el consentiment en qualsevol moment. Això no alterarà la relació amb el seu metge i no es produirà cap prejudici en l'atenció sanitària que rebi.

DESCRIPCIÓ DE L'ESTUDI

Actualment, la Quimioembolización transarterial (TACE) és el tractament de primera línia per a la malaltia en estadi intermedi segons el sistema BCLC, que inclou als pacients asimptomàtics amb lesions multinodulars limitades i irresecables, sense invasió vascular ni disseminació extrahepática i que tenen una funció hepàtica ben conservada.

En el HUDJT s'ha plantejat, després d'una llarga avaluació de l'evidència científica disponible, l'opció d'emprar la radioembolización (TARE) com el tractament de primera línia en l'estadi intermedi BCLC (BCLC B).

Aquest projecte busca comparar totes dues tècniques en aquest grup de pacients. Amb aquest estudi es pretén conèixer si la hipòtesi és vàlida. Pretenem demostrar que la Radioembolización en els pacients classificats com BCLC B aporta una major supervivència, major temps fins a la progressió de la malaltia, menor aparició d'efectes adversos, una millor resposta global i millor qualitat de vida.

D'aquesta manera busquem aconseguir suficient evidència científica per a validar la tècnica en un futur com a teràpia d'elecció en els pacients diagnosticats amb un carcinoma hepatocel·lular classificat com BCLC B.

PROCEDIMENTS DE L'ESTUDI

En l'estudi dividirem a tots els pacients en dos grups de manera aleatòria. Els dos grups tindran el mateix nombre de pacients. Un grup serà tractat mitjançant DEB-TACE (un subtipus de TACE) i l'altre mitjançant TARE.

A continuació, se li descriuen les tècniques que es compararan en l'estudi:

QUIMIOEMBOLIZACIÓN HEPÀTICA AMB DEBs (Drug-Eluting Beads)

QUÈ ÉS I COM ES REALITZA?

La quimioembolización és un tractament eficaç per a algunes lesions tumorals del fetge. Mitjançant un catèter dipositem selectivament unes microesferes sintètiques que contenen una substància anticancerosa en la lesió al mateix temps que ocloem (embolizamos) les artèries que nodreixen el tumor, tractant així de destruir-lo. D'aquesta manera, aniran alliberant el fàrmac directament a les cèl·lules tumorals de manera gradual durant els dies següents.

Se li punxarà l'artèria femoral en l'engonal utilitzant anestèsia. A continuació, se li introduirà un tub molt fi (catèter) pel qual s'injecta un líquid (mitjà de contrast), que permet veure els vasos sanguinis del fetge i obtenir radiografies. Una vegada localitzat el lloc exacte es procedirà a la quimioembolización.

La durada aproximada d'aquesta intervenció és aproximadament d'1 a 3 hores. A vegades són necessàries entre diverses sessions cadascuna d'elles distanciades per un mínim de 6 setmanes.

PER A QUÈ SERVEIX?

La quimioembolización serveix per a prolongar la vida en pacients amb tumors del fetge.

QUINES CONSEQÜÈNCIES IMPORTANTS PRODUIRÀ LA INTERVENCIÓ?

Control de la seva malaltia i augment de la supervivencia.

QUINS RISCOS POT HAVER-HI?

Riscos freqüents

- Síndrome Postembolización: No és una complicació sinó una conseqüència del tractament. Té una gran variabilitat personal quant a incidència i intensitat dels símptomes. La seva durada és autolimitada entre 1 dia i 3 setmanes. No apareix en tots els casos i el seu tractament és simptomàtic.

Consisteix en febre de <38,5 i/o leucocitosis i/o dolor i/o nauseas. Pot a vegades acompanyar-se de dolorimiento en el flanc i/o espatlla dreta.

Riscos poc freqüents

- Insuficiència hepàtica.

- Abscés hepàtic.

- Colecistitis.

- Embolización no desitjada d'àrees de mucosa del tub digestiu.

Amb una adequada selecció dels pacients i tècnica acurada aquestes complicacions ocorren entre el 3-7 % dels casos.

- Insuficiència renal < 1%

- Anèmia que requereixi transfusió <1 %

- La mortalitat a 30 dies de la intervenció és d'1 – 4 %

- Sagnat o hematoma en el punt de punció femoral.

- Reacció al·lèrgica al contrast. Exantema cutani i pruïja fins a un 4% dels casos. Les reaccions greus avui dia són excepcionals.

- Rares vegades hi ha caiguda del cabell.

De totes maneres, si ocorregués qualsevol complicació no dubti que tots els mitjans tècnics i humans d'aquest hospital estan disposats per a intentar solucionar-les.

HI HA ALTRES ALTERNATIVES Al PROCEDIMENT?

La cirurgia de resecció convencional no és possible en aquesta mena de pacients. Depenent de les seves circumstàncies personals, es podrà tractar el seu tumor amb tècniques d'ablació percutània. El trasplantament hepàtic en persones joves i amb unes característiques molt concretes.

La quimioteràpia fins al moment només és eficaç en estat avançat de la malaltia per a prolongar uns mesos la vida.

La radioembolizacion amb microesferes radioactives és una alternativa que s'aplica en casos concrets i actualment encara en fase d'estudi.

Si desitja més informació o té qualsevol dubte, no tingui objecció a preguntar-nos. Li atendrem amb molt de gust.

QUINES CONSEQÜÈNCIES SÓN PREVISIBLES DE LA NO REALITZACIÓ?

Disminució del temps de vida del pacient.

OBSERVACIONS I CONTRAINDICACIONS

Prèviament a la realització de la intervenció, s'ha de comunicar al metge el patiment d'alguna mena d'al·lèrgia, especialment a l'anestèsia o al mitjà de contrast.

RADIOEMBOLIZACIÓN HEPÀTICA

La Radioembolización transcatéter s'utilitza per a alguns pacients amb càncer primari de fetge o metàstasi al fetge d'altres tumors. L'objectiu és intentar controlar el creixement de les cèl·lules tumorals i en alguns casos destruir-les. Per a això, s'usen les imatges de raigs-X en un monitor de televisió per a inserir un catèter a través d'una petita punció en la pell (generalment de l'engonal) amb anestèsia local i guiar-ho a través de l'artèria que alimenta el tumor. S'injecten directament en el tumor partícules molt petites que s'han carregat prèviament amb agents radioactius, en aquest cas Itri-90. Depenent de les seves circumstàncies personals, aquest procediment es realitzarà sota sedació.

Al final del procediment es retira el catèter i el pacient ha de romandre en llit durant 12 hores. La majoria de pacients tornen a la seva vida normal en una setmana, però alguns poden trigar un mes.

La intervenció es realitzarà en dos temps, una primera fase d'estudi i planificació 14 dies abans d'introduir en el fetge les microesferes radioactives pròpiament dites. La durada de cada procediment és, aproximadament, de dues hores.

Els resultats que s'obtenen compensen els possibles riscos que a continuació li exposem.

ALTERNATIVES

Depenent de les seves circumstàncies personals, es podrà tractar el seu tumor amb tècniques d'ablació, quimioembolización o quimioteràpia sistèmica. En algun cas particular l'alternativa pogués ser la intervenció quirúrgica.

RISCOS I COMPLICACIONS DEL TRACTAMENT.

Per la tècnica que estem realitzant:

- A conseqüència de la intervenció es pot presentar malestar, febre, nàusees i dolor que persisteixen entre 3 i 10 dies i solen cedir amb tractament mèdic. Durant les dues primeres setmanes és normal que senti cansament i pèrdua d'apetit.

- Obstrucció de gots en òrgans no desitjats, que pot conduir a complicacions greus (insuficiència hepàtica, necrosi o abscés hepàtic, inflamació de la vesícula o del pàncrees).

- Infecció.

- Neumonítis per radiació.

- Ulcera rádica en estómac o duodè que pot ser refractària al tractament convencional.

En general, les complicacions greus ocorren en 5 de cada 100 pacients. La mort per insuficiència hepàtica ocorre en 1 de cada 100 pacients.

Pel mitjà de contrast:

Reaccions al·lèrgiques, que poden ser:

- Lleus com a nàusees, picors o lesions en la pell.

- Rarament greus com a alteracions dels ronyons o sensació d'ofec.

- Excepcionalment la mort (1 de cada 1.000.000 pacients).

De totes maneres, si ocorregués qualsevol complicació, no dubti que es prendran les mesures adequades per a intentar solucionar-los.

OBSERVACIONS I CONTRAINDICACIONS

Prèviament a la realització de la intervenció, s'ha de comunicar al metge el patiment d´algun tipus d'al·lèrgia, especialment a l'anestèsia o al mitjà de contrast.

Li sol·licitem permís per a recopilar totes les dades necessàries per a l'estudi. Aquests es recolliran tant abans de la intervenció com després d'ella cada sis setmanes durant el seguiment de dos anys que se li realitzarà a tots els pacients.

BENEFICIS I RISCOS DERIVATS DE LA SEVA PARTICIPACIÓ EN L'ESTUDI

Les dades recaptades en aquesta recerca tenen com a fi confirmar la nostra hipòtesi i proporcionar suficient evidència per a validar la TARE com a nova tècnica estàndard per al tractament dels carcinomes hepatocel·lulars BCLC B.

És possible que els coneixements derivats de la recerca no li beneficiïn a vostè, però si a futurs pacients amb el mateix problema.

Si en algun moment desitja conèixer els resultats de la recerca aconseguits gràcies a la seva col·laboració, haurà de posar-se en contacte amb els responsables de l'estudi.

Els pacients seran avaluats contínuament i en aquells que la seva malaltia progressi seran tractats amb els millors recursos disponibles.

CONFIDENCIALITAT

Totes les dades recopilades seran tractats d'una manera confidencial. Només podran accedir a les seves dades mèdiques persones sotmeses al secret professional i sempre amb autorització de l'investigador principal.

El tractament, comunicació i cessió de totes les dades de caràcter personal dels participants en l'estudi s'ajustarà a la Llei 03/2018, de protecció de dades de caràcter personal. Respecte a la legislació esmentada i després de dirigir-se al metge responsable de l'estudi, podrà exercir els drets d'accés, modificació, oposició i cancel·lació de dades. Les dades estaran identificades mitjançant un codi que únicament els investigadors responsables podran relacionar amb vostè. En cap concepte el seu nom apareixerà en la publicació dels resultats.

Si en algun moment desitgés retirar el seu consentiment per a participar en l'estudi, cap dada nova serà afegit a la base de dades i es procedirà a la destrucció de tota la informació personal que hagi estat recopilada.

CONTACTE AMB L'INVESTIGADOR

Per a qualsevol dubte o informació addicional que necessiti, o sobre els seus drets com a participant en un assaig clínic, no dubti a contactar amb l'investigador.

15.10. ANNEX 10: CLINICAL TRIAL INFORM SHEET (Spanish Version)

Hospital Universitari de Girona Doctor Josep Trueta

Av. França s/n 17007 Girona

HOJA DE INFORMACIÓN AL PACIENTE

Y-90 PERSONALISED DOSIMETRY TARE VERSUS DEB-TACE IN THE TREATMENT OF BCLC B HEPATOCELLULAR CARCINOMA

INTRODUCCIÓN

Nos dirigimos a usted para invitarlo a participar en un estudio de investigación que se está llevando a cabo en el servicio de Radiología Intervencionista del Hospital Doctor Josep Trueta de Girona.

Mediante este documento queremos facilitarle toda la información necesaria para que pueda evaluar si quiere participar o no en el estudio. Antes de aceptar o denegar la participación, le pedimos que lea detenidamente este documento.

No dude en formular todas las preguntas necesarias y solicitar cualquier información extra. Puede consultar la decisión con quien considere oportuno.

PARTICIPACIÓN VOLUNTARIA

Su participación en el estudio es totalmente voluntaria. Puede decidir no participar, cambiar su decisión y retirar el consentimiento en cualquier momento. Eso no alterará la relación con su médico y no se producirá ningún prejuicio en la atención sanitaria que reciba.

DESCRIPCIÓN DEL ESTUDIO

Actualmente, la Quimioembolización transarterial (TACE) es el tratamiento de primera línea para la enfermedad en estadio intermedio según el sistema BCLC, que incluye a los pacientes asintomáticos con lesiones multinodulares limitadas e irresecables, sin invasión vascular ni diseminación extrahepática y que tienen una función hepática bien conservada.

En el HUDJT se ha planteado, tras una larga evaluación de la evidencia científica disponible, la opción de emplear la radioembolización (TARE) como el tratamiento de primera línea en el estadio intermedio BCLC (BCLC B).

Este proyecto busca comparar ambas técnicas en este grupo de pacientes. Con este estudio se pretende conocer si la hipótesis es válida. Pretendemos demostrar que la Radioembolización en los pacientes clasificados como BCLC B aporta una mayor supervivencia, mayor tiempo hasta la progresión de la enfermedad, menor aparición de efectos adversos, una mejor respuesta global y mejor calidad de vida.

De esta forma buscamos conseguir suficiente evidencia científica para validar la técnica en un futuro como terapia de elección en los pacientes diagnosticados con un carcinoma hepatocelular clasificado como BCLC B.

PROCEDIMIENTOS DEL ESTUDIO

En el estudio dividiremos a todos los pacientes en dos grupos de forma aleatoria. Los dos grupos tendrán el mismo número de pacientes. Un grupo será tratado mediante DEB-TACE (un subtipo de TACE) y el otro mediante TARE.

A continuación, se le describen las técnicas que se compararán en el estudio:

QUIMIOEMBOLIZACIÓN HEPÁTICA CON DEBs (Drug-Eluting Beads**)**

¿QUÉ ES Y CÓMO SE REALIZA?

La quimioembolización es un tratamiento eficaz para algunas lesiones tumorales del hígado. Mediante un catéter depositamos selectivamente unas microesferas sintéticas que contienen una sustancia anticancerosa en la lesión al mismo tiempo que ocluimos (embolizamos) las arterias que nutren el tumor, tratando así de destruirlo. De esta forma, las esferas irán liberando el fármaco directamente a las células tumorales de forma paulatina durante los días siguientes.

Se le pinchará la arteria femoral en la ingle utilizando anestesia. A continuación, se le introducirá un tubo muy fino (catéter) por el que se inyecta un líquido (medio de contraste), que permite ver los vasos sanguíneos del hígado y obtener radiografías. Una vez localizado el sitio exacto se procederá a la quimioembolización.

La duración aproximada de esta intervención es aproximadamente de 1 a 3 horas. En ocasiones son necesarias entre varias sesiones cada una de ellas distanciadas por un mínimo de 6 semanas.

¿PARA QUÉ SIRVE?

La quimioembolización sirve para prolongar la vida en pacientes con tumores del hígado.

¿QUÉ CONSECUENCIAS IMPORTANTES PRODUCIRÁ LA INTERVENCIÓN?

Control de su enfermedad y aumento de la supervivencia.

¿QUÉ RIESGOS PUEDE HABER?

Riesgos frecuentes

- Síndrome Postembolización: No es una complicación sino una consecuencia del tratamiento. Tiene una gran variabilidad personal en cuanto a incidencia e intensidad de los síntomas. Su duración es autolimitada entre 1 día y 3 semanas. No aparece en todos los casos y su tratamiento es sintomático. Consiste en fiebre de <38,5 y/o leucocitosis y/o dolor y/o nauseas. Puede en ocasiones acompañarse de dolorimiento en el flanco y/o hombro derecho.

Riesgos poco frecuentes

- Insuficiencia hepática.
- Absceso hepático.
- Colecistitis.
- Embolización no deseada de áreas de mucosa del tubo digestivo.

Con una adecuada selección de los pacientes y técnica cuidadosa estas complicaciones ocurren entre el 3-7 % de los casos.

- Insuficiencia renal <1 %.
- Anemia que requiera transfusión <1 %.
- La **mortalidad a 30** días de la intervención es de 1 – 4 %.
- Sangrado o hematoma en el punto de punción femoral.
- Reacción alérgica al contraste. Exantema cutáneo y prurito hasta en un 4% de los casos. Las reacciones graves hoy en día son excepcionales.
- Rara vez hay caída del cabello.

De todas formas, si ocurriera cualquier complicación no dude que todos los medios técnicos y humanos de este hospital están dispuestos para intentar solucionarlas.

¿HAY OTRAS ALTERNATIVAS AL PROCEDIMIENTO?

La cirugía de resección convencional no es posible en este tipo de pacientes. Dependiendo de sus circunstancias personales, se podrá tratar su tumor con técnicas de ablación percutánea.
El trasplante hepático en personas jóvenes y con unas características muy concretas.

La quimioterapia hasta el momento solo es eficaz en estado avanzado de la enfermedad para prolongar unos meses la vida.

La radioembolizacion con microesferas radiactivas es una alternativa que se aplica en casos concretos y actualmente todavía en fase de estudio.

Si desea más información o tiene cualquier duda, no tenga reparo en preguntarnos. Le atenderemos con mucho gusto.

¿QUÉ CONSECUENCIAS SON PREVISIBLES DE LA NO REALIZACIÓN?

Disminución del tiempo de vida del paciente.

OBSERVACIONES Y CONTRAINDICACIONES

Previamente a la realización de la intervención, se debe comunicar al médico el padecimiento de algún tipo de alergia, en especial a la anestesia o al medio de contraste.

Si desea más información o tiene cualquier duda, no tenga reparo en preguntarnos. Le atenderemos con mucho gusto.

RADIOEMBOLIZACIÓN HEPÁTICA

La Radioembolización transcatéter se utiliza para algunos pacientes con cáncer primario de hígado o metástasis al hígado de otros tumores. El objetivo es intentar controlar el crecimiento de las células tumorales y en algunos casos destruirlas. Para ello, se usan las imágenes de rayos-X en un monitor de televisión para insertar un catéter a través de una pequeña punción en la piel (generalmente de la ingle) con anestesia local y guiarlo a través de la arteria que alimenta el tumor. Se inyectan directamente en el tumor partículas muy pequeñas que se han cargado previamente con agentes radiactivos, en este caso Itrio-90. Dependiendo de sus circunstancias personales, este procedimiento se realizará bajo sedación.

Al final del procedimiento se retira el catéter y el paciente tiene que permanecer en cama durante 12 horas. La mayoría de los pacientes vuelven a su vida normal en una semana, pero algunos pueden tardar un mes.

La intervención se realizará en dos tiempos, una primera fase de estudio y planificación 14 días antes de introducir en el hígado las microesferas radioactivas propiamente dichas. La duración de cada procedimiento es, aproximadamente, de dos horas.

Los resultados que se obtienen compensan los posibles riesgos que a continuación le exponemos.

ALTERNATIVAS

Dependiendo de sus circunstancias personales, se podrá tratar su tumor con técnicas de ablación, quimioembolización o quimioterapia sistémica. En algún caso particular la alternativa pudiera ser la intervención quirúrgica.

RIESGOS Y COMPLICACIONES DEL TRATAMIENTO.

Por la técnica que estamos realizando:

- Como consecuencia de la intervención se puede presentar malestar, fiebre, náuseas y dolor que persisten entre 3 y 10 días y suelen ceder con tratamiento médico. Durante las dos primeras semanas es normal que sienta cansancio y pérdida de apetito.
- Obstrucción de vasos en órganos no deseados, que puede conducir a complicaciones graves (insuficiencia hepática, necrosis o absceso hepático, inflamación de la vesícula o del páncreas).
- Infección.
- Neumonítis por radiación.
- Ulcera rádica en estómago o duodeno que puede ser refractaria al tratamiento convencional.

En general, las complicaciones graves ocurren en 5 de cada 100 pacientes. La muerte por fallo hepático ocurre en 1 de cada 100 pacientes.

Por el medio de contraste:

Reacciones alérgicas, que pueden ser:

- Leves como náuseas, picores o lesiones en la piel.
- Raramente graves como alteraciones de los riñones o sensación de ahogo.

- Excepcionalmente la muerte (1 de cada 1.000.000 pacientes).

De todas formas, si ocurriera cualquier complicación, no dude que se tomarán las medidas adecuadas para intentar solucionarlos.

OBSERVACIONES Y CONTRAINDICACIONES

Previamente a la realización de la intervención, se debe comunicar al médico el padecimientode algún tipo de alergia, en especial a la anestesia o al medio de contraste.

Le solicitamos permiso para recopilar todos los datos necesarios para el estudio. Estos se recogerán tanto antes de la intervención como después de ella cada seis semanas durante el seguimiento de dos años que se le realizará a todos los pacientes.

BENEFICIOS Y RIESGOS DERIVADOS DE SU PARTICIPACIÓN EN EL ESTUDIO

Los datos recaudados en esta investigación tienen como fin confirmar nuestra hipótesis y proporcionar suficiente evidencia para validar la TARE como nueva técnica estándar para el tratamiento de los carcinomas hepatocelulares BCLC B.

Es posible que los conocimientos derivados de la investigación no le beneficien a usted, pero si a futuros pacientes con el mismo problema.

Si en algún momento desea conocer los resultados de la investigación conseguidos gracias a su colaboración, deberá ponerse en contacto con los responsables del estudio.

Los pacientes serán evaluados continuamente y en aquellos que su enfermedad progrese serán tratados con los mejores recursos disponibles.

CONFIDENCIALIDAD

Todos los datos recopilados serán tratados de una manera confidencial. Sólo podrán acceder a sus datos médicos personas sometidas al secreto profesional y siempre con autorización del investigador principal.

El tratamiento, comunicación y cesión de todos los datos de carácter personal de los participantes en el estudio se ajustará a la Ley 03/2018, de protección de datos de carácter personal. Con respecto a la legislación mencionada y tras dirigirse al médico responsable del estudio, podrá ejercer los derechos de acceso, modificación, oposición y cancelación de datos. Los datos estarán identificados mediante un código que únicamente los

investigadores responsables podrán relacionar con usted. Bajo ningún concepto su nombre aparecerá en la publicación de los resultados.

Si en algún momento desease retirar su consentimiento para participar en el estudio, ningún dato nuevo será añadido a la base de datos y se procederá a la destrucción de toda la información personal que haya sido recopilada.

CONTACTO CON EL INVESTIGADOR

Para cualquier duda o información adicional que necesite, o sobre sus derechos como participante en un ensayo clínico, no dude en contactar con el investigador.

15.11. ANNEX 11: TRIAL CONSENT FORM (Catalan version)

Hospital Universitari de Girona Doctor Josep Trueta

Av. França s/n 17007 Girona

CONSENTIMENT INFORMAT

Y-90 PERSONALISED DOSIMETRY TARE VERSUS DEB-TACE IN THE TREATMENT OF BCLC B HEPATOCELLULAR CARCINOMA

Jo (Nom i Cognoms)…… amb DNI/NIE …….

• He rebut i he realitzat una lectura de la totalitat de la fulla d'informació per al pacient.

• He pogut fer preguntes sobre l'estudi i se m'ha facilitat una quantitat d'informació adequada a elles.

• Comprenc que la meva participació és voluntària i que no obtindré benefici econòmic en formar part de l'estudi.

• He estat informat dels potencials riscos i beneficis derivats de la participació en aquest estudi.

• Comprenc que puc revocar el meu consentiment en qualsevol moment, sense haver de donar explicacions i sense que això alteri la meva assistència sanitària.

• Comprenc que totes les meves dades seran confidencials.

En conseqüència:

- Accedeixo al fet que els investigadors principals del projecte puguin contactar amb mi en un futur si ho consideren oportú.

- Dono lliurement la meva conformitat per a participar en l'estudi i dono el meu consentiment per al maneig i utilització de la meva informació en les condicions detallades en la fulla d'informació.

☐ SI ☐ NO

Signatura del pacient: Signatura de l´investigador:

Data: _____ / _____ /_____ Data: _____ /_____ /_____

15.12. ANNEX 12: TRIAL CONSENT FORM (Spanish version)

Hospital Universitari de Girona Doctor Josep Trueta

Av. França s/n 17007 Girona

CONSENTIMIENTO INFORMADO

Y-90 PERSONALISED DOSIMETRY TARE VERSUS DEB-TACE IN THE TREATMENT OF BCLC B HEPATOCELLULAR CARCINOMA

Yo (nombre y apellidos) .....con DNI/NIE.....

• He recibido y he realizado una lectura de la totalidad de la hoja de información para el paciente.

• He podido hacer preguntas sobre el estudio y se me ha facilitado una cantidad de información adecuada a ellas.

• Comprendo que mi participación es voluntaria y que no obtendré beneficio económico al formar parte del estudio.

• He sido informado de los potenciales riesgos y beneficios derivados de la participación en este estudio.

• Comprendo que puedo revocar mi consentimiento en cualquier momento, sin tener que dar explicaciones y sin que ello altere mi asistencia sanitaria.

• Comprendo que todos mis datos serán confidenciales.

En consecuencia:

- Accedo a que los investigadores principales del proyecto puedan contactar conmigo en un futuro si lo consideran oportuno.

- Doy libremente mi conformidad para participar en el estudio y doy mi consentimiento para el manejo y utilización de mi información en las condiciones detalladas en la hoja de información.

☐ SI ☐ NO

Firma del paciente: Firma del investigador:

Data: _____ /_____ /_____ Data: _____ /_____ /_____

15.13. ANNEX 13: WITHDRAWAL OF TRIAL INFORMED CONSENT (Catalan version)

Hospital Universitari de Girona Doctor Josep Trueta

Av. França s/n 17007 Girona.

REVOCACIÓ DEL CONSENTIMENT INFORMAT

Y-90 PERSONALISED DOSIMETRY TARE VERSUS DEB-TACE IN THE TREATMENT OF BCLC B HEPATOCELLULAR CARCINOMA

Jo, (Nom i Cognoms) ……, amb DNI/NIE …… revoco el consentiment informat per la participació en l'estudi especificat en aquest mateix document.

Signatura del pacient

Signatura del responsable/investigador/a

Lloc i data: _____, _____ de _____ del 20____.

15.14. ANNEX 14: WITHDRAWAL OF TRIAL INFORMED CONSENT (Spanish version)

Hospital Universitari de Girona Doctor Josep Trueta

Av. França s/n 17007 Girona.

REVOCACIÓN DEL CONSENTIMIENTO INFORMADO

Y-90 PERSONALISED DOSIMETRY TARE VERSUS DEB-TACE IN THE TREATMENT OF BCLC B HEPATOCELLULAR CARCINOMA

Yo, (Nombre y Apellidos) ……, con DNI/NIE …… revoco el consentimiento informado para la participación en este estudio especificado en este mismo documento.

Firma del paciente	Firma del responsable/investigador/a

Lugar y fecha: _____, _____ de _____ del 20____.


dIBGi
Institut d'Investigació
Biomèdica de Girona
Dr. Josep Trueta


Universitat de Girona
Facultat de Medicina


/Salut
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