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Radioembolization: clinical indications and comparison between three different systems

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR

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Radioembolization: clinical indications and comparison between three different systems

Dissertação de Candidatura ao grau de **Mestre em Oncologia – Especialização em Oncologia Clínica** submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto

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Abstract

Introduction: Radioembolization or Selective Internal Radiation Therapy (SIRT) is a treatment for unresectable and secundary hepatic tumors, which consists on radiolabeled microspheres administration directly into liver tumors through the arteries that irrigate liver. These microspheres, due to their small size and weight, will lodge in the small vessels inside and/or surrounding the tumor, depositing high level radiation within and close to the tumor to destroy all tumor cells, limiting healthy liver tissue exposition to within acceptable levels. Until 2015, microspheres labelled with yttrium-90 were the radiopharmaceutical available for SIRT purpose by 2 different types, yttrium-90 resin microspheres (SIR-Spheres) and yttrium-90 glass microspheres (TheraSphere). Thenceforth, holmium-166 microspheres (QuiremSpheres) were introduced and are available in Europe for SIRT. It is therefore essential to understand the role of this new radiopharmaceutical, as well as the advantages and disadvantages inherents of its use in comparison with the two available yttrium-90 procedures.

Methods: In the first part, a meta-analysis was performed using retospective clinical trials and prospective studies available in PubMed scientific database. This literature review aims to show clinical evidence of the inherent advantages of ^{90}Y-SIRT used in several clinical contexts and explore ^{166}Ho-SIRT as a new therapeutic approach, allowing us to compare the three procedures. In the second part, we evaluated possible factors that can interfere with the percentage of lung shunt (LS) obtained in SIRT. The last 80 patients with hepatic pathologies that underwent SIRT in IPO Porto were included. One patient was excluded by contraindicated LS and 4 by insufficient data. Hence, 75 patients were included in the study. For data base elaboration, variables “shunt”, “age”, “height”, “weight”, “interval between pre-therapeutic and therapeutic phases”, “gender”, “hepatic disease” “tumor type” and “type of microspheres” were considered.

Results: The meta-analysis showed clinical evidence of the benefits of using Sir-Spheres and TheraSphere in various clinical indications, as well as highlighting the important role of QuiremSpheres introduction in SIRT. In clinical practice, we obtained statistically significant results in Spearman Rho correlation between “shunt” and “weight” ($p=0.006$; $p<0.01$) and “shunt” and “BSA” ($p=0.008$; $p<0.01$). Statistically significant differences between ^{90}Y-SIRT groups and ^{166}Ho-group were observed in Mann-Whitney U test for “shunt” data distribution in “type of microspheres” group, being the LS inferior in QuiremSpheres group compared with SIR-Spheres ($p=0.000$; $p<0.01$) and TheraSphere ($p=0.02$; $p<0.05$) groups.

Conclusion: We conclude that ^{166}Ho-SIRT has advantages over ^{90}Y-SIRT, in terms of dosimetry and imaging, but mainly by efficacy and safety of ^{166}Ho-scout use for LS

evaluation. The obtained results in clinical practice corroborate the review analysis and show that SIRT can be improved by using ^{166}Ho-scout use instead by ^{99m}Tc-MAA.

Key Words: radioembolization; yttrium-90 microspheres; lung shunt; holmium-166 microspheres; scout dose; dosimetry

Resumo

Introdução: A radioembolização (SIRT) é uma abordagem terapêutica para tumores hepáticos de origem primária e secundária que consiste na administração de microesferas radiomarcadas que serão administradas e conduzidas diretamente ao tecido hepático tumoral através do sistema arterial. Essas microesferas, devido ao seu pequeno tamanho e baixo peso, alojar-se-ão nos pequenos vasos envolvendo o tumor, depositando aí altas doses de radiação, destruindo assim as células tumorais alvo, e, simultaneamente, limitando a exposição do tecido hepático saudável a níveis aceitáveis. Até 2015, microesferas marcadas com ítrio-90 eram o radiofármaco disponível para a SIRT, estando disponível sob duas formas: microesferas de resina marcadas com ítrio-90 (SIR-Spheres) e microesferas de vidro marcadas com ítrio-90 (TheraSphere). Posteriormente, microesferas marcadas com hólmio-166 (QuiremSpheres) foram introduzidas no mercado e estão disponíveis na Europa para a SIRT. Assim sendo, é essencial entender o papel deste novo radiofármaco, bem como as vantagens e desvantagens inerentes ao seu uso em comparação com os dois procedimentos disponíveis com ítrio-90.

Métodos: Na primeira parte, foi realizada uma meta-análise utilizando estudos clínicos retrospectivos e prospectivos disponíveis na base de dados científica PubMed. Esta revisão da literatura tem como objetivo apresentar evidências clínicas dos benefícios inerentes à utilização da ^{90}Y-SIRT em diversos contextos clínicos, bem como explorar a ^{166}Ho-SIRT como uma nova abordagem à terapêutica, permitindo assim uma comparação dos três procedimentos. Na segunda parte, avaliamos possíveis fatores que podem interferir na percentagem de shunt pulmonar (LS) obtida na SIRT. Foram identificados os últimos 80 doentes com patologias hepáticas que efetuaram SIRT no IPO Porto. Um paciente foi excluído por LS contraindicado e 4 por dados insuficientes. Assim, 75 pacientes foram incluídos no estudo. Para a base de dados, consideramos as variáveis “shunt”, “idade”, “altura”, “peso”, “intervalo entre as fases pré-terapêutica e terapêutica”, “género”, “doença hepática” “tipo de tumor” e “tipo de microesferas ".

Resultados: A meta-análise mostrou evidência clínica dos benefícios da utilização da SIRT com SIR-Spheres e TheraSphere em várias indicações clínicas, permitindo também destacar o importante papel da introdução das QuiremSpheres na SIRT. Na prática clínica, obtivemos resultados estatisticamente significativos na correlação de Spearman Rho entre “shunt” e “peso” ($p=0,006$; $p <0,01$) e entre “shunt” e “BSA” ($p=0,008$; $p<0,01$). Diferenças estatisticamente significativas entre os grupos de ^{90}Y-SIRT e o grupo ^{166}Ho-SIRT foram observadas no teste U de Mann-Whitney para distribuição de dados de “shunt” nos grupos de “tipo de microspheras”, sendo o valor de LS inferior no grupo Quirem-Spheres em

comparação com os grupos SIR-Spheres (p=0,000; p<0,01) e TheraSphere (p=0,02; p<0,05).

Conclusão: Concluímos que a ^{166}Ho-SIRT revela vantagens em relação à ^{90}Y-SIRT, em termos de dosimetria e imagiologia, mas principalmente pela eficácia e segurança do uso da ^{166}Ho-scout para avaliação de LS. Os resultados obtidos na prática clínica corroboram a análise da revisão de literatura e mostram que a SIRT pode ser melhorada com o uso do ^{166}Ho-scout em vez de ^{99m}Tc-MAA.

Palavras-Chave: radioembolização, microsferas marcadas com ítrio-90, shunt pulmonar, microsferas marcadas com hólmio-166, dose de scout, dosimetria

List of Abbreviations

AFP	Alpha-fetoprotein
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCLC	Barcelona Clinic Liver Cancer
BRCLM	Breast Cancer Liver Metastases
BSA	Body Surface Area
CA	Cystic Artery
CC	Cholangiocarcinoma
CLCC	National Cancer Centre Singapore's Comprehensive Liver
CLIP	Cancer Clinic Cancer of the Liver Italian Program
CRC	Colorectal Cancer
CRCLM	Colorectal Cancer Liver Metastases
cTACE	Conventional TACE
CUPI	Chinese University Prognostic Index
DEB-TACE	Drug-eluting Bead Transarterial Chemoembolization
DSA	Digital Subtraction Angiography
EASL	European Association of the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society of Medical Oncology
GBq	Gigabecquerel
GDA	Gastroduodenal Artery
GEP	Gastro-enteropancreatic
HCC	Hepatocellular Carcinoma
^{166}Ho	Holmium-166
IACT	Intra-arterial CT
ICC	Intrahepatic Cholangiocarcinoma
LET	Linear Energy Transfer
LS	Lung Shunt
MAA	Macroaggregated Albumin
MBq	Megabecquerel
mCi	Milicurie
^{99}Mo/^{99m}Tc generator	Technetium-99 metastable generator
MWU	Mann-Whitney U
NCCN	National Comprehensive Cancer Network

NETLM	Neuroendocrine Tumor Liver Metastases
NICE	National Institute for Health and Clinical Excellence
OMLM	Ocular Melanoma Liver Metastases
ORR	Overall Response Rate
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression-free Survival
PLLA	Poly-L-lactic Acid
PRRT	Peptide Receptor Radionuclide Therapy
PVT	Portal Vein Thrombosis
QoL	Health-related Quality of Life
QS	QuiremSpheres
RECIST	Response Evaluation Criteria in Solid Tumors
REILD	Radioembolization-induced Liver Disease
RFA	Radiofrequency Ablation
RGA	Right Gastric Artery
RILD	Radiation-induced Liver Disease
RR	Response Rate
SD	Stable Disease
SIRT	Selective Internal Radiation Therapy
SPECT	Single-Photon Emission Computed Tomography
SRC	Spearman Rho Correlation
SS	SIR-Spheres
T/N	Tumor/Non-tumor
TACE	Transarterial Chemoembolization
TARE	Transarterial Radioembolization
TNM	Tumor-Node Metastasis
TS	TheraSphere
TTP	Time to Progression
UMCS	Utrecht Monte Carlo System
WHO	World Health Organization
^{90}**Y**	Yttrium-90

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I. Introduction

1. Liver Cancer Epidemiology

1.1. Primary Liver Cancer

Cancer is the major public health problem worldwide since decades. The more recent globocan data available are presented in figure 1 (1), showing 18 078 957 new cancer cases were observed in 2018, being lung and breast cancer the pathologies with higher incidence, 11.6% of all incidence. In what mortality concerns, 9 555 027 people died from cancer in 2018. Lung cancer was the type of cancer with more mortality associated, with 1 761 007 cases of related death, corresponding to 18,4% of all cases of mortality.

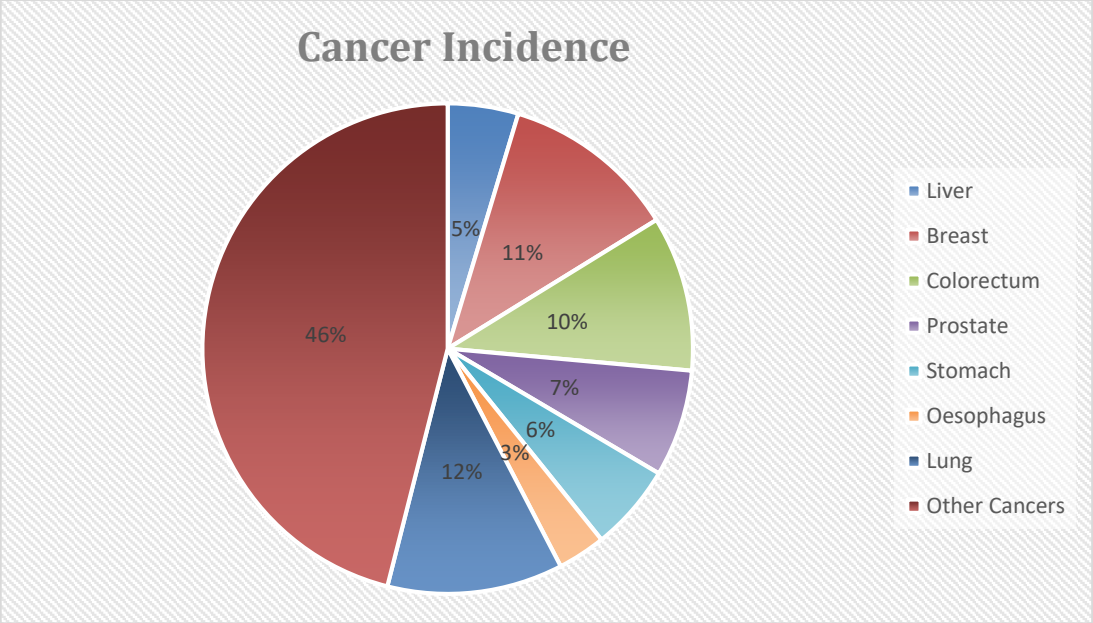

Figure 1: Estimated percentage of new liver cancer cases in 2018, in both genders and all ages. Adapted from [1].

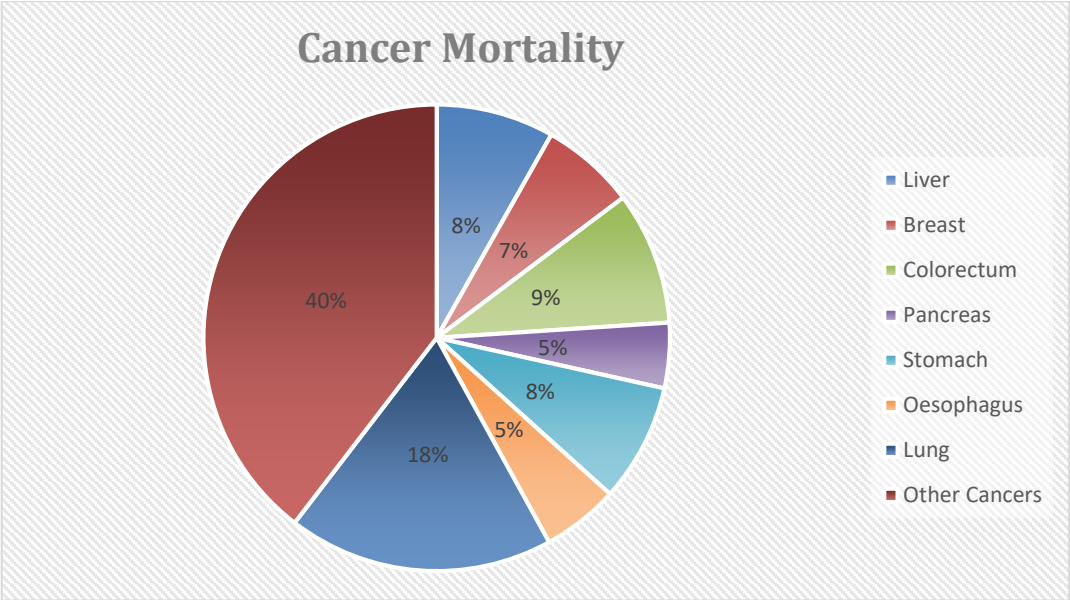

Figure 2: Estimated percentage of liver cancer related deaths in 2018 worldwide, in both genders and all ages. Adapted from [1].

Primary liver cancer is one of the most common cancers. In 2018, it was the sixth more incident cancer all over the world, with 841 080 new cases, which represents an incidence of 4.7%. There were 781 631 deaths from liver cancer in 2018, corresponding to 8,2% of all the cases of cancer related mortality. In figure 2, it is possible to verify a highest age-standardized incident and mortality rates of liver cancer in typical regions, such as Eastern Asia, South-Eastern Asia, Northern Africa and Southern Africa.

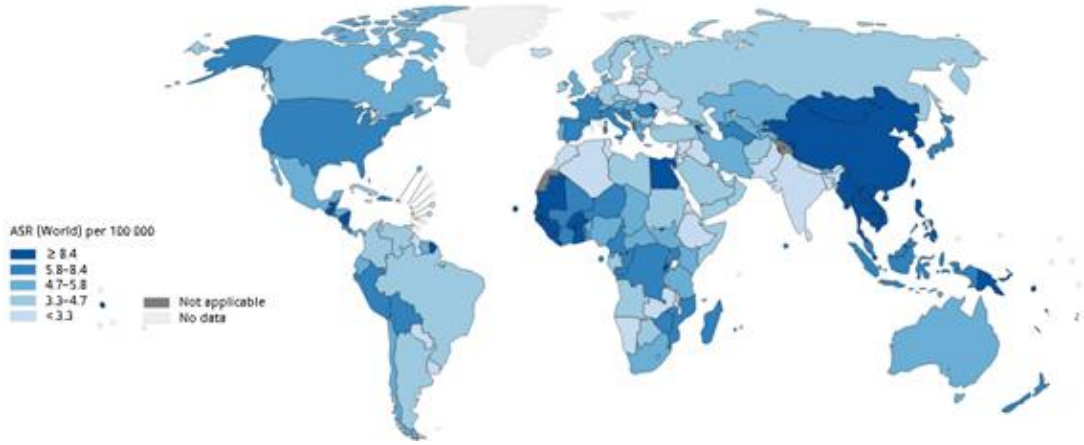

Figure 3: Estimated age-standardized incident rate in 2018 by liver cancer, in both genders and all ages. From [1].

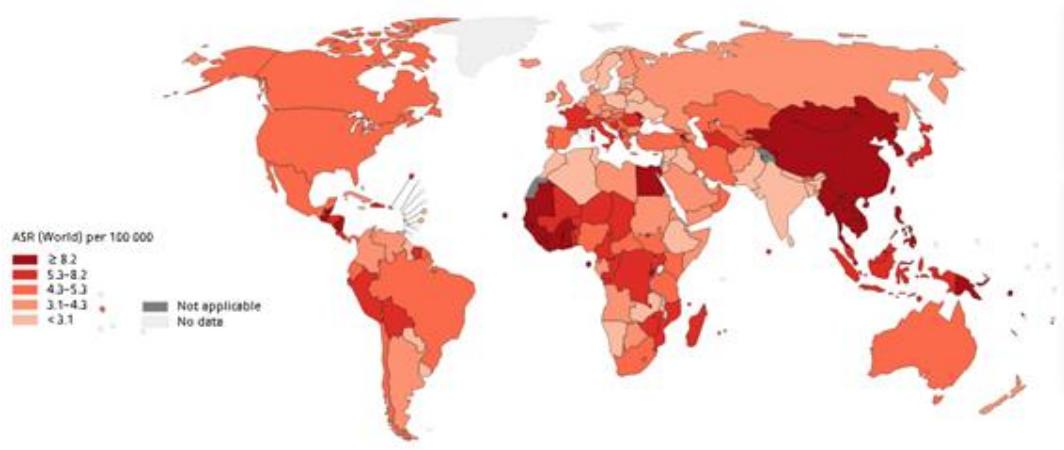

Figure 4: Estimated age-standardized mortality rate in 2018 by liver cancer, in both genders and all ages. From [1].

Among these, Asia represents the region with more contribution to the numbers of incidence and mortality observed in 2018, with 609 596 new cases and 566 269 deaths, corresponding to 72.5% of the new cases and 72.4% of deaths througout the world (1). This type of cancer is significantly more common in men. In 2018, 443 744 new cases were observed in males in Asia and 165 852 new cases in females. The number of deaths by liver cancer in Asia was 410 223 in males and 156 046 in females. The highest estimate age-standardized incidence and mortality rates are observed in Mongolia, with an age-standardized incidence rate of 93.7 cases per 100.000 standard population and an age-standardized mortality rate of 75.4 deaths per 100.000 standard population (figure 3). However, more than half of new cases and deaths from liver cancer all over the world occur in China, with 392 868 new cases and 368 960 deaths in 2018, resulting in a huge discrepancy in numbers between Asian and remaining regions, as described in figure 4. A huge part of this rising in cancer burden can be explained by population growth, socio-demographic changes, aging and exposition to risk factors, what will be covered below. Additional information on epidemiology is described in Appendix I.

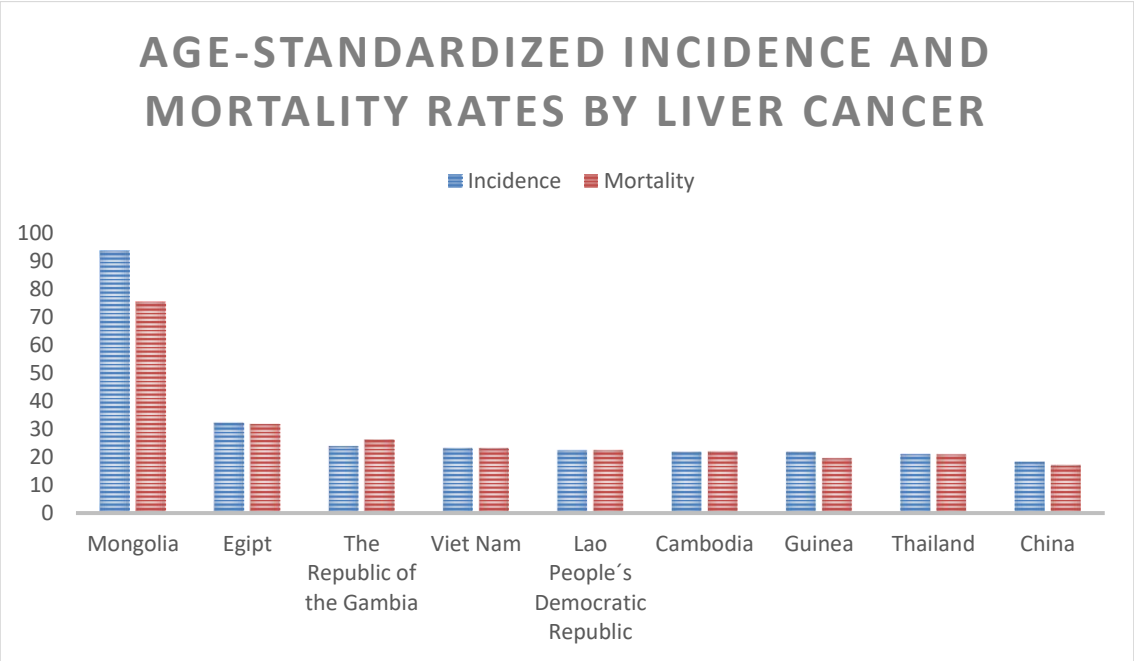

Figure 5: Estimated age-standardized incidence and mortality rates (World) in 2018 by liver cancer, in both genders and all ages [ASR (world) per 100 000]. Adapted from [1].

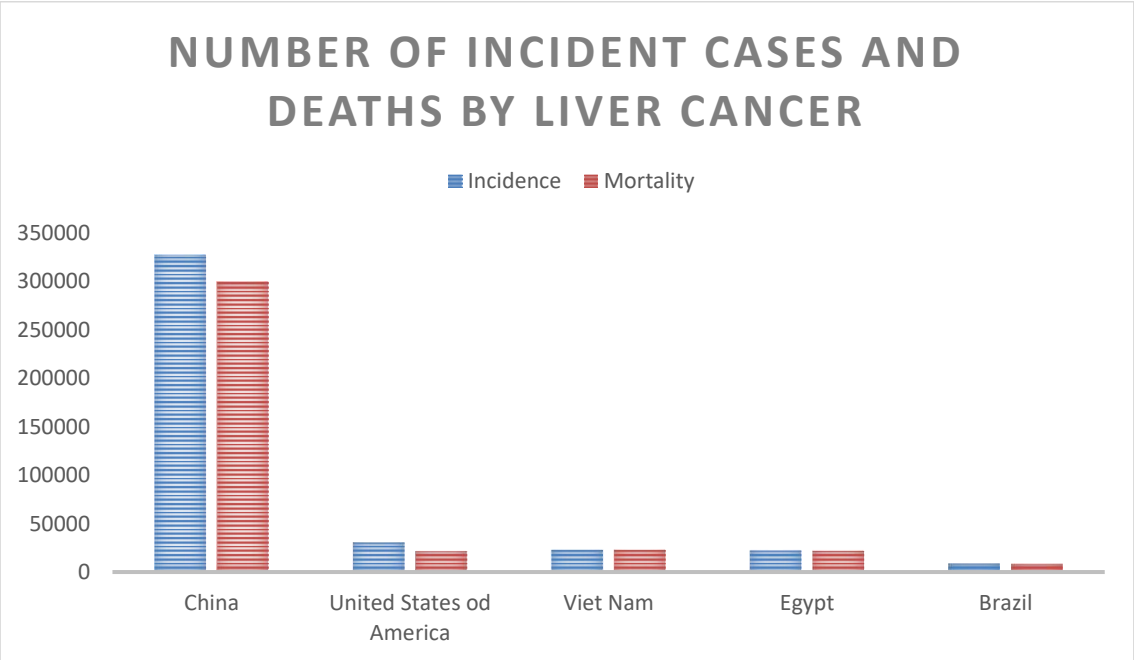

Figure 6: Estimated number of incident cases and deaths by liver cancer, in both genders and all ages. Adapted from [1].

1.1.1. Hepatocellular Carcinoma (HCC)

Hepatocellular carcinoma (HCC) is one of the most prevalent and lethal malignant neoplasm on a global scale, representing the most common type of primary liver cancer (2). This malignant tumor is usually associated to cirrhosis and it is composed by hepatocyte-like cells, however, with several degrees of differentiation. The cirrhosis arises from the evolution of chronic hepatitis, caused mainly by the HBV and HBC viruses, which will be discussed in more detail later as the main risk factors for the development of HCC. In cirrhotic livers, it is possible to find regenerative nodules, resulting from a high rate of hepatocytes proliferation. Differentiation between these nodules and HCC can vary based on their size, an important factor to define the patients prognosis (3).

Unfortunately, HCC is much often diagnosed in advanced stages and hepatic synthetic function is poor. There, the potential treatment options are limited and least effective, and, for that fact, key advances in the treatment of HCC have been made (4). In order to have the best result in HCC treatment and, consequently, the best prognosis, early diagnosis is the key. Surveillance programs for early detection of HCC and more accurate imaging techniques allow its identification at an earlier stage, which increases the treatment effectiveness and, consequently, the chances of survival (4). Nowadays, to diagnose HCC, imaging techniques such Single-Photon Emission Computed Tomography/Computed Tomography (SPECT/CT), Positron Emission Tomography/ Computed Tomography (PET/CT), Magnetic Resonance Imaging (MRI) are available, as well as blood tests to measure liver function based on alpha-fetoprotein (AFP) levels, and liver biopsy (2) (3).

1.2. Liver Metastases

Metastases formation results from the spread of cancer cells from their primary site to other distant sites, where they multiply and form new cell colonies. After growth and vascularization processes, local primary tumor cells will invade the circulatory or lymphatic system and be transported in the form of a tumor embolus. The tumoral embolus will then be captured by a secondary organ, in this case the liver, where, after establishing itself, it will create a tumor microenvironment, through processes of accelerated growth, angiogenesis and immune system cells recruitment. The liver is one of the most commonly involved organs in metastatic disease, only surpassed by the lymph nodes, revealing several characteristics that make it an avid place for metastasis (5).

As noted above, the liver is an organ of the reticuloendothelial system, represented by Kupffer cells. This system is based on a set of cells disseminated in the body, comprising macrophages and monocytes, which play important roles in immune defense by cellular debris removal from the bloodstream. This characteristic makes the liver, in addition to being highly irrigated by vessels of the lymphatic system, an organ where cells from the lymphatic system are more easily recruited by tumor cells through its close interaction with Kupffer cells (6). The blood supply and lymphatic drainage patterns of each organ may explain why each primary tumor type present characteristic metastatic patterns, with a tendency to metastasize for certain target tissues. Consequential, gastrointestinal primary tumors will have associated high frequency of liver metastases, once, as previously mentioned, the liver is, due to its functions, largely irrigated by blood vessels, where venous blood from the digestive system organs and accessory glands is drained through the hepatic portal vein. Any tumor embolus coming from an organ of the digestive system will be transported in the circulation and will pass through the liver, thus having a higher possibility of being fixed there in relation to other organs. Metastatic disease is the most common malignant pathology of the liver and a sign of disseminated disease and consequent poor prognosis (6) (7).

This logic is corroborated by a study performed by *Hess et al.* , who collected adenocarcinoma registry data on 11 primary tumor and 15 metastatic sites in 4399 patients between 1994 and 1996, showing that liver has predominance to be the metastatic site for pancreatic (85%), colon (78%) and rectum (71%) esophagus (52%), stomach (39%) and liver (49%) cancer (5).

Kasper et al. epidemiological study shows that liver metastases of solid tumors were the largest group of malignant neoplasia in liver (45.0%). Adenocarcinoma is the largest group of liver metastases (29.48%), followed by neuroendocrine tumors (7.20%). Hepatocellular carcinoma is described as the second most frequent event (28.00%) (7).

2. Risk Factors for HCC

Major risk factors for HCC include infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) and liver fat accumulation. Diabetes mellitus type 2, aflatoxins, smoking, alcohol consumption, parasitic infection, obesity, gender or ethnicity are other risk factors for HCC, as well as hepatic metabolic diseases as hemochromatosis, type I glycogenosis, alpha-1-antitrypsin or Wilson´s, however less often (2) (3). These risk factors could lead to cirrhosis formation and progression, which is present in 80 to 90% of HCC patients, making HCC the leading cause of death among patients with cirrhosis (2) (8) (3).

Despite HBV can cause HCC in the absence of cirrhosis, it is related that most of HBV-related HCC patients have cirrhosis (about 70% to 80%). It can also explain the fact of HCC risk in patients infected with HCV being superior to people who are not infected, related by *Serag et al*, to be 15 to 20 times upper. Beyond the cause, it was demonstrated that region and ethnic group are also related with the occurrence of HCC. 5-year cumulative risk for HCC development in cirrhotic patients ranges between 5% to 30%, depending on all three factors (8).

A prospective cohort of 23.820 Taiwan patients in a trial of *Huang et al.* in 2011 concluded that the effect of HBV and HCV in HCC varies in terms of gender and age. They showed that the risk of HCC associated to HBV decreases with age in men, and the risk of HCC associated with HCV increases with age in women. Furthermore, in patients with 65 years or older with dual infection had a significantly higher HCC risk comparing to those with single infection (9).

Chronic infection with HBV and HCV is the most common cause for liver cancer. HBV is the main risk of in East Asia region, meanwhile, HCV is the major risk for HCC in Mediterranean countries (10). The majority of HBV and HCV infected population are seen in developing countries, which corroborates the highest incidence rates of liver cancer in these areas. The estimated risk of developing HCC by people with HCV versus patients not infected ranges between 20% and 30% (11).

Aflatoxin is a chemical product produced by *Aspergillus fungus* with toxic and carcinogenic properties. It is also a consensual risk factor for the high incidence of HCC, mainly in developing countries, since impoverished poor countries have less access to goods and services, making them more vulnerable to food contamination with aflatoxin. The exposition to this risk factor is seen mainly in Africa and Asia, mainly South China, and, in that area, it was demonstrated that the interaction of aflatoxin exposition with HBV infection exponentially increases the risk of HCC (11).

China was the country with higher incidence rate of liver cancer in 2018, justified, then, by a large-scale exposure to HCC risk factors by chinese population. However, this high liver cancer incidence in China was described a few years ago, as well as its fatality. Risk factors like HBV, HCV, aflatoxin, alcohol and tobacco were shown by *Fan et al.* in 2005 as the reason for 86% of liver cancer incidence and mortality in China in 2005 (10). In 2010, *Ferlay et al.* showed that liver cancer deaths in China attributed to these risk factors represent about 42% of all liver cancer deaths worldwide. The authors also related a high overall mortality/incidence ratio related to this cancer, 0.93, therefore, liver cancer has a high fatality associated (12).

Other reasons that explain this higher incidence of HBV and HCV in China population is the hereditary transmission, inappropriate lifestyles and habits. Where we can

include exposure to environmental factors including smoking and alcohol consumption, and other reasons related to genetic sensitivity or hereditary disorders associated with HCC, for example, hemochromatosis (11).

In terms of gender, HCC is more common in men (appendix 1), what could be explained due to a higher body mass index than women and more exposition to risk factors like alcohol or tobacco. Another factor that explains a higher incidence in men is the correlation found between serum testosterone levels and HCC risk in HBV and HCV male patients. Some studies had been performed to show that elevated testosterone levels are associated with increased risk of HCC. *Yuan et al.* demonstrated, in 1995, that testosterone promotes progression to chronicity following primary HBV infection, thereby indirectly contributing to the development of HCC (13).

More recently, in 2012, *White et al.* showed an association between total serum testosterone in HCV-infected men and increased risk of both advanced hepatic fibrosis and advanced hepatic inflammatory activity, which can lead to pathologies like HCC, contributing to an increased incidence of HCC in males (14).

Obesity, once it can lead to fatty liver disease and, consequently, cirrhosis, is a risk factor to HCC. Normally, people with diabetes mellitus type 2 tend to have obesity problems, which could explain the high risk comparing to people with no diabetes mellitus type 2 to develop HCC. As preventive factors, consumption of vegetables, milk, fruits or eggs, but mostly, vegetables, white meat and fish are described as preventive factors due to its potential protective role for this cancer (11).

Together with the aggressiveness of HCC, the frequent diagnosis in advanced stages makes it pathology with high mortality all over the world. In developing countries, in addition to the aggressiveness of the disease, there is a high exposure to risk factors, as well as lower conditions in access to health care services compared to developed countries, especially in Africa. These factors explain the higher incidence and mortality associated with HCC in developing countries. Vaccination plans against HBV and HCV are important preventive measures in the fight against HCC, however, in a vast majority of cases, it is only possible in developed countries. This measure against these virulent agents will prevent cirrhosis development associated with its infection and thus prevent HCC development.

3. Available Staging Systems in HCC

A reliable system for HCC staging should be able to categorize patients in subgroups based on theirs shared characteristics, allowing to predict outcomes and

determine the potential to undergo specific therapies (4). These programs include important determinants of overall surival (OS), as tumor size, tumor extension into adjacent structures or tumor metastases, but also some patient-dependent variables, such as the cirrhosis severity or a tumor-dependent variable regarding the HCC extent. There are some staging systems for HCC prognosis, such as, among others, Tumor-Node Metastasis (TNM) staging system, Okuda System, Barcelona Clinic Liver Cancer (BCLC), Liver Italian Program (CLIP) score and Chinese University Prognostic Index (CUPI) system.

TMN staging system considers fibrosis score of the subjacent liver as a clinically significant prognostic factor, instead of using the presence of liver cirrhosis or tumor grade for tumor stage attribution. *Vauthey et al.* concluded that TNM staging system provides the best prognosis stratification for patients undergoing liver transplantation for HCC in a cohort of 490 patients (15). The prognostic value of TNM staging system has been validated prospectively in patients undergoing surgical resection or liver transplantation for HCC (15). However, using this system, unresectable HCC patients cannot be accurately staged by this system. TNM staging system had low approval due to the little relevance given to liver function status and difficulty to clear vascular infusion, mainly microvascular infusion (16).

Okuda staging system incorporates tumor size, functioning hepatic mass and cirrhosis severity, both measured by the amount of ascites, serum albumin and bilirubin levels. However, it does not include pathologic characteristics as vascular invasion or eventual nodal metastases.

Okuda et al. categorized patients in 3 stages, each one described in table 1:

Table 1: Okuda System Classification [17].

Okuda Stage	Definition
Stage I	Not advanced: tumor size <50% involvement, no ascites, albumin >3 g/dl and bilirubin <3 mg/dl
Stage II	Moderately advanced: presence of one or two signs of advanced disease.
Stage III	Very advanced: three or all the signs of advanced disease are present.

In its turn, CLIP score combines liver cirrhosis severity (Child-Pugh stage), tumor morphology and extension, α-fetoprotein (AFP) serum level and portal vein thrombosis (PVT) to assess patients prognosis, classifying patients between levels 0 to 6 (17). CLIP classification was more accurate than Okuda system in identification of patients with a good prognosis in a cohort of 257 patients with HCC in Toronto. In the same cohort, CLIP criteria correctly identified patients with a poor Okuda score, but the Okuda system failed to assign

a poor prognosis to 2 out to 3 patients with high CLIP scores. This staging system is simple, uses common clinical criteria, and appears to be more accurate than the Okuda and Child-Pugh staging systems (18). *CLIP et al.* confirmed that CLIP score seems the best available prognostic system for patients with HCC. Comparing these two staging systems, the authors related that CLIP is more precise and statistically more efficient, takes into account more detailed information on the pathology and has a greater predictive power on survival than Okuda (17).

The BCLC staging system identifies the clinical stage based on the primary tumor extension, vascular invasion, and extrahepatic spread by tumor, individual patient performance status, and baseline liver function (Child–Pugh stage). The very early and early stage (stage 0 and A, respectively) includes patients which have tumors that are amenable to potentially curative treatment, such as surgical resection, liver transplantation, or local ablation techniques. Intermediate stage (stage B) patients are characterized by multinodular tumors, being Transarterial Chemotherapy (TACE) the recommendable therapy for this stage. Advanced stage (stage C) patients have tumors with vascular invasion and/or extrahepatic spread. For these patients, sorafenib treatment is recommended. Finally, patients with stage D tumors have cirrhosis and the worst performance status, where supportive care is the most advised option.

The Chinese University Prognostic Index (CUPI) score was introduced in 2002, following an investigation in a Hong-Kong hospital. This stage system is based on TMN stage system, with the addition of other relevant prognostic factors, such as ascites, serum AFP, serum alkaline-phosphatase and serum bilirubin to a cox proportional hazards model (19). *Leung et al.*, in addition to describing it, mentioned that CUPI is more discriminant in classifying patients into different risk groups and was better at survival prediction comparing to TMN, CLIP or Okuda staging systems (19). One year later, *Kudo et al.* published a new classification system, called Japan Integrated Staging (JIS), that combines TNM staging by the LCSGJ criteria (score 0, 1, 2 and 3 correspond to stage I, II, III and IV, respectively), and the Child-Pugh criteria staging (score 0, 1 and 2 correspond to stage A, B and C, respectively). Furthermore , the authors related its better predictive value in identification of the best prognostic HCC patient group and in discriminating the advanced-stage HCC patient groups (20).

Since patients geographical and, mainly, pathological heterogeneity, it is difficult to choose universal staging system involving all pathological variants or say which one is the best. So, the staging system that best fits each population must be the chosen. The TNM staging system should be superior to clinical systems for prognosis classification in patients able to undergo surgical resection, but not in patients with unresectable HCC. In patients with advanced HCC and cirrhosis who are not candidates for surgical resection, BCLC and

CLIP systems may have a superior prognostic value, once they give more relevance to clinical aspects.

In a study by *Huitzil-Melendez et al.*, 187 patients with advanced HCC were staged using seven different staging systems. CLIP, GETCH and CUPI were the most informative staging systems in predicting survival in patients with advanced HCC (21). Despite the mentioned advantages, CLIP scoring system has limited utility to predict OS after liver transplantation in HCC patients (15). One hundred and thirty-one patients with HCC who underwent transarterial chemoembolization were evaluated by *Cho et al.* by 7 different systems and compared their performance. CLIP system was the best prognostic system for predicting OS in HCC who underwent TACE comparing with the remain systems analyzed (22). *Marreto et al.* compared 7 available prognostic staging systems in 239 patients with cirrhosis and HCC and verified that BCLC staging system provided the best prognostic stratification (23).

It is utopian to hierarchize all the staging systems. Although some of them have undeniable advantages over others, all staging systems have their qualities and limitations in different aspects of disease assessment and it is expected that authors of each one of the staging systems try to highlight the positive and differentiating aspects of their staging system in relation to the others. Although all of them have positive and negative aspects, BCLC is the one that is most accepted and used for the staging of patients with HCC.

The BCLC system is widely used and highly recommended in the literature to HCC staging. Despite the great diversity of criteria in the classification of the best staging system, it is evident from the analysis of comparative studies between the available staging systems that BCLC and CLIP are the most reliable staging systems. However, the BCLC staging system has still a very important and unique feature, which is the advice on the most appropriate therapy for each HCC staging, distinguishing itself positively from other staging systems (16, 21, 22, 24).

4. Response Evaluation Criteria in Solid Tumors

Since the hepatic disease diagnosis is made, it is mandatory to choose a therapy according to the stage of the disease, which will define the patient´s prognosis. As previously related, BCLC classification system is the one which provides a better stratification of prognosis in HCC patients.

Among all the factors that define the prognosis of a patient, it is worth highlighting his:

- tumor status, defined by presence or not of extrahepatic spread and vascular invasion and the number and size of the hepatic nodules;
- performance status, evaluated by the Eastern Cooperative Oncology Group (ECOG) classification to the presence or absence of symptoms and its typology (Appendix II);
- liver function, defined by Child-Pugh criteria, as well as serum bilirubin, albumin levels and portal vein hypertension (Appendix III).

To access the efficacy of the chosen treatment or drug in hepatic cancer therapeutics, as well as establish a comparison term between the new methods and hitherto used, it is mandatory to define criteria for assessing tumor response rate (RR), with the purpose of verifying the level of response of the patient to a particular therapeutic approach. So, it is extremely important to define standard criteria to convert the radiology image findings into a quantitative and statistical framework, in order to evaluate the tumor response to the chosen therapy.

To the tumor response evaluation, the definition of endpoints is essential. Endpoints are measurable biological and clinical findings considered to acess the treatment options or the development of new ones. Endpoints can be categorized in two groups: "patient-centered clinical endpoints" that include OS (OS) and health-related quality of life (QoL), and "tumor-centered clinical endpoints", such as progression-free survival (PFS) (25). OS is considered the gold standard of endpoints to demonstrate patient clinical benefit. However, with the increase of effective salvage treatments for many types of cancer, it becomes difficult to achieve a significant statistic power. That happens due to the need for more patients and an extensive follow-up period necessary to observe the number of deaths required, which brings a cost increment of clinical trials. So, tumor-centered clinical endpoints are most often used because they can be assessed earlier and used as surrogates for OS. (25)

Each one of the response criteria developed and/or updated over the years establishes its own definition for the different endpoints that can be considered in the assessment of the tumor response and, consequently, the effectiveness of the therapy. The most used tumor-centered clinical endpoints in clinical trials to assess the therapy efficacy are Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD). The definition of each endpoint varies according to the response criteria used. In Appendix IV, it is presented the mentioned end points definition according to World Health Organization (WHO) criteria, Response Evaluation Criteria in Solid Tumors (RECIST) criteria, European Association of the Study of the Liver (EASL) criteria and modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.

Since the 80s, WHO response criteria had adopted as the standard method for evaluating the tumor response. The WHO criteria were published in 1981 and established that the total tumor size is determined by bidimensional measurements, for example, the sum of the products of the two longest diameters in the perpendicular dimensions of all tumors. *Therasse et al.* related some problems that arise from the use of WHO criteria, among which are the disparities found between research groups about to the definition of the size of the lesion and the number of lesions that must be measurable, and consequent variation in the definition of progressive and stable disease or partial and complete response between groups. Besides, there was a difficulty in evaluating the RR using 3D imaging techniques, such as SPECT, MRI or CT, due to the difficulty in processing these images in order to obtain a reliable response assessment (26).

After the 80s, the scientific community put a lot of effort, not only in WHO criteria improvement, but also in new criteria definition for treatment response assessment and constantly reviewing its applicability. Therefore, based on changes in WHO criteria, RECIST criteria was created and published in 2000, being a response-criteria widely used in oncology clinical trials nowadays. Conventional RECIST criteria are based just on one-dimensional measurements, defining the tumor response and progression by an isolated increase in a single lesion, and a different shrinkage threshold (27). *Choi et al.* demonstrated the similarity of effectiveness in the application of RECIST and WHO criteria in patients with metastatic colorectal cancer (CRC) (28).

However, in the early 2000s, many investigators raised several questions about the feasibility of adopting these criteria by itself in assessing the tumor response. Adopting RECIST criteria and, consequently, one dimension based-criteria, treatment induced necrosis areas would be interpreted as stable or progressive disease. Nevertheless, that is not true because there is no residual disease in this situation, being a confounding factor between residual disease and necrotic area (29). In 2001, the EASL guidelines for HCC management was published and they recommend measuring only enhancing tissue in the tumor, focusing on the prediction of tumor necrosis and not as much as assessing tumor size as the WHO and RECIST criteria. Besides, the measurable lesions are assessed following a bi-dimensional evaluation (30). *Llovet et al.* trial, in 2008, is one of many studies that report the limitation of RECIST criteria in this subject. However, conventional RECIST criteria are applicable to non-enhancing atypical lesions but have some limitations in distinguishing between necrotic and proliferative zones of the tumor (31). *Llovet* trial was one of a lot of studies which fostered the development of an update version of these criteria, the revised RECIST guideline version 1.1.

RECIST 1.1 criteria was published in 2009 and uses a unidimensional-based criteria like conventional RECIST in lesion measurements, however, it provides some changes,

among others, in what number of lesions to be assessed concerns or the incorporation of pathological lymph nodes assessment that did not verify itself in standard RECIST (27). This update also provides more clarified information about the requirements to verify the complete or partial response by a patient and new methods for a more efficient measurement in disease progression.

Conventional RECIST, RECIST 1.1. and EASL, together, evaluate tumor response by tumor size and necrotic areas, however, using any of these criteria, it is not possible to assess the arterial enhancement of the tumor. Hereupon, in 2010, the American Association for the Study of Liver Disease drafted an update to RECIST criteria, making them more complex and reliable. This update was defined as mRECIST criteria (32). Particularly, knowing the HCC arterial enhancement, the use of mRECIST is suitable, because, after an update, it includes that feature as a prognosis factor (32) (33).

According to EASL guidelines, currently, mRECIST are the recommended criteria to assess response to sorafenib. (30) That recommendation is corroborated by *Takada et al.*, concluding that mRECIST provides a better OS stratification, in comparison to RECIST 1.1. in patients with HCC. However, the authors observed a higher response predictive value of RECIST but only in non-measurable lesions by mRECIST (34). *Riaz et al.* compared the role of RECIST, WHO and EASL criteria in the assessment of tumor response in HCC patients, verifying better results provided from the combination of WHO and EASL comparing with other criteria combination or the use of just one criteria.

In my personal opinion, *Ria et al.* results are expected since the combination of using WHO criteria and EASL criteria allows to evaluate the tumor response to treatment in terms of variation in size and necrotic area, respectively, a more complete assessment that if it was make based on just one criteria.

The creation of new tumor response evaluation criteria over time, as well as their constant updating, allows the evaluation of additional characteristics. As the tumor size, as necrotic area or arterial enhancement, allowing the identification of patients in PD who even then, by assessing the tumor response based on the RECIST criteria, they were classified as SD. The mentioned criteria are the most used with the purpose of RR assessment purpose and have been constantly updated in line with the evolution of new therapeutic procedures. It is possible to conclude that criteria based on viable tumor measurement allow a more efficient treatment response assessment comparing with criteria based on whole-tumor measurement (29).

4.1. BCLC Staging System

HCC treatment involves very specific procedures and requires a multidisciplinary team to provide knowledge in several relevant areas such as hepatology, radiology or oncology, essentials subjects to better preparation, performance and therapy success. In order to choose an appropriate therapeutic approach for HCC patients, it is mandatory to establish the disease stage at the diagnosis moment. Several staging systems are available. As already mentioned, BCLC classification is currently the standard classification and it is widely used in trial design and clinical management of HCC patients.

BCLC is approved as the standard system for HCC management by the American Association for the Study of Liver Disease, American Gastroenterology Association, European Association for the Study of Liver and the European Organization for the Research and Treatment of Cancer (35) (36).

At the diagnosis moment, four essential elements must be considered in clinical case evaluation:

- tumor status, involving the number of nodules and its size and the presence of vascular invasion or extrahepatic spread;
- general health status, defined by ECOG classification;
- liver function, defined by Child–Pugh classification, serum bilirubin and albumin levels and portal vein hypertension;
- presence or absense of related symptoms (24) (31).

The diagnosis will allow the patient inclusion on the corresponding stage, according to the classification obtained in the four parameters mentioned above. Unfortunately, the diagnosis is often at a late stage, when potentially curative therapies are least effective, resulting in a reduced average life expectancy for most patients after HCC diagnosis.

The BCLC staging system recommends the therapeutic approach that should be performed for each HCC stage. This is a great advantage of its use since the therapeutic approach must be as individualized as possible. However, a multidisciplinary team meeting is mandatory before the treatment choice, because several patients, although included in the same BCLC stage, can present several differences in the anatomical, histological and physiological levels of the pathology.

The BCLC algorithm divides HCC into 5 stages: very early stage, early stage, intermediate stage, advanced stage and terminal stage and, in table 2, it is mentioned the pathology characteristics that define each HCC stage, as well as the correspondent recommended therapy.

Table 2: BCLC criteria in HCC staging.

Stage	Anatomical Features	Vascular Invasion	Extrahepatic Spread	Child-Phug	ECOG	Treatment choice
Very Early Stage (0)	Single nodule <2 cm	No	No	A	0	○ Resection ○ Ablation ○ Liver Transplantation
Early Stage (A)	Single or 3 nodules < 3 cm	No	No	A-B	0	○ Resection ○ Ablation ○ Liver Transplantation
Intermediate Stage (B)	Large multinodular	No	No	A-B	0	○ TACE ○ SIRT
Advanced Stage (C)	Large multinodular	Yes	Yes	A-B	1-2	○ Sorafenib
Terminal Stage (D)	Large multinodular	Yes	Yes	C	>2	○ Best supportive care

The early stage includes patients in an initial stage of the disease, with a single or until three <3cm nodules, confined to the liver whose function is preserved. In the case of a single <2cm nodule, the patient is in very early stage. This group of patients is a candidate for curative treatments including ablation, resection or liver transplantation, with an associated 5-year survival rate of 50% (31).

The intermediate stage includes patients with large multifocal tumors, where liver function is preserved. The pathology is classified as unresectable and did not have any extrahepatic spread or vascular invasion. The prognosis of patients with unresectable HCC is considered poor, with a median OS less than 1 year (31). In this stage, there are no symptoms related to the disease. These patients are candidates to embolization treatments, transarterial chemoembolization (TACE) or transarterial radioembolization (SIRT).

The advanced stage is related to the patients with vascular invasion and extrahepatic spread, sometimes with mild cancer-related symptoms. Untreated patients with advanced-stage disease have a median OS of 6 to 7 months (31).

Sorafenib is a multitarget tyrosine kinase inhibitor sorafenib which has an antiproliferative and antiangiogenic activity and delay the tumor progression. It was approved in 2007 and it is considered the gold standard therapy for advanced HCC patients. Sorafenib is the only pharmacological treatment proven to be successful in survival purposes for advanced-stage HCC (31). This drug was found to improve the OS in the patients with HCC advanced stage, since the median OS obtained was 10.7 months, versus 7.9 months in placebo group (37).

Terminal-stage disease (BCLC D) represents patients with poor liver function, who are no candidates for liver transplantation, and/or very advanced cancer with intense cancer-related symptoms, usually reflecting extensive tumor burden at radiological assessment (4).

Unfortunately, many patients show disease recurrence that quickly progresses to advanced stages, where vascular invasion and multiple intrahepatic metastases are verified. It is related only a 5-year relative survival rate for this group (2).

5. Therapeutic Approaches in HCC Intermediate Stage

BCLC staging system defined a subset of patients categorized as intermediate-stage HCC (BCLC B). BCLC B HCC is defined by the absence of vascular invasion, extrahepatic spread or cancer-related symptoms. This stage includes patients who are considered ineligible for curative surgical treatment (ablation, resection, or

transplantation), however, despite the unresectable disease, they can benefit from locoregional treatments.

Embolization treatment aims to slow and/or block the blood supply to a specific tissue. For oncology purpose, its use is directed to block the arterial feeding to a tumor, causing cancer cells death.

In one hand, radioembolization, selective internal radiation therapy (SIRT) or TARE is a locoregional therapeutic technique for liver tumors in which radioactive microspheres are injected into the hepatic artery to embolize terminal tumoral arterioles and irradiate the tumor (38-40). On the other hand, TACE is a specific type of chemoembolization where the particles are used for occlusion of the tumor feeding artery (3–10 times larger than those used in radioembolization), resulting in tumor ischemia, and, in addition, delivering chemotherapeutic drugs (38-40).

Beyond these, drug-eluting bead transarterial chemoembolization (DEB-TACE) is a new therapeutic approach introduced 10 years ago. DEB-TACE purpose is to improve the way to deliver chemotherapy drugs to the tumor and, at the same time, diminish the side effects of the procedure. For this purpose, microspheres are used in order to exploit ionic bonds are used. They should be able to actively sequester and then slowly release the cytotoxic drug inside the target tumor tissue (41).

So, for HCC intermediate stage treatment, SIRT or TACE techniques are the choice. Although both provide satisfactory results, comparative studies between the two techniques were carried out and some of them are mentioned in table 3.

Table 3: Comparative clinical trials between TARE and TACE in unresectable HCC.

Author	Year	N	Treatment	ORR (CR + PR) (%)	SD (%)	Median TTP (months)	OS (months)
Lewandowski et al. (42)	2009	43	TARE	RECIST: 61 EASL: 86	RECIST: 37 EASL: 14	33.3	41.6
		43	TACE	RECIST: 37 EASL: 71	RECIST: 49 EASL: 26	18.2	19.2
Kooby et al. (43)	2010	27	TARE	RECIST: 11			6
		44	TACE	RECIST: 4			6
Salem et al. (44)	2010	123	TARE	RECIST: 49% EASL: 72%		13.3	20.5
		122	TACE	RECIST: 36% EASL: 69%		8.4	17.4
Carr et al. (45)	2011	99	TARE	RECIST: 41 (38 + 3)	RECIST: 35		11.5
		691	TACE	RECIST:60 (55 + 5)	RECIST: 29		8.5

In the case of patients with unresectable HCC, TARE with ^{90}Y-microspheres appears to be a less invasive and toxic procedure compared to TACE.

Carr et al. investigated the long-term survival of TACE and TARE and to verified that the OS was similar, however slightly higher in patients from TARE group compared with the TACE group (11.5 months vs 8.5 months) (45). *Salem et al.* also had similar results of OS between SIRT and TACE (17.2 and 17.5, respectively) by the analysis from 463 patients treated with TACE or SIRT over 9 years. However, TTP was longer in SIRT (13.3 vs 8.4) and appeared to have less toxicity associated. TACE patients were more likely to exhibit abdominal pain and a significantly higher hepatic transaminase elevation (44). *Kooby et al.* compared the effectiveness and toxicity of TACE and SIRT in patients with unresectable HCC. Looking at a similar OS (6 months for TACE and SIRT) and greatest overall toxicity in patients treated with chemoembolization, though a similar percentage of high-grade toxicity in both groups (43). *Lewandowski et al.*, in 2009, compared the rates of downstaging in T3 patients to T2 treated with TACE or SIRT. RR was superior in SIRT than in TACE according to RECIST (61% vs 37%) and EASL criteria (86% vs 71%) and TTP was higher in TARE too (33.3 months vs 18.2 months). Besides, OS was superior in SIRT patients (41.6 months vs 19.2 months) (42).

So, and although very similar results in the presented trials in what survival concerns, TARE appears to have better results in patients with unresectable HCC. It is referred that SIRT is associated with a low toxicity profile, what explains the shorter period of hospital stay for TACE patients related for *Salem*, *Kooby* and *Lewandowski* (44) (43) (42).

The incorporation of DEBs in TACE has facilitated procedure, due to a high treatment reproducibility. It also improves treatment tolerability, although a conclusive benefit in terms of tumor response and outcome has not been demonstrated yet (4). DEB-TACE is a recent technique, therefore, clinical trials have been performed to evaluate the effectiveness and safety of its use and compared with the techniques defined as first-line choices for intermediate stage HCC.

There is no consensus in the literature on the benefit of DEB-TACE over Conventional TACE (cTACE). Some studies did not show a difference in RR and OS between DEB-TACE and cTACE.

PRECISION study was the first to suggest the absence of superiority of DEB-TACE over cTACE. This study compares the clinical outcomes of 2 groups of patients, DEB-TACE group and cTACE group. The complete response (27% vs 22%), objective response (52% vs 44%) and disease control (63% vs. 52%) were obtained for DEB-TACE and cTACE group, respectively, and it is possible to verify that, despite the slightly superior results in DEB-TACE, there are no significant differences between them (46).

Golfieri et al. did also not find differences in local and overall tumor response in comparison to outcomes of patients treated with cTACE and DEB-TACE. The 1-year survival rate was 86.2% for DEB-TACE group and 83.5% for cTACE group and the 2-year survival rate was 56.8 % for DEB-TACE group and 55.4% for cTACE group (47). However, *Song et al.* demonstrated different results and showed better results in tumor RR and overall RR comparing the two techniques. Objective RR were 81.6% in DEB-TACE group and 49.4% in cTACE group. TTP was slightly better in DEB-TACE group than in TACE group, 11.7 and 7.6 months, respectively (48).

DEB-TACE appears to be associated with a better safety profile (41) (46) (49).

The PRECISION study demonstrated that DEB-TACE, by DC Bead use, was related to an improved tolerability and to a reduction in serious liver toxicity. (46) *Zou et al.* related that DEB-TACE therapy had less common adverse events than cTACE (49). A recent study performed by *Mokkarala et al*. in 2019 compares the outcomes for patients with CRC liver metastases who underwent TARE and DEB-TACE. The authors verified a more acceptable toxicological profile in TARE patients than in DEB-TACE patients. Besides, treatment response and survival were superior in TARE, with a partial response of 15.2 and 11.1 and stable disease in 27.3 and 13.9 for TARE and DEB-TACE, respectively (50).

SIRT is considered the gold standard treatment for HCC intermediate stage, however, its effectiveness remains under discussion and radioembolization appears to be a very well positioned alternative to TACE (51). SIRT proved to be a very effective therapy in patients with intermediate stage HCC. In the clinical trials presented, a greater OS is observed in patients that underwent SIRT in comparison to TACE. Furthermore. SIRT can also be a valid option for the treatment of other primary hepatic pathologies besides HCC, such as intrahepatic cholangiocarcinoma (ICC), and for the liver metastases treatment.

II. Radioembolization

1. Definition and treatment principle

Radioembolization, TARE or SIRT is an interventional radioactive oncologic treatment. The aim of this treatment is the radioactive microspheres administration by percutaneous transarterial techniques into the hepatic arteries that supply the liver and, consequently, its tumors (52-54).

It is known that hepatic malignances are supplied by arterial blood, which is the key to SIRT treatment principle. Therefore, the administration of embolic particles (“embolization”) into the hepatic artery will drive themselves until the malignances by the small tumor arterioles (figure 7). The embolic effect of the particles is essential for the technical purpose, since particles deposition in the terminal arterioles will allow tumor cells irradiation ("radio”) by the isotope beta-emissions. The particles are the vehicle that is going to deliver radiation to the tumor parenchyma (figure 8). (52, 54)

Beta-radiation is a radiation with high linear energy transfer (LET) that lodges a large amount of radiation in a short range. The properties of high LET radiation are ideal for SIRT purpose. In addition of a high degree of radiation deposition in the tumor, it is verified a low irradiation of healthy tissues, due to the limited reach of this type of radiation. Besides, the healthy liver tissue is predominantly supplied by the portal vein, so the radioactive microspheres administration into the hepatic artery means tumor irradiation without an unnecessary heath tissue irradiation. This treatment is increasingly used in patients with primary and secondary hepatic malignancies (52, 53).

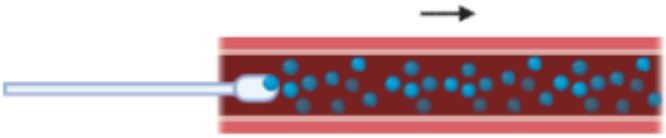

Figure 7: Intrarterial microcatheter releasing radioactive microspheres into the hepatic artery.

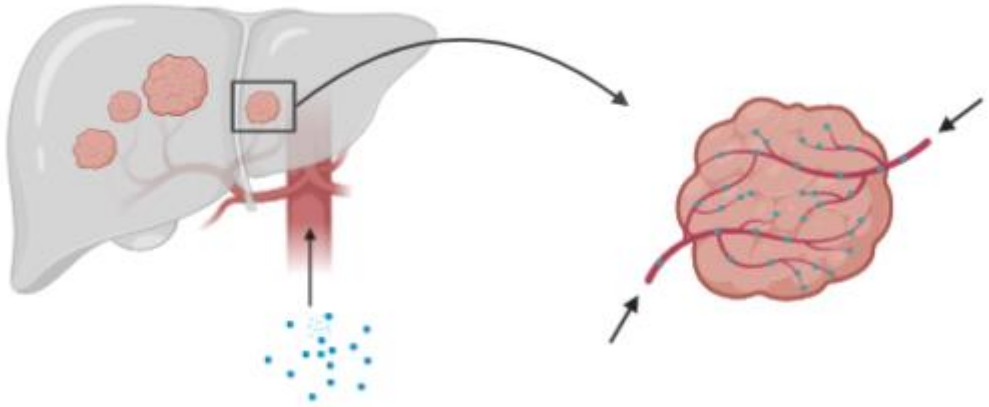

Figure 8: SIRT treatment principle.

For SIRT correct planning, a multidisciplinary team is required to combine complementary skills necessary for the procedure. It includes nuclear medicine, diagnostic radiology, interventional radiology, medical physics, radiation oncology, surgical oncology and medical oncology. SIRT algorithm comprehends 4 main phases, regardless of the available techniques: clinical case evaluation, pre-treatment evaluation, treatment and post-treatment evaluation.

The first and essential step is the evaluation of each specific clinical indication by the multidisciplinary team to check if the patient presents the inclusion criteria to carry out the treatment or possible contraindications that can stop the procedure. If the patient fulfilled the requirements can undergo the pretreatment phase. There, a digital subtraction angiography (DSA) and corresponding intra-arterial CT (IACT) are performed in the interventional radiology department for mapping the arterial hepatic vascular anatomy, not only to access the presence of portal vein thrombosis or other malformations in the vessels but also to define the most propitious injection site. DSA and IACT are essential tools to define the places to perform prophylactic coiling too.

In some patients, there is the possibility of abnormalities in the hepatic arterial vessels. Vascular abnormalities can cause extrahepatic organs deposition of a large part of the infused microspheres. To avoid extrahepatic deposition and to ensure the safety and accuracy in delivery of microspheres, there is the possibility of non-target vessels occlusion which could be safety embolized. This procedure denominates prophylactic coil embolization and it is performed mainly in arteries those that connect the liver to the gastrointestinal system, such as gastroduodenal artery (GDA) or right gastric artery (RGA).

The undesirable delivery of microspheres to the gastrointestinal tract can cause severe consequences, like gastrointestinal bleeding, ulceration or pancreatitis. So, gastroduodenal artery prophylactic coil embolization will minimize microspheres delivery to gastrointestinal tract and, concomitantly, maximize microspheres delivery to target tissue.

After that, a small number of particles labeled with a radioactive isotope are administered to the hepatic artery to simulate the effect of the microspheres at the therapy. Their distribution will be verified in nuclear medicine department, by planar and SPECT images, allowing the hepatopulmonary shunt assessment and the gastrointestinal tract deposition too. Shunt evaluation is a crucial step in SIRT. It provides microspheres distribution rate prediction in intrahepatic and extrahepatic space, becoming possible hepato-pulmonary shunt calculation. The hepato-pulmonary shunt percentage is decisive to figure out the patients who can carry out the treatment.

A percentage superior to 20% of hepatopulmonary shunt is a contraindication to perform SIRT, since, in addition to have low therapeutic profitability due to a considerable number of microspheres that will never be delivered, there will be unwanted pulmonary or gastrointestinal deposition. This large-scale deposition can cause pneumonitis or ulceration due to both embolization and tissue exposure to radiation (55). In these cases, SIRT advantages do not exceed the inherent disadvantages from its use, so the therapy must not be carried out.

Satisfactory results obtained in the anterior phase (acceptable % GI and hepatopulmonary shunt) means that the treatment can continue. After the microcatheter placement in the hepatic artery, radioactive microspheres are administrated to embolize the terminal arterioles of the tumor and, simultaneously, to avoid as much healthy liver tissue exposure as possible. The period between pretreatment and posttreatment phases varies depending on the chosen technique. Microspheres will be implanted surrounding the tumor cells and the main goal of its implantation is to get an uniform tumor coverage. The cumulative radiation absorbed by the tumor will exceed tumor radiation tolerance, leading its successful elimination. To reach that full coverage, it is mandatory to calculate radiolabeled microspheres activity necessary to get it. Therefore, adequate therapeutic planning is essential. Pre-therapeutic images allow liver and tumor mass and volume calculation, to define a reliable liver dosimetry and, consequently, a precise activity calculation. Inaccurate therapeutic planning can result in less activity being administered than would be necessary for total tumor coverage. In this case, the microspheres will be insufficient to deposit and irradiate the required area. An activity underestimation will lead to irradiation and destruction of parts of the lesion but also to tumor growth in non-irradiated areas.

Due to its importance in the therapy effectiveness, the activity calculation is done considering the whole multidisciplinary team opinion. Since anatomical and physiological tumor characteristics, radioisotope and/or type of microspheres used, and associated dosimetry are relevant aspects that must be deeply discussed by all groups for that purpose. It is utopian to assume all microspheres administered into the hepatic artery will be entirely delivered to a tumor-feeding arm and, consequently, to the tumor area. However, although some dose is delivered to normal liver tissue, preclinical and clinical studies prove that most of the administered dose is delivered and remains implanted in tumor tissue, making SIRT an extremely effective therapy.

2. Historic Evolution

The idea of using radiolabeled microspheres for tumor treatment started to be implemented in 1964, *by Ariel et al.*, where they use yttrium-90 (^{90}Y) microspheres for hepatic metastases from CRC cancer in animals and two human volunteers. Encouraging results were obtained, involving an admissible survival rate and no harmful effects (56).

In 1967, *Simons et al.* related ^{90}Y-radioembolization therapy in 5 patients with carcinoid tumors of the liver. The therapy was described as worthwhile, since side-effects of the procedure were low comparing to the severe effects of carcinoid syndrome (57). Five years later, in 1969, *Nolan and Grady* used ^{90}Y oxide in the treatment of hepatocellular carcinoma in humans. After these satisfactory results obtained by these pioneer studies, many clinical trials were being performed in order to assess the potential role of SIRT in clinical practice. One of them is a study performed in 1975, by *Grady et al.*, which evaluates the efficacy of internal hepatic radionuclide therapy in reducing hepatic metastases. They concluded that this treatment should be applied to patients with liver metastases in colon and rectal cancer (58). Another trial, performed by *Ariel and Padula*, in 1978, ^{90}Y-microspheres radioembolization role was evaluated into a chemotherapy regimen with 5-fluoracil for treatment of hepatic metastases. It was demonstrated that ^{90}Y microspheres use was related with the increased period of survival, instead of chemotherapeutic agent (59). In 1979, *Grady et al.* reported the efficacy of SIRT with ^{90}Y-resin microspheres in patients with liver metastases of colon cancer. 17 of 25 patients who underwent SIRT showed an acceptable regression of their tumors, improvement of symptoms and better OS. This study was an important milestone in the evolution of therapies with radiolabeled microspheres, since a complete organ has been successfully treated for the first time using this therapeutic approach. (60)

In addition to the RR and side effects, important aspects such as particle size and dosimetry had been evaluated in other clinical trials, in order to increase safety, reliability and effectiveness of the procedure. In a clinical trial in 1987, *Meade et al.* mentioned that microspheres with diameters between 15 and 32.5 µm were 3 times more likely to lodge into hepatic tumors comparing with normal liver tissue in a population of rats (61). 7 years later, a phase I dose escalation trial was performed by *Andrew et al.* in way to evaluate the hepatic tolerance to ^{90}Y-glass microspheres. It was demonstrated an excellent tolerance to a whole liver absorbed dose of 15.000 cGy (62).

^{90}Y-microspheres SIRT has been established as an efficient and no harmful therapeutic choice in control of primary and metastatic liver tumors.

Since the results obtained were effective, in all measures, the use of glass microspheres in patients with unresectable HCC was approved by FDA in 1999. Later, in 2002, the use of ^{90}Y-resin microspheres was premarket approval by FDA for CRC liver metastases in 2002. ^{90}Y glass microspheres (TheraSphere; MDS Nordion, Ottawa, Canada) have been given a Humanitarian Device Exception from the Food and Drug Administration (FDA) for the treatment of unresectable HCC, in the USA. In Europe and other countries, glass ^{90}Y microspheres are approved for the treatment of unresectable liver tumors (39). The use of ^{90}Y resin microspheres (SIR-Spheres; SirtexMedical, Lane Cove, Australia) is approved for treatment of unresectable liver tumors. And has a premarket approval by the FDA in the United States for CRC liver metastases in combination with floxuridine hepatic arterial chemotherapy (39). So, until 2015, only ^{90}Y-labelled microspheres were used in radioembolization, on two types: glass microspheres (TheraSpheres) and resin microspheres (SIR-Spheres).

Recently, a new product has been developed for that purpose: holmium-166 (^{166}Ho) labelled microspheres (QuiremSpheres, Quirem Medical BV, Deventer, the Netherlands), an alternative to ^{90}Y-labelled microspheres with the same principle. In April 2015, QuiremSpheres received Conformité Européenne (CE) mark approval for the treatment of unresectable liver tumors. This new radiopharmaceutical is currently available in Europe and in a few countries outside it (52).

Nowadays, it is possible to perform SIRT using three types of techniques: two of them using ^{90}Y as the radionuclide in microspheres, by 2 forms: glass microspheres (TheraSphere) and resin microspheres (SIR-Spheres) and the new technique, using ^{166}Ho as the radionuclide labeling microspheres (63).

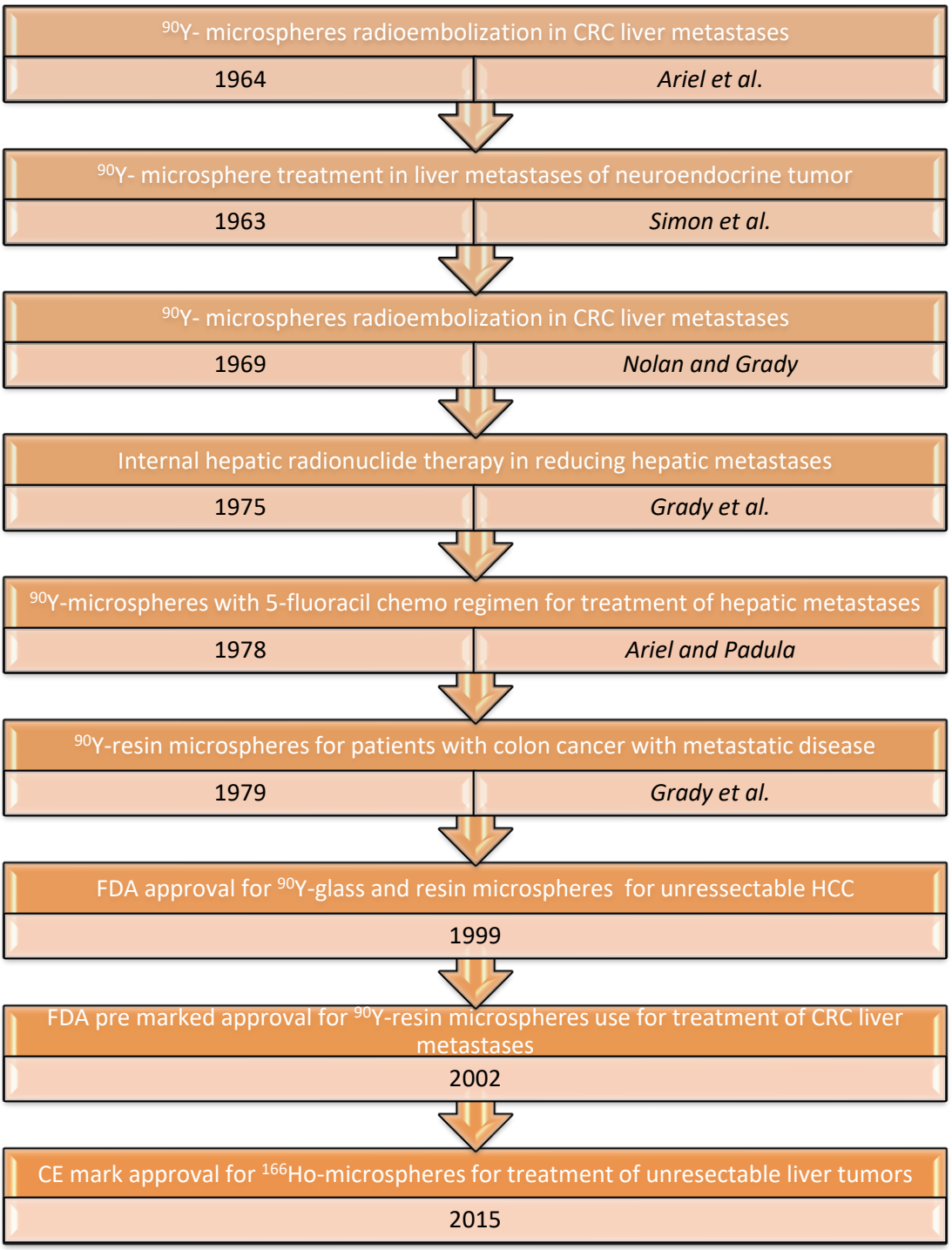

Figure 9: SIRT historical evolution timeline

3. Guidelines

SIRT is indicated by the generality of the guidelines for the therapeutic approach in patients with primary and secondary liver diseases, aiming to slow the tumor growth and increase the OS, maintaining as much of the quality of life as possible. For that purpose, level of evidence of SIRT therapy on a given clinical indication is presented in guidelines, which will be stronger or weaker depending on both study design and considered end-points.

In the tables 4 and 5, it is described level evidence for Adult and Pediatric Cancer Treatment Studies (PDQ®) according to the National Cancer Institute. The types of study and the end-points considered are described in descending order of strength (from level 1 to 3 and A to D, respectively) (36).

Table 4: Strength of evidence according to study design (64).

Strength of Evidence	Study Design
I	Randomized controlled clinical trials or meta-analyzes of randomized studies **i.** Double-blinded. **ii.** Nonblinded treatment delivery.
II	Non-randomized controlled trials
III	Case series or other observational study designs **i.** Population-based, consecutive series. **ii.** Consecutive cases (not population-based). **iii.** Nonconsecutive cases or other observational study designs (cohort or case-control studies).

Table 5: Strength of evidence according to end-points (65).

Strength of Evidence	End-point
A	Total mortality (or OS from a defined time)
B	Cause-specific mortality (or cause-specific mortality from a defined time)
C	Carefully assessed quality of life
D	Indirect Surrogates **i.** Event-free survival **ii.** Disease-free survival **iii.** PFS **iv.** Tumor RR

In the guidelines of National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), National Institute for Health and Clinical Excellence (NICE) or National Cancer Centre Singapore's Comprehensive Liver Cancer Clinic (CLCC) are presented the clinical indications for HCC radioembolization, which are practically similar between the guidelines, all based on appropriate vascular access, acceptable pulmonary shunt and good liver function (66) (67).

National Cancer Centre Singapore's Comprehensive Liver Cancer Clinic (CLCC) guideline suggest SIRT as Locoregional Therapy for advanced local HCC with good liver function (Child-Pugh A/B) and with or without vascular invasion, with a level of evidence II, B (66). According to ESMO, the role of SIRT with ^{90}Y resin or glass microspheres may be competitive with sorafenib or TACE in groups of patients with prior TACE failure, excellent liver function, macrovascular invasion and the absence of extra-hepatic disease, with a level of evidence III, C (67). NICE guideline suggests radioembolization for increment of OS and quality of life in patients with predominant liver disease and adequate liver function, which are poor candidates to surgical resection or other ablation treatments (68, 69) (70). However, in some of these patients, surgical removal with curative intent could be possible, by downstaging the tumor using other treatment modalities in first place. Treatment options include chemotherapy, surgical excision, transarterial chemoembolisation (TACE) and radiofrequency ablation (RFA) (68, 69) (70).

4. Selection Criteria in SIRT

In radioembolization, despite the possibility to carry out therapy using 3 different techniques, the selection criteria are common to all of them since the inherent therapeutic principle is the same.

4.1. Inclusion Criteria

- Histological proven liver-dominant, unresectable, chemorefractory primary liver disease or liver metastases of any primary tumor;
- Failed to respond to other types of treatment modalities (surgical, medical or local ablative);
- ECOG ≥ 2;
- Adequate hematologic function:
    - Granulocyte count >1.5 x 10^9/l;
    - Platelets count >60 x 10^9/l;
- Adequate liver function:
    - Bilirubin <2.0 mg/dl;
- Adequate renal function:
    - Creatinine >2.0 mg/dl;
- Aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase <5 times upper limit of normal;
- Ability to undergo catheterization and angiography procedures;
- Karnofsky performance score > 70%;
- No tumor invasion into portal vein, hepatic artery or vein or inferior cava vein;
- Non compromised pulmonary function;
- Ability to comprehend and provide written informed consent;
- Free from distant metastases;
- Age >18;
- < 20% pulmonary shunt fraction;
- No clinical evidence of radiation induced liver disease (RILD), pneumonitis or gastritis.

4.2. Exclusion Criteria

- Pregnancy or breastfeeding;
- Previous external beam radiation therapy to the liver;
- Ascites or evidence of clinical liver failure;
- Life expectancy <3 months;
- Allergy to contrast media not controlled by medication;
- Abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel;
- Hepatic arterial perfusion scintigraphy with ^{99m}Tc or ^{166}Ho shows any deposition to the gastrointestinal tract that cannot be corrected by angiographic procedures;
- Lung shunt superior to 20% of the hepatic artery blood flow;
- Dose greater than 30 Gy to be delivered in one administration or 50 Gy in multiple administrations;
- Impossibility to carry out accurate dosimetry;
- Severe liver dysfunction or pulmonary insufficiency;
- Inadequate liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase over five times the upper limit of normal, or serum bilirubin 1.5 times over the upper limit of normal];
- Significantly abnormal synthetic and excretory liver function tests (LFTs);
- Inadequate kidney function;

5. Radiopharmaceuticals and Systems Used in SIRT

The ideal properties of the radiolabeled microspheres include high chemical and mechanical stability, uniform size, macrophage removal or radiolysis, unit density, uniform size, ease in labelling with high energy beta-emission radionuclide, low photo fraction and intermediate half-life (71).

The three systems/technique available for SIRT purpose, ^{90}Y-resin microspheres, ^{90}Y-glass microspheres and ^{166}Ho-microspheres, have different physical and chemical characteristics, due the different radiopharmaceuticals and/or microspheres used in each one. Therefore, the technique that conveys greater confidence and the parameters that are believed to lead to a more effective therapeutic approach in a patient with a certain clinical indication should be chosen.

The chosen system must be the one which, due to its radiopharmaceutical characteristics, tends to be more reliable and effective in the therapeutic approach for a given clinical indication.

5.1. Yttrium-90 (^{90}Y) Microspheres

5.1.1. ^{90}Y Physical Characteristics

^{90}Y is a pure-beta emitter that decays to stable zirconium-90 with a maximal energy of 2.26 mega electron-volt (MeV) and a mean energy of 0.94 MeV. Physical half-life is 2.67 days (64.2 hours). It is produced by neutron bombardment of yttrium-89 (^{89}Y) in a commercial reactor, yielding ^{90}Y beta radiation. This radiation is characterized by a tissue penetration of 2.5 millimeters (mm) and a maximum range of 11 mm, allowing tissue only near the embolized microspheres to be treated (72) (73).

It can be delivered until 94% of the ^{90}Y-microspheres in the first 11 days of the treatment. An activity of 1 gigabecquerel (GBq) [27 milicurie (mCi)] of ^{90}Y allows the delivery of 50 gray (Gy)/ kilogram (kg) to the target tissue (72) (74, 75).

5.1.1.1. SIR-Spheres (SS)

SIR-Spheres (SS) (resin microspheres; Sirtex Medical Limited, MSW, Australia) were approved in 2002 by FDA for the treatment of colorectal metastases together with intrahepatic floxuridine (75). SS are biodegradable microspheres composed of resin with bound yttrium and present a density of 1.6 grams (g) / milliliters (mL) and a diameter range between 20 to 60 µm, with a diameter mean of 32 micrometre (µm) (75) (76).

SIR-Spheres are available as 3, 4 and 10 GBq vials. In a SS vial of 3 GBq, it is expected to have 40 to 80 million of microspheres and the activity per microsphere is 50 becquerel (Bq) (75). The usable shelf-life of SS is between 48 and 72 hours from calibration date (76).

5.1.1.2. TheraSphere (TS)

TheraSphere (TS) (glass microspheres, BTG, London, UK) was approved by FDA in 1999 for unresectable HCC purpose (74) (77). TS vials are available in a range of activity between 3 and 20 Gbq. It is possible to order vials of 3, 5, 7, 10, 15, and 20 GBq, corresponding to 1.2 million, 2 million, 2.8 million, 4 million, 6 million, and 8 million microspheres incorporated into it, respectively (77).

TS are non-biodegradable microspheres made up of glass with yttrium in matrix, having a density of 3.3 g/mL and a diameter range of 20 to 30 µm, with a diameter mean of 25 µm. A vial of 3GBq has 1.2 million of microspheres, therefore, the activity per microsphere is quite high, 2500 Bq. The usable shelf life of a TS dose is 12 days from the calibration date (76).

5.1.2. ^{90}Y-microspheres SIRT Algorithm

Despite some differences in procedure due to different microspheres, the same radioisotope (^{90}Y) is used in both SS and TS radioembolization and, therefore, the treatment algorithm is similar.

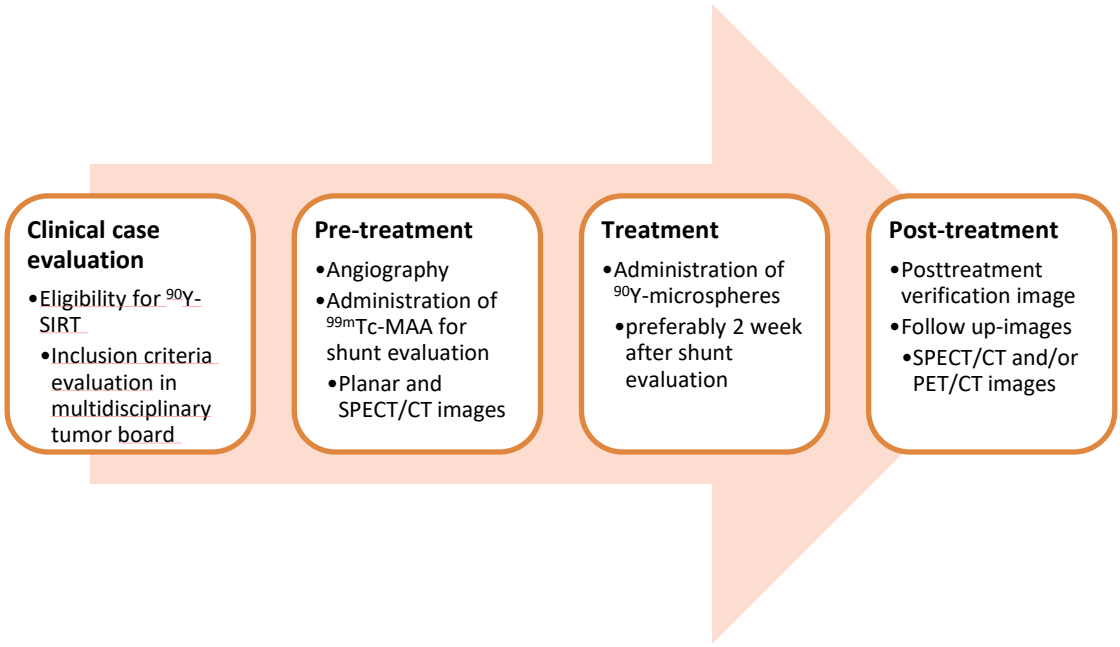

Figure 10: Treatment algorithm in ^{90}Y-microspheres SIRT.

5.1.2.1. Pre-Therapeutic Evaluation

The first step in pre-therapeutic evaluation consists of an angiography to map the tumor irrigation flow, and assess portal vein patency and, eventually, prophylactic coiling of the collateral vessels. In ^{90}Y-SIRT, *Gaba et al.* mentioned that prophylactic coil embolization must be used in ^{90}Y-resin microspheres SIRT when the administration site is close in proximity to the GDA or RGA. (78).

DSA and IACT combined use in pre-therapeutic phase have an important role in effective coil embolization by mapping the arterial vessels with high accuracy. Some authors, like *Tong et al.*, have the same point of view regarding these two techniques combination benefits and., at the same time, devalues the use of the prophylactic embolization of GDA, RGA and HFA in ^{90}Y-radioembolization clinical practice (79). *Schelhorn et al.* showed that coil embolization of the GDA may induce arterial hepatic-intestinal damages, which could make the procedure unfeasible and avoidable whenever possible (80). According to *Theysohn et al.*, most of patients do not require Cystic Artery (CA) embolization during the procedure. However, it can be performed to minimize the risk of radiation induced cholecystitis or vasospasm induction (81).

It is mandatory, before ^{99m}TC-MAA administration, pretherapeutic medications are administration, like antiemetics (ondansetron 8 mg i.v.), corticosteroids (dexamethason 10 mg i.v.), antiemetics (ondansetron 8 mg i.v.) and proton pumb inhibitors (pantoprazol 1 dd 40 mg) since the day of angiography until the last follow-up image (103).

Shunt evaluation using ^{99m}Tc-MAA is performed, using approximately 150 MBq (4 mCi) or 150 000 particles, to check not only the intrahepatic distribution but also an eventual hepatopulmonary shunt (52, 82).

The percentage of shunt is assessed by the following equation (82):

- ***Equation 1*** $$\text{LS (\%)} \frac{\text{counts of total lung}}{\text{counts of total lung+ counts of liver}} \text{ x } 100$$

The maximum acceptable lung shunt value is less than 20%. It means that treatment cannot be performed in patients whose lung shunt is superior to that value. However, in patients who undergo ^{90}Y-SIRT using resin microspheres (SS) with a shunt percentage inferior to 20% but superior to 10%, the treatment can be performed with reduces activities, as mentioned in table 6. For ^{90}Y-glass microspheres (TS) patients, the dose limit is imposed for the lungs dose and should not exceed 30 Gy.

Table 6: ^{90}Y-resin microspheres activity reduction according to lung shunt (82).

Lung Shunt (%)	^{90}Y-microspheres Activity Delivered
<10	Full activity
10 to 15	Reduction by 20%
15 to 20	Reduction by 40%
>20	Not able to perform SIRT

Gaba et al. escalate lung shunt fraction in low (<10%), intermediate (10%–20%) and high (>20%) in a clinical trial to verify which tumor characteristics are more associated to each one of that stages, in ^{99m}Tc-MAA shunt evaluation of 141 patients who underwent ^{90}Y-SIRT. They verified that infiltrative morphologic structure, tumor burden superior to 50%, portal vein invasion, and shunting had confirmed association with high LSF in a multivariate analysis. Furthermore, high shunt occurred in 14% of all HCC cases but just in 3% of other tumors (83).

^{99m}Tc-MAA use is considered safe because, beyond low activity required, the MAA will dissolve in the bloodstream some hours after the procedure. However, ^{99m}Tc-MAA are composed by varied shaped particles, so shaking the syringe a little before administration is mandatory, preventing particles aggregation, which can cause serious damage to the patient as well as erroneous results in the intra-hepatic distribution and shunt evaluation calculation. Damage in lungs by radiation has a cumulative effect. Excessive and repetitive ^{90}Y-SIRT use can lead to radiation pneumonitis, specially in large tumors, in which large doses of radiation are needed for full coverage and probably leading to an increased lung shunt.

This preparatory phase needs to be very accurate and, despite ^{99m}Tc-MAA provides acceptable results and be used in clinical practice, the radiopharmaceutical used to perform shunt evaluation is different from which used in therapy. So, once the physical characteristics of the two radiopharmaceuticals are different, the images obtained in the preparatory phase will not fully correspond to the distribution of ^{90}Y-microspheres, consequently they can under or overestimate the activity required for the treatment. To corroborate this fact, in 2013, *Wondergen et al.* presented a study where showed that ^{99m}Tc-MAA distribution does not accurately predict the therapeutic ^{90}Y-microspheres activity distribution. The volume of interest (VOI) was delineated in 39

patients and, in each, at least 1 VOI segment presented an under or overestimation superior to 10% (84). In pre-therapeutic image, *Elschot et al.* showed that planar images overestimate the lung absorbed dose during ^{99m}Tc-MAA shunt evaluation, therefore, SPECT or SPECT/CT must be the imaging techniques chosed in this step (85).

5.1.2.1.1. ^{99m}Tc-MAA Administration

In shunt evaluation, since we are addressing particles, more properly, macroaggregates of albumin (MAA), it is mandatory a slow injection in a way to a soft infusion, either for ^{99m}Tc-MAA in shunt evaluation or later in ^{90}Y-microspheres in therapy. Furthermore, ^{99m}Tc-MAA kit must be gently shaken after its preparation and the syringe with the activity just before administration. Being large diameter particles, their constant and gentle agitation will avoid some possible aggregation of particles before their administration and, consequently, prevent not only erroneous results in the therapeutic planning phase but also damage to the patient due to microembolisms. ^{99m}Tc-MAA administration is made via hepatic artery catheter.

5.1.2.1.2. Lung Shunt Image Acquisition

Shunt evaluation with ^{99m}Tc-MAA provides an acceptable image quality, once it results from gamma photons emission of 140 KeV, within 100-200KeV range defined as ideal for the detection of gamma radiation. Besides, the radiopharmaceutical preparation is easy, since it is only necessary ^{99m}Tc-pertecnetate dilution from a ^{99}Mo/^{99m}Tc generator and its addition to the MAA kit. The patient is positioned under a gamma camera in way to include the lungs and liver, the regions of interest. Anterior and posterior thoracic and abdominal images of abdomen and thorax are taken, as well as right lateral images of abdomen. So the dose of ^{99m}Tc-MAA particles which, after normal biodistribution, pass through the liver and lodge in the lungs can be calculated by these scintigraphic images.

Due to the different radiopharmaceutical used in pre-therapeutic and therapeutic phase, planar and/or SPECT images in hepatopulmonary shunt evaluation with ^{99m}Tc-MAA will lead to problems of ^{90}Y-microspherss therapeutic dose overestimation, as related by *Wondergen et al.* and *Elschot et al.* in their reports (84) (85).

5.1.2.2. Dosimetry

Dosimetric calculation is essential for the effectiveness of therapy. Searching the most individualized dosimetry possible will evidently lead to a more effective therapy for each patient and with less adverse effects associated with it, since this calculation allows us to administer an activity that suits the pathology in question.

Therapeutic dose administration can trigger different responses: the patient fails to respond to radiation treatment, have a slight response in case the administered activity is not enough and lower than the dose required to carry out the therapeutic effect or develop complication like radioembolization-induced liver disease (REILD) when the activity administered is higher and conduces to an overdose, which leads to a liver toxicity (86). Thus, development of an appropriate dosimetric plan for each patient is fundamental for a good unwinding of therapy. For that purpose, the medical physicist in the nuclear medicine department should consider information about patient medical history as well as relevant angiographic findings. The results of the pre-therapeutic phase regarding pulmonary mass, evaluation of the pulmonary shunt and tumor/non-tumor ratio will be essential factors to verify the favorable or unfavorable dosimetric characteristics and define the most appropriate dosimetric plan for these characteristics of the patient. Dosimetric uncertainty is a factor that must be predicted, since favorable or unfavorable dosimetric parameters associated with the patients will define the greater or lesser width of the dose safety margin calculated for each patient. In some cases, SIRT should even be ruled out in patients whose dosimetric parameters endanger the effectiveness of the therapy and, above all, its safety (79).

The calculation of the activity to be administered and, consequently, the intra and extra-hepatic dose obtained is different in SS and TS.

5.1.2.2.1. SS Dosimetry Calculation

When SS are used, there are three accepted models to calculate the prescribed activity for each patient: the empirical model, the BSA model and the partition model. Despite the different relevance that each of the methods gives to tumor and liver characteristics for dosimetry delineation, dose reduction in cases of pulmonary shunt is similar. It is known that a hepatopulmonary shunt superior to 20% is a SIRT contraindication. However, the procedure is possible in patients that have a lung shunt between 10-20% by reducing the activity to be administered (87).

- **Empirical model**

By empirical model, the activity to be administrated is related with the percentage of tumor involvement in the liver. For an involvement inferior to 25%, the recommended dose is 2.0 GBq, for an involvement between 25% and 50% is 2.5 GBq and for an involvement superior to 50%, the recommended dose is 3.0 GBq (75). The empirical model is not personalized, not adjustable for different tumor size and liver size and perfusion. Empirical Model is based on whole liver infusion (87).

- **BSA model**

The Body Surface Area (BSA) model is a semi-empirical model, frequently used due to its simplicity. This method uses the body surface area of the patients, by their weight and height, and the percentage of tumoral involvement in the liver (75) (88).

The formula of calculation of the activity by BSA traditional method (BSA-1) is (75) (88) :

- *Equation 2* $$\mathrm{A\ (GBq)} = [\mathrm{BSA\ (m^2)} - 0.2] + \frac{(\mathrm{tumor\ involvement\ \%})}{100}$$

The tumor involvement (%) is calculated by (75):

- *Equation 3* $$\mathrm{Tumor\ involvement\ (\%)} = \frac{tumor\ volume\ x\ 100}{tumor\ volume + total\ liver\ volume}$$

BSA is calculated by (75) :

- *Equation 4* $$\mathrm{BSA} = 0.20247\ \mathrm{x\ weight\ (m)^{0.725}\ x\ height\ (kg)^{0.425}}$$

In lobar treatment cases, SIRTEX provides an adaptation of the equation 2, calculating the ratio between the volumes of the pathological lobe and the whole liver, denominated BSA-K method (88) :

- *Equation 5*: $$\mathrm{A\ (GBq)} = [(BSA - 0.2) + \frac{tumor\ volume}{lobe\ volume}]\ \mathrm{x}\ [\frac{volume\ of\ lobe}{total\ liver\ volume}]$$

However, this method is unusual in clinical practice. When lobar treatments are performed, despite different volumes of the hepatic lobes in each person, it is considered a factor for the lobe volume calculation of 2/3 of total liver volume for the right lobe and

1/3 of total liver volume for the left lobe, thus allowing a more practical adjustment of the activity (88).

Another method is mentioned in the literature, the BSA-2 method, was used in colorectal cancer clinical context. There is no related activity calculation equation, however, SIRTEX provides three abacuses that relate the activity to be administrated with the lung breakthrough, divided in 3 intervals: 0%-10%, 11%- 15%, 16%-20%. For each one of the intervals, the abacus in question provides the activity to be administered according to BSA value and the tumor involvement. Patients with a lung breakthrough superior to 20% are not able to perform the therapy (88).

BSA model is a strong historical background of its use in several clinical contexts. However, *Kennedy et al.* showed that the empiric and BSA models overestimate the activity of ^{90}Y-resin microspheres that can be delivered (89). Furthermore, *Lam et al.* concluded that when BSA method is not much reliable for calculation of the activity to be administered. Once it is based in the size of liver and it varies from patient to patient, the whole liver dose does not correspond totally to the actual absorbed dose resulted from the activity administrated to a patient, which could lead to a higher toxicity level (86). Therefore, it is possible to verify that BSA method is an option in several clinical contexts, not only in primary liver disease but also in liver metastases. This method is the chosen one for dosimetry calculations in most clinical trials accessing ^{90}Y-SIRT in liver metastases of ocular melanoma (90-93). Therefore, BSA application is advised for cases of very small tumors and/or where its margins are difficult to define.

In cases of elevated hepatopulmonary shunt percentage, the desired activity is calculated with little degree of accuracy by an adjustment based on tabulated values. According empirical model, SIRTEX recommends an activity reduction by 20% if the lung shunt is between 10-15%, or by 40% if the lung shunt is between 15-20% (75). So, BSA method is not very personalized and effective, giving little relevance to the microspheres radiobiology. BSA methodology is considered more conservative in comparison to empirical model (87). This method is based on whole liver infusion, but tumor and liver perfusion are not considered and, therefore, the use of an activity calculation method based on absorbed dose could bring more advantages.

- **Partition model**

The partition model was developed by *Ho et al.* in 1996. They showed a mathematic model that allows calculating the therapeutic activity of ^{90}Y-resin microspheres. This methodology is also known as Medical Internal Radiation Dose

(MIRD) macrodosimetry or multi-compartmental dosimetry model, since it is calculated an estimation of activity that will be delivered to three different dosimetry compartments: tumor, normal liver and lungs, which provides a personalized predictive dosimetry (94). The pre-therapeutic phase image with ^{99m}TC-MAA allows the estimation of the hepatopulmonary shunt and tumor/non tumor ratio (T/N ratio), providing an estimation of the absorbed doses in each of the mentioned areas and, consequently, the calculation of the activity to be administered (79).

The partition model is more accurate, since it considers the tumor avidity and liver involvement for dosimetry purpose (79), scientifically sound for the activity calculation and personalized, but less popular due to its relative complexity. While the tumor dose has no limit, liver and lung dose should not exceed certain levels and this model allows the use of maximum radiation possible safeguarding the maximum accepted doses for these two organs. For that purpose, the radiation dose to the normal liver parenchyma should not exceed 80Gy in patients with normal liver and 70Gy in cirrhotic patients. The dose to the lung should not be superior to 25Gy, preferably, inferior to 20Gy (75) (87).

For dose calculation, it is necessary to perform a CT scan for the calculation of the volume of pathological and normal liver and. In a second phase, a small dose of ^{99m}Tc-MAA is administrated to simulate the behavior of the ^{90}Y-resin microspheres, assessing the percentage of accumulated dose in tumor and liver and the percentage of pulmonary shunt (75). SIRTEX guideline provides 3 equations to perform correctly the steps to calculate the activity to be implanted, taking into account, besides tumor received activity, the normal liver and pulmonary particles capture too. (75)

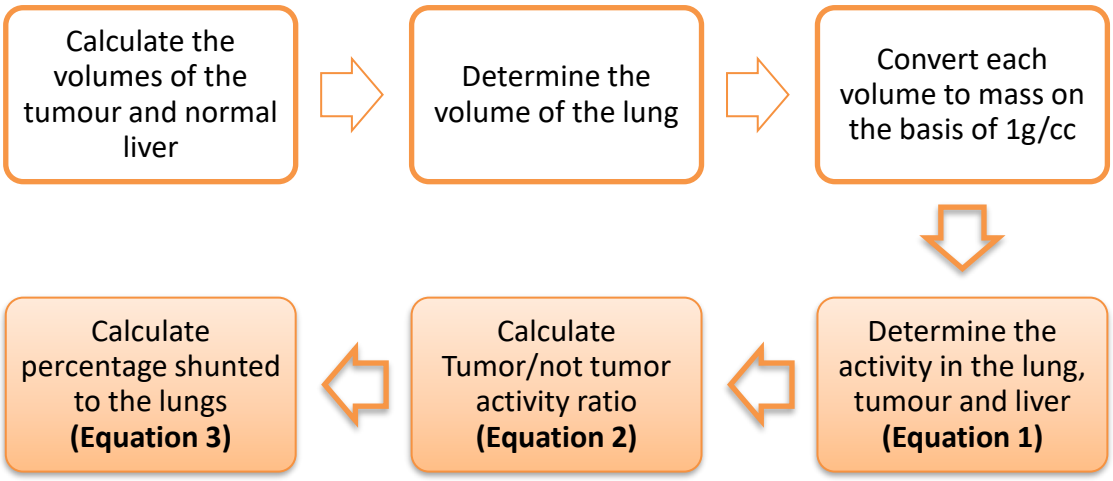

Figure 11: Partition model algorithm for dosimetry planning in Sir-Spheres (SS).

The first step calculates the tissue radiation dose (Gy), in this case, the radiation dose delivered to the liver:

- ***Equation 5*** $$\text{Dose(Gy)} = \frac{50\left(\frac{\text{J}}{\text{GBq}}\right) \text{x [Total yttrium}-90 \text{ activity in the organ or tissue (GBq)]}}{\text{Mass of the organ or tissue (Kg)}}$$

The second step is the calculation of T/N ratio:

- ***Equation 6*** $$\text{T/N ratio} = \frac{\text{Activity in tumor (GBq) / Mass of tumor (Kg)}}{\text{Activity in normal liver (GBq) / Mass of the normal liver (Kg)}}$$

The third step is to determine the percentage shunted to the lungs:

- ***Equation 7*** $$\text{LS (\%)} = 100 \text{ x} \frac{\text{Activity in lung}}{\text{Activity in lung+ Activity in liver+ Activity in tumor}}$$

In certain patients, due to high values of shunt and/or low liver performance status, there is the need to adapt the dose taking a limiting lung or liver dose into account and, consequently, the equations used.

Towards a case of limiting lung dose:

- ***Equation 8*** $$\text{Activity (GBq)} = \frac{\text{Dose to the lung (Gy) x Mass of the lung (Kg)x 100 / percentage lung shunting}}{50\left(\frac{\text{J}}{\text{GBq}}\right)}$$

Towards a case of limiting lung dose:

- ***Equation 9*** $$\text{Activity (GBq)} = \frac{\text{Dose to the liver (Gy) x (tumor/normal ratio x Mass of the tumor (kg))+Mass of the liver (Kg)}}{50\left(\frac{\text{J}}{\text{GBq}}\right) \text{x [1}-\text{(percentage lunh shunting/100)]}}$$

The partition model should be used in cases where the tumoral area is well-defined, once in the case of diffuse areas it is very difficult to define the tumor parenchyma and normal parenchyma for tumor/normal ratio which is indispensable in this method (75). This model was designed for single nodules, however it can be applied to multiple lesions if appropriate modifications were performed (87).

One of the first studies made in ^{90}Y-SIRT context, performed by *Ariel et al.*, showed a uniform distribution of the ^{90}Y-resin microspheres in the normal liver, but not in the tumor area due to differences in blood supply (59). However, nowadays, there is clinical evidence that ^{90}Y distribution is heterogeneous in normal liver too, so, this

method, in spite of not defining the dose actually received, it presents a very reliable estimate (94) (95).

The partition model, despite its complexity and less historical data, is more personalized than BSA method. Comparing to BSA model, *Bernardini et al.* showed that the empirical model better predicted the uptake differences between healthy and tumoral liver in 32 patients, while the BSA methods activity prescription did not correlate with the tumor/not tumor liver ratio (88). According to this methodology, activity calculation is based on the predicted liver absorbed dose, allowing a better control of tumor and normal liver and lung radiation dose. Therefore, when we are before a patient with lung shunt, the activity reduction is calculated based on the predicted lung radiation dose (88) (95). The inclusion of T/N ratio in partition model makes it much more reliable than the others. It is a very important step, once it can predict the success or failure of ^{90}Y SIRT. T/N ratio is obtained from gamma scintigraphy and its calculation is possible due to differences in vascularity of tumoral and normal liver tissues. The usefulness of T/N ratio in BSA method limits the physician's ability to personalize the therapy plan for each patient. Besides, the T/N ratio is calculated based in ^{99m}Tc-MAA administration, which presents different physical characteristics from ^{90}Y-resin microspheres, such as gravity, density and, of course, size and diameter of the particles. This difference could lead to different embolic patterns and, consequently, to a different blood flow, so it does not fully correspond to the true T/N value (95).

So, with the partition model, the ideal dose to tumor, normal liver and lungs and, consequently, the activity to be administrated could be better determined and with more accuracy (94).

5.1.2.2.2. TS Dosimetry Calculation

The prescribed activity calculation in TS assumes some differences from SS. The dosimetry estimation is established by a mono-compartmental MIRD macrodosimetry model, a dosimetry method like the partition model in SS but simplified. This method for TS dosimetry calculation is based on multicompartmental model equations, however, an absorbed dose to the one compartment is considered (whole liver or lobe). It is assumed a homogeneous distribution of microspheres in the whole liver, assuming an absorbed dose of 50 Gy for every 1 GBq activity/kg tissue, and there is not make any distinction for different tumor avidity or involvement, so, a separate calculation of tumor and non-tumor absorbed dose is not performed (87) (86).

The initial step is similar in 2 types of microspheres and consists in a pre-therapeutic administration of ^{99m}Tc-MAA before the dose calculation. An activity between 75 MBq to 150 MBq (2 mCi to 4 mCi) is administrated via hepatic artery to verify the hepatocyte response as well as pulmonary and gastrointestinal shunt (74) (96).

The upper limit of pulmonary shunt is defined as $\frac{0.61\ GBq}{Therapeutic\ Activity}$ (74).

In the case of the value of pulmonary shunt obtained in pre-therapeutic administration is superior to the value given by the equation, for a given value of therapeutic activity, the dose to be applied to that patient will have to be reduced (74) (96). If the percentage of shunt is acceptable, the patient is considered able to perform the therapy and CT scan is mostly performed for liver mass calculation, assuming an homogeneous distribution of the microspheres throughout liver volume (74) (96).

According to TS guideline, the empirically prescribed dose of ^{90}Y-glass microspheres to the deliver to the liver is between 80 Gy to 150 Gy and it is calculated by the following formula (74) :

- ***Equation 10*** $$\text{Activity Required (GBq)} = \frac{\text{[Desired Dose (Gy)]}\ .\ \text{[Liver Mass (Kg)]}}{50}$$

Kennedy et al. mentioned that a dose between 100 Gy and 120 Gy is able to ensure an acceptable RR and hepatic fibrosis risk. The dose range considered by the authors is lower than in TS guideline (96) (87). Furthermore, it is extremely important to consider ^{90}Y Physical Decay Table for the establishment of the right moment to TS administration (74).

To calculate the radiation dose that is in the liver after administration, this equation should be use (74) :

- ***Equation 11*** $$\text{Dose (Gy)} = \frac{50\ \text{[Injected Activity (GBq)]}\ .\ \text{[}1-\text{ fraction of injected radioactivity in the lungs]}}{\text{Liver Mass (Kg)}}$$

Either using TS or SS, a more personalized dosimetry can increase SIRT efficacy. It was shown by *Garin et al*. that dosimetry based on ^{99m}Tc-MAA SPECT/CT predicts accurately the response, survival and toxicity in patients with unresectable HCC who underwent SIRT with TS. *Lam et al.* developed a dual-tracer SPECT fusion imaging protocol that combine radioactive distribution data with physiologic liver mapping, accessing this way, to both tumors and healthy tissue absorbed dose. So, the authors were able to demonstrate the prognostic value and dose–response relationships for both toxicity and efficacy of this personalized method (97).

5.1.2.3. Therapy

The ^{90}Y-microspheres therapeutic activity is administrated in the interventional radiology department, only after satisfactory results obtained in shunt evaluation and an individual dosimeter plan was established for the patient. In pre-therapeutic phase, the most favorable injection site is also achieved.

5.1.2.3.1. ^{90}Y-Administration

Since we are labelling microspheres, that are particles like ^{99m}Tc-MAA, it is mandatory a slow injection in a way to a soft infusion of ^{90}Y-microspheres in therapy, avoiding particles aggregation and backflow too. The ^{99m}Tc-MAA is injected via catheter and it is mandatory the same placement in ^{90}Y-microspheres administration. In some cases, there is the possibility to practice whole liver and lobar infusions. Lobar infusion reduces liver toxicities (98).

It is related that less than half of the patients have a standard hepatic arterial anatomy, and, consequently, multiple arteries are supplying the delivery of ^{90}Y-microspheres (98). Abnormalities in the hepatic artery bring many complications to the therapeutic planning process. Therefore, alternative options are necessary to the detriment of “standard administration”, such as a single administration via catheter. *Ray et al.* provide some administration options in patients with multiple arteries, in order to make SIRT as effective as possible, within the difficulties derived from this condition. They mentioned, among others, the possibility of two distinct administration setups on the same day or two distinct procedures in two different days. (98).

The administration process requires implanting an hepatic artery catheter via radial or femoral artery, guided by x-ray, usually performed in pre-therapeutic phase. The catheter position maintenance must be checked during all the process to ensure the correct delivery of microspheres. The administration should be made at a slow rate (>5 ml per minute). The possibility of contrast injection allows the detection of stasis or microspheres reflux. Both SS and TS requires individual administration sets for ^{90}Y-resin and glass microspheres delivery, respectively, and the steps to set up the administration system are described in detail in SS and TS guidelines (82) (77).

5.1.2.3.2. Therapeutic Image

Yttrium-90 is a beta-emitter, so, the SPECT images become possible due to SPECT capture of the photons from bremsstrahlung effect. However, the images have low quality and sometimes have blur, because of the high range of energy of ^{90}Y-photons released (99) (87). So, when we are talking about ^{90}Y-imagiology, we need to talk about PET. Its internal pair production allows PET acquisition by its annihilation and positron emission (99).

In spite of the problem of detector saturation caused by high photons emission rate from bremsstrahlung X-rays and low true-coincidence rate, there is evidence of the important role of ^{90}Y-PET/CT role post-SIRT (87) (52). Due to its high sensibility and special resolution, PET/CT is highly recommended to the treatment evaluation by establishing and evaluating the distribution pattern of ^{90}Y intra and extra-hepatic, as well as quantification of absorbed dose or extrahepatic deposition and prediction of SIRT related complications such as REILD (87, 100). Besides, ^{90}Y-SPECT tends to underestimate the dose quantification in high-dose regions. ^{90}Y-PET/CT provides better results in comparison with ^{90}Y-SPECT in terms of higher contrast at similar noise levels or ability to detect small accumulation of activity. However, ^{90}Y-bremsstrahlung SPECT is commonly used in post-treatment due to be cheaper and more available (100).

5.2. Holmium-166 (^{166}Ho) microspheres

5.2.1. ^{166}Ho Physical Characteristics

Holmium-166 (^{166}Ho) is an isotope with a physical half-life of 1.1 days (26.8 hours) that emits high-energy beta and low-energy gamma radiation. More than 90% of the radiation is delivered within the first 4 days following the implantation procedure. The maximum energy of its beta radiation is 1.85 MeV (50.5%) and 1.77 MeV (48.7%) and the energy of its gamma radiation is 80.6 KeV (6.7%). The beta emission results from the decay to its stable form, Erbium-166, by electron emission. The maximum range of ^{166}Ho emitted beta particles emitted in tissue is 8.7 mm, with a mean of 2.5 mm (101) (102).

5.2.1.1. Quirem-Spheres (QS)

QuiremSpheres (QS) (Quirem Medical BV, Deventer, the Netherlands) are approved by Conformité Européenne (CE) in April 2015 for treatment of unresectable liver tumors (101). QS are made up of poly-L-lactic acid (PLLA), having a diameter range of 15-60 μm and a density of 1.4 g/cm^3. An activity of 3 GBq of QS contains about 40 million of microspheres. Contrary to SS and TS, it is possible to order QS vials with personalized activity according to the dosimetry planning early established for each patient (102).

5.2.2. ^{166}Ho-microspheres SIRT Algorithm

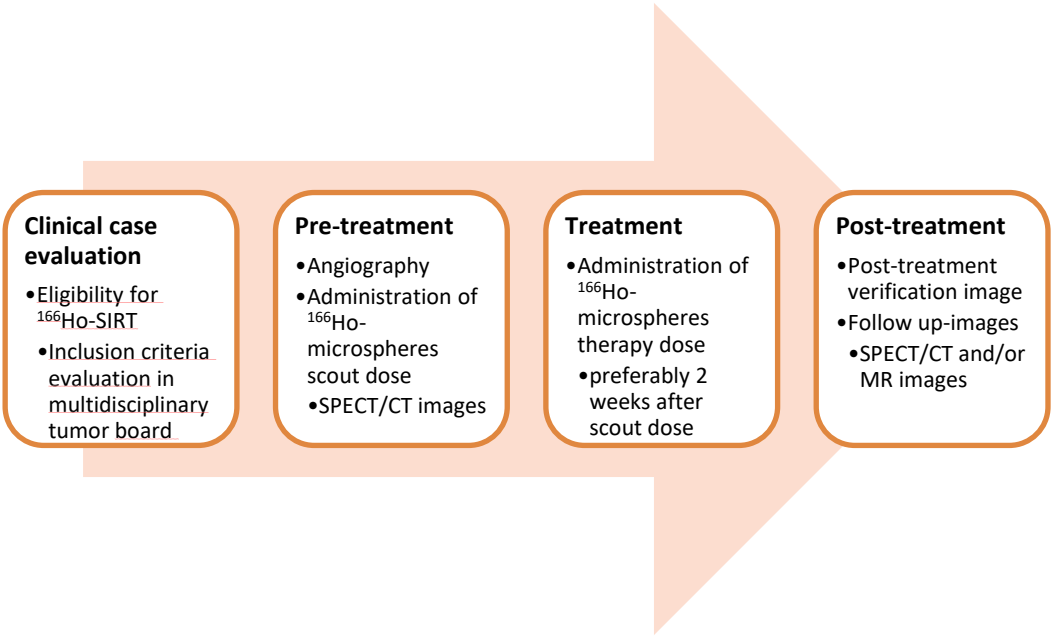

Figure 12: Treatment algorithm in ^{166}Ho-microspheres SIRT.

5.2.2.1. Pre-Therapeutic Evaluation

As it happens in ^{90}Y-SIRT, the pre-therapeutic procedure in ^{166}Ho-SIRT initiates with an angiography of the upper abdominal vessels to map the hepatic arterial flow and eventually coiling the vessels of hepatic artery that supply extra hepatic tissues, such as GDA and RGA. These steps are performed by an interventional radiologist.

As it happens with ^{99m}Tc-MAA shunt evaluation in ^{90}Y-SIRT, some pretherapeutic medications are administered since the day of angiography until the last follow-up image in ^{166}Ho-SIRT (103).

In ^{166}Ho-SIRT, hepatopulmonary shunt evaluation is performed by a small activity of ^{166}Ho-microsferes themselves. Unlike the procedure using ^{90}Y- microspheres, the use of the same radiopharmaceutical predicts better the intra-hepatic distribution and extra-hepatic shunts (52). In ^{166}Ho-SIRT, the dose administered for hepatopulmonary shunt evaluation (shunt dose in ^{99}Y-SIRT) is named scout dose. It consists in a low activity, about 250 MBq of ^{166}Ho-microspheres, used in almost all clinical trials in this subject. A small activity used means a small amount of particles used and, consequently, a low embolic effect, about 60 g, corresponding to 3 million particles (52).

The distribution between the ^{99m}Tc-MAA and ^{166}Ho-microspheres is different, and *Elschot et al.* showed that the use of ^{99m}Tc-MAA ovestimates the lung absorbed dose when it is used for shunt evaluation in ^{166}Ho-radioembolization procedure, and, the use of ^{166}Ho-microspheres in scout dose is more accurate (85). *Prince et al.* related the safety of the shunt evaluation using ^{166}Ho-microspheres and its overcoming in relation to ^{99m}Tc-MAA in SIRT procedure with ^{166}Ho-microspheres. The ^{166}Ho-microspheres used in shunt dose are the same shape and size of ^{166}Ho-microspheres used in therapy, allowing a better access to the safety profile and future toxicity for the patient comparing to ^{99m}Tc-MAA (55). In a recent study, *Smits et al.* performed a quantitative analysis to compare the use of ^{99m}Tc-MAA and ^{166}Ho-mirospheres for shunt evaluation in patients who underwent ^{166}Ho-radioembolization. ^{166}Ho-scout provided better results than ^{99m}Tc-MAA, revealing a median score of 4 versus 2.5, respectively (104). In addition, the use of ^{99m}Tc-MAA presupposes treatment about one week after shunt evaluation, which could lead to differences in blood flow and intra and extra-hepatic microspheres distribution between the two moments. When ^{166}Ho-microspheres is used, we have not that problem, once the therapy is performed at the same day of scout dose (104).

Analyzing most of trials included in this meta-analysis, literature recommends and establishes that in ^{166}Ho-SIRT, when lung shunt is superior to 20%, therapy cannot be performed. However, in patients with lung shunt superior to 10%, the treatment procedure goes on, but the dose absorbed should be decreased, so, the administrated activity should be minor. If a dose is superior to 30Gy is observed in planar or SPECT/CT scout image, the therapeutic activity must be reduced too.

5.2.2.1.1. ^{166}Ho-microspheres Scout Dose Administration

^{166}Ho-microspheres scout dose (^{166}Ho-scout/QuiremScout) is administered intra-arterially, via hepatic artery, by microcatheter whose diameter should be, at least, 0,65 mm. ^{166}Ho-scout is administrated with saline solution (0,9% NaCl), using an injection rate inferior to 5 mL saline per minute. It is mandatory to maintain the catheter tip in the same position for the therapeutic SIRT phase.

5.2.2.1.2. ^{166}Ho-microspheres Scout Image

^{166}Ho emits gamma photons with 81 KeV and bremsstrahlung photons, allowing gamma scintigraphy or SPECT acquisition. As it happens in ^{99m}Tc-MAA, SPECT has a very important role in scout phase with ^{166}Ho-microspheres, once images allow assessing hepatopulmonary shunt and intra and extra-hepatic deposition with more accuracy in comparison to planar images. However, due to the bremsstrahlung photons emission, SPECT images can have a limited quality because of its interaction with patient and SPECT gamma camera. It is expectable that it will degrade the image and difficult the hepatic and shunt quantification, so, the use of a proper collimator and sophisticated reconstruction methods, as Monte Carlo-based reconstruction, is mandatory (105). *Elschot et al.* showed that the use of ^{166}Ho-microsphere planar images to lung absorbed dose quantification should not be used without taking correction for photopeak scatter and attenuation effects into account. It is related that despite the fast shunt assessment by planar image, SPECT image provides attenuation and improved scatter correction and accurate tissue delineation (85).

5.2.2.2. Dosimetry

As *Smits et al.* suggest at the beginning of HEPAR trial I, the activity must be calculated by (106) :

- ***Equation 12*** $\text{Activity (GBq)} = \frac{\text{A (MBq)}}{\text{Liver Weight (Kg)}} = \text{liver dose (Gy)x 63 } (\frac{\text{MBq}}{\text{J}})$

Setting the liver weight value to 2.5 kg, which represents the standard value of normal human liver weight, we can rewrite the equation 12:

- ***Equation 13*** $\text{Activity (GBq)} = \text{Liver dose (Gy) x 63 } \left(\frac{\text{MBq}}{\text{J}}\right) \text{x 2.5 Kg}$

Taking the dose escalation conclusions of HEPAR trial I into account, the aimed whole liver absorbed dose is defined as 60 Gy. Thus, to calculate the activity to be administered, the following formula is used (106) :

- ***Equation 14*** $\text{Activity (GBq)} = 60\ Gy\ x\ 63\ \left(\frac{MBq}{J}\right)\ x\ 2.5\ Kg$

So, an activity about 9450 MBq or 9.45 GBq of the ^{166}Ho-microspheres should be administered to a patient who underwent ^{166}Ho-SIRT to theoretically maximize the RR without increasing toxicity.

If only a lobe or specific segments are the target of treatment, an adjustment should be made to the equation, considering the weight of the lobe or segment to be treated instead of the weight of the entire liver.

The delineation of the tumoral area and health tissue is essential to perform an accurate dosimetry in radioembolization, especially in cases of liver specific segments treatment. Even in situations where there is involvement of the total liver, it is practically guaranteed that there are areas with greater tumor involvement than others. Therefore, the division of the liver into different areas will allow a more effective and accurate dosimetry, since this way, in areas with greater tumor involvement, greater activity will be administered in relation to areas with less.

For a therapeutic planning session, the dosimetry calculation is based on SPECT images, but, once available, using additional technical imaging techniques is possible to make the procedure even more precise and individualized. *Bol et al.* mentioned that multimodality use, more properly SPECT and MRI, allows image acquisition with more precision in their contours and with less chance of missing any parts of the targeted tissue (107). Furthermore, *Smits et al.* showed that *in vivo* dosimetry based on SPECT and MRI imaging is quite reliable and appropriate for activity calculation to liver tumors (53).

To apply MRI based dosimetry using the SPECT based dosimetry as reference method, the liver of each patient is divided into several VOIs. According Bismuth´s adaptation of the Couinaud classification, the MRI divides the liver into 8 functionally independent segments. The contours of all discriminated tumors should be segmented in pre and post-treatment phases. These segmented contours of the liver are manually registered to the contour of the liver of SPECT/CT pre and post-treatment images and MRI post-treatment images. After that, by combining SPECT or SPECT/CT with MRI activity images, we can calculate ^{166}Ho-microspheres absorbed dose maps, considering the appropriate voxel size for the case. The number of ^{166}Ho-microspheres in each voxel

is determined by using voxel volume, and then convert the amount into activity (mg into MBq) by multiplication by the specific activity of the microspheres. The total amount of ^{166}Ho-microspheres (mg) in each voxel was determined by using the voxel volume. This amount is then converted into units of activity (MBq) by multiplication by the specific activity of the microspheres (53, 107).

Following these steps, we can determine the number of microspheres that arrived in the tumor and the number of microspheres that arrived in the normal liver (T/N ratio) by analyzing SPECT and MRI images combination of patients who undergo ^{166}Ho-SIRT.

5.2.2.3. Therapy

5.2.2.3.1. ^{166}Ho-microspheres Administration

In ^{166}Ho-therapeutic dose administration, QuiremSpheres Delivery Set and Customer kit should be used, without first carefully reading the instructions for use.

^{166}Ho-microspheres implantation is performed in interventional radiology, by microcatheter insertion via femoral or radial artery, with x-ray guidance. Transarterial catheter can be inserted in hepatic artery branches to decrease the risk of reflux of ^{166}Ho-microspheres to small arteries which supplies other G.I. organs. Catheter implantation should be done in a way to ensure that the target liver area is adequately supplied.

Similar to ^{166}Ho-scout, catheter should be a diameter of, at least, 0.65 mm to prevent occlusion during QS delivering. Furthermore, the deliver must be performed slowly, never exceeding the maximum advised of 5 ml per minute, and saline solution (0.9% NaCl) into the hepatic artery in way to prevent stasis and microspheres reflux. Administration of a contrast agent allows detecting events like stasis and backflow and must be done regularly, avoiding an incorrect microspheres delivery. The regular infusion of salinue solution should be performed too in order to avoid blockage by microspheres.

5.2.2.3.2. Therapeutic Image

After ^{166}Ho-microspheres administration, post-administration images as well as follow-up images are mandatory to assess intra and extra-hepatic microspheres distribution and, consequently, the effectiveness of delivery. As in therapeutic planning

phase, planar images and, more frequently, SPECT/CT acquisition is the choice. Additionally, MRI can also be obtained with ^{166}Ho-SIRT, not because of its radiation emission but due to its paramagnetic characteristics. This technique provides high resolution images and the correction of some breathing-motion artifacts, one of the SPECT major problems. However, MRI is not appropriate for air-filled cavities like respiratory and gastrointestinal organs. Besides, patients with surgical implants or any type of metal cannot do that treatment and the MRI quantification protocols in this context still need to be optimized. ^{166}Ho-microspheres demonstrate superior imaging capabilities for both SPECT/CT and MRI in comparison to ^{90}Y-microspheres. Besides, QS kit comes with Q-Suite, a software tool that allows the absorbed dose calculation based on the SPECT/CT and MRI images, providing some advantages in imaging quantification (108).

^{166}Ho-SIRT has also the advantage of multimodal detection. We can simultaneously use the 81 KeV gamma-rays of ^{166}Ho emission for SPECT imaging, with an high mass attenuation coefficient provided by CT imaging and with the magnetic susceptibility provided by MRI imaging (55).

III. Prospective and Retrospective Studies on ^{90}Y-microspheres SIRT

1. Primary Liver Disease

HCC is the more frequent primary liver cancer type, representing almost 90% of all cases worldwide. Therefore, the scientific community has made efforts in order to evaluate the efficiency and safety in the application of therapies to this pathology, translated by a vast array of clinical trials published in the literature. As cTACE or DEB-TACE, SIRT shows satisfactory results in the therapeutic response in unresectable HCC patients but also in unresectable ICC, another kind of primary hepatic disease, however with much lower incidence.

1.1. Prospective and Retrospective Studies of SIRT for unresectable Hepatocellular Carcinoma (HCC)

In 1994, *Lau et. al* performed one of the first trials showing ^{90}Y-SIRT was safe and had very little morbidity as treatment approach in unresectable HCC patients. Eighteen patients were assessed and the authors concluded that tumor response is dose related, once PD occurred in a higher number of patients whose tumors received 120 Gy (median OS of 55.9 weeks) than those whose tumors received lower doses (median OS of 26.2 weeks). So, the authors recommended a tumor dose higher than 120 Gy (109).

Four years later, *Lau et al.* related a median OS of 9.4 months in 71 HCC patients which underwent ^{90}Y-SIRT, revealing the same toxicological profile of the first study (110).

In 2004, *Greshwind et al.* divided patients that underwent ^{90}Y-SIRT in Okuda stage I and Okuda stage II and the median OS after treatment was 628 days and 364 days, respectively. One year survival rate was superior in Okuda stage I, 63%, where in Okuda stage II group the rate is 51%, showed a better prognostic in Okuda stage I patients (111). In the same year, *Carr et al.* evaluates ^{90}Y-SIRT in 65 unresectable HCC patients, classifying them into Okuda stage I and II. Like *Greshwind et al.* verified, median survival was superior in Okuda stage I group than Okuda stage II group (649 vs 302 days, respectively). CT scan demonstrated that 42 patients (64.6%) had a substantial therapy response by revealing a decrease in tumor vascularity (64.6%), and PR was achieved in 25 patients (38.4%) (111) (112).

Goin et al. compared ^{90}Y-glass microspheres SIRT vs TACE in 63 patients, 29 TACE-treated and 34 TS SIRT-treated patients. Similarities between median OS in TS SIRT (20 patients) and TACE (29 patients) groups was observed (378 days and 343 days, respectively). However, the incidence of post-embolization syndrome was 3.8-

times higher after TACE [20 patients (69%)] than after TS [6 patients (18%)] treatment, where by SIRT is safe and with less toxicity associated and, at least, as efficacious as TACE on what OS concerns (113).

It is refereed by *Salem et al.* that ^{90}Y microspheres treatment is safety, showing clinical evidence of tumor viability reduction in this clinical context (114).

In 43 patients, divided in 3 risk groups (0: segmental; 1: lobar low-risk; 2: lobar high-risk), 20 patients (47%) revealed an objective tumor response based on the reduction in tumor size and 34 patients (79%) had a tumor response when reduction and/or tumor necrosis were used as a composite measure of tumor response (114). The authors also proved that a low hepatic performance status is associated with a decreased RR and consequent decreased median OS. Median OS was 46.5 months for group 0, 16.9 months for group 1 and 11.1 months for group 2. For Okuda I and II, it was obtained a median OS of 24.4 months and 12.5 months, respectively. Patients had median OS of 20.5 months and 13.8 months according to Child class A and class B/C disease, respectively (114).

Goin et al. categorized 121 patients with unresectable HCC, treated with TS, into high and low risk group. The median OS after SIRT was 466 days for low-risk patients and 108 days for high risk patients, thus it was once again proven that high degree of vascular infiltration tumors are associated with a decreased median survival, among other variables described in the study (115). In the same year and as a complement to the previous study, *Goin et al.* performed an analysis of the occurrence of liver toxicities and eventual pretreatment factors associated with liver toxicities after TS treatment. The risk of toxicities was related to total bilirubin level and to the liver radiation dose (116).

Furthermore, *Goin et al.* related that maximum doses of 150 Gy on a single administration and of 268 Gy on several administrations were well tolerated (116).

Sangro et al. demonstrated the antitumoral effect of SIRT with ^{90}Y-resin microspheres in unresectable HCC and in a clinical context of cirrhosis, with adjustments in the calculation of the activity to be administered and strict selection criteria. The median OS was 7 months and 1-year survival rate of 30% was related. Only 1 patient did not reveal a reduction size of tumor size (117).

In 2006, *Kulik et al.* presented a clinical data of 35 patients with staging UNOS T3 unresectable HCC that underwent ^{90}Y-SIRT, with the objective of downstaging and allowing the performance of transplantation, surgical resection, or RFA. Using WHO criteria, OS was 84%, 54%, and 27% at 1, 2, and 3 years, respectively and median survival obtained was 800 days. This therapeutic strategy showed very satisfactory results, once 19 of 34 patients (56%) were successfully downstaged from T3 to T2 (118).

One year later, *Kulik et al.* showed that ^{90}Y glass microspheres use, which present of minimally embolic, was safe, not imparting an increased risk for hepatic failure or encephalopathy in patients with branch or no PVT compared with main PVT and present favorable tumor RRs (119).

In 2009, a study performed by *Scanlon et al.* compares the efficacy and safe of TACE and ^{90}Y-SIRT in 93 patients with no metastatic HCC. The authors reported that SIRT was related with a better OS in non-transplanted patients compared to TACE (21 months for TACE group and 29 months for ^{90}Y-SIRT group). Besides, SIRT appears to have better RRs [9 TACE patients and 27 ^{90}Y-SIRT patients showed WHO partial response (20% vs 56%)], longer TTP (median TTP was 15.1 months for TACE and 27 months for ^{90}Y-SIRT) and lower toxicity when compared to TACE (serious adverse effects in 22% of patients of TACE group and 11% in ^{90}Y-SIRT group) (120).

In case of multinodular pathology, *Carpanese et al.* showed a safe and effective role of ^{90}Y-SIRT and also an improvement of portal vein thrombosis in 7 patients of 21 patients with this pathology (33%) (121).

A study performed by *Lewandowski et al*., in 2009, already mentioned above in the dissertation for comparison between TACE and SIRT, compared the rates of downstaging to T2 in T3 status patients after being treated with the two mentioned techniques. SIRT provided better results in downstaging T3 to T2 status, once a better OS and event-free survival (17.7 vs. 7.1 months) compared to TACE (42).

Woodall et al. evaluated the role of SIRT in HCC with portal or cava vein thrombosis, or both. Patients were divided into 3 groups. Group 1, composed by treated patients without thrombosis, reveals a median OS of 13.9 months, while group 2, including patients treated with thrombosis, had a median OS of 2.7 months. Median OS of 5.2 months was obtained for the group 3, untreated patients given best supportive care only. These results reinforce the concept of safety in SIRT, once it is associated with an acceptable toxicological profile. The authors also verified an increased median OS for patients with without major venous thrombosis, whatever the tumor staging, and, by itself, it does not provide any benefit in patients with venous thrombosis (122).

Finally, a recent study by *Floridi et al.*, is one more clinical evidence showing SIRT safety and efficacy in unresectable HCC patients. Besides, the authors showed a relation between administrated dose and RR, being that higher as higher the administrated activity. Using RECISCT, median PFS and OS were 27.7 and 16.8 months, respectively, so authors conclusion was that ^{90}Y-SIRT could be potentially useful for HCC treatment, particularly in patients with locally advanced tumor (123).

Table 7: Prospective and Retrospective Studies of SIRT for unresectable HCC.

Author	Year	Design	N	Treatment	ORR (CR + PR) (%)	SD (%)	Median TTP (months)	OS
Lau et al. (109)	1994	Perspective phase I and II	18	^{90}Y Resin Microspheres SIRT				>120 Gy: 55.9 weeks <120 Gy: 26.2 weeks
Lau et al. (110)	1998	Prospective cohort	71	^{90}Y Resin Microspheres SIRT	26.7			9.4 months
Geschwind et al. (111)	2004	Prospective	80	^{90}Y Glass Microspheres SIRT				Okuda stage I: 628 days Okuda stage II: 384 days
Carr et al. (112)	2004	Retrospective cohort	65	^{90}Y Glass Microspheres SIRT	38.4			Okuda stage I: 649 days Okuda stage II:302 days

Goin et al. (113)	2004	Retrospective cohort	34	^{90}Y Glass Microspheres SIRT				378 days
Salem et al. (114)	2005	Prospective phase II	43	^{90}Y Glass Microspheres SIRT				Okuda stage I: 24.4 months Okuda stage II: 12.5 months
Goin et al. (115)	2005	Retrospective and prospective study	121	^{90}Y Glass Microspheres SIRT				High risk: 466 days Low risk: 108 days
Goin et al. (116)	2005	Retrospective cohort	88	^{90}Y Glass Microspheres SIRT				CLIP 0: 26.7 months CLIP 1 or 2: 11.6 months Clip > 2: 7.1 months
Sangro et al. (117)	2006	Prospective cohort	24	^{90}Y Resin Microspheres SIRT	RECIST: 24	RECIST: 64		7 months
Kulik et al. (118)	2006	Retrospective cohort	35	^{90}Y Glass Microspheres SIRT				800 days

Kulik et al. (119)	2007	Retrospective phase II	71	^{90}Y Glass Microspheres SIRT				EASL: No PVT: 467 days EASL: Branch PVT: 304 days EASL: Main PVT: 305.5 days
Scanlon et al. (120)	2009	Prospective cohort	48	^{90}Y Glass Microspheres SIRT				36 months
Carpanese et al. (121)	2009	Retrospective cohort	60	^{90}Y Microspheres SIRT at midterm follow-up	78			Child-Pugh Class A: 14 months Child-Pugh Class B: 8 months
Lewandowski et al. (42)	2009	Retrospective cohort Non-randomized	43 43	^{90}Y Glass Microspheres SIRT TACE	61 37	37 49	33.3 18.2	41.6 months 19.2 months
Woodall et al. (122)	2009	Retrospective cohort		^{90}Y Glass Microspheres SIRT				

		Non-randomized	20 15 17	G1 (SIRT, stage I-II, no PVT) G2 (SIRT, stage III, PVT) G3 (no SIRT, with/no PVT, stage II-IV)				13.9 months 3.2 months 5.2 months
Floridi et al. (123)	2017	Prospective cohort	48	^{90}Y Resin Microspheres SIRT	1 months: 18.2 3 months: 47.6 6 months: 53.9	1 months: 45.45 3 months: 14.2 6 months: 15.4		27.7 months

1.2. Prospective and Retrospective Studies of SIRT for Unresectable Intrahepatic Cholangiocarcinoma (ICC)

The literature review provided clinical evidence that ^{90}Y SIRT should be a viable therapeutic option in patients with unresectable ICC.

Ibrahim et al. present a cohort study in which ICC patients who underwent ^{90}Y-microspheres SIRT whose median OS was 14.9 months. By EASL criteria, follow-up images showed a PR, SD and PD in 6, 15 and 1 patients, respectively, and 17 patients (77%) showed tumor necrosis superior to 50%. Adverse effects like fatigue [18 patients (75%)], transient abdominal pain [10 patients (42%)], grade 3 bilirubin toxicity [1 patient (4%)] and a gastroduodenal ulcer [1 patient (4%)] was seen, however, SIRT satisfactory in terms of RR may overcome the potential adverse effects in this clinical context (124).

Saxena et al. also demonstrates ^{90}Y-SIRT safety and efficiency in unresectable ICC. By RECIST criteria, the median OS after ^{90}Y SIRT was 9.3 months and follow up images showed PR in 6 patients (24%), SD in 11 patients (48%) and PD in 5 patients (20%). The authors also showed a toxicological profile similar to *Ibrahim et al.* and conclude that peripheral tumor type and ECOG 0 are associated with an improved survival (125).

OS and TTP was prolonged in patients with ECOG 0, tumor burden ≤25% and radiologic response. That was the main conclusion in a study of *Hoffmann et al.,* which mentioned an high effectiveness of ^{90}Y-radioembolization in ICC patients, due a PR observed in 12 patients, SD in 17 patients and PD in 5 patients, 3 months after therapy. The median OS was 22 months after treatment and 43.7 months after diagnosis. Median TTP obtained was 9.8 months, adopting RECIST criteria (126).

Mouli et al. demonstrated the safety and RR after ^{90}Y-SIRT for patients with unresectable ICC patients. SIRT was responsible by triggering antitumoral response. Mild side effects as fatigue and transient abdominal pain occurred in 25 patients (54%) and 13 patients (28%), respectively. Radiologic response by WHO criteria showed a PR in 11 patients, SD in 33 patients and PD in 1 patient. By EASL criteria, partial or complete response was seen in 33 patients and SD in 12 patients. The authors showed that satisfactory results are more pronounced in solitary tumors, due to the possibility the downstaging to a state in which curative resection could be possible (127).

For the same purpose, *Mosconi et al.* obtained median OS of 17.9 months an ORR were 15% and 45%, using RECIST 1.1 and mRECIST criteria respectively. The authors related that Radioembolization offers a survival benefit especially in responders at 3 months as defined by mRECIST or the EASL criteria (128).

^{90}Y-SIRT can also be extremely favorable in a clinical context where ICC does not respond to chemotherapy.

Camacho et al. mentioned significant differences between mRECIST and EASL versus RECIST criteria in classification of the patient into responders and nonresponders to the therapy. For that conclusion, they analyzed patients in this clinical context and a median OS (OS) from the time of ^{90}Y therapy of 16.3 months was achieved. Therefore, authors suggest the use of several radiologic response criteria and despite just one (32).

Jia et al. evaluated the efficient and safe of ^{90}Y-resin microspheres SIRT for unresectable ICC that failed first line chemotherapy regimen using cisplatin plus gemcitabine. Satisfactory results in RR was obtained, being the median OS from the time of ICC diagnosis, beginning of first-line chemotherapy and first ^{90}Y procedure were 24.0, 16.0 and 9.0 months respectively, using mRECIST criteria. It is proved its benefit, despite some adverse effects. Furthermore, *Jia et al.* related a significant influence in lymph node metastases on OS, as well as performance status (129).

Manceau et al. evaluate SIRT dosimetry in ICC context. For that purpose, 40 patients with unresectable ICC underwent SIRT using ^{90}Y-glass microspheres (TS) combined with chemotherapy as first-line treatment and it was shown that radioembolization is highly effective when combined with chemotherapy with a tumor dose superior to 158Gy. Median PFS was 12.7 months and median OS was 28.6 months. Little tolerance to that dose was seen just in a small number of patients which reveals low hepatic performance status (130).

Table 8: Prospective and Retrospective Studies of SIRT for unresectable ICC.

Author	Year	Design	N	Treatment	ORR (CR + PR) (%)	SD (%)	Median TTP (months)	OS (months)
Ibrahim et al. (124)	2008	Prospective Cohort	24	^{90}Y Glass Microspheres SIRT in unresectable ICC	EASL: 86 WHO: 27	WHO: 68		14.9
Saxena et al. (125)	2010	Prospective	25	^{90}Y Resin Microspheres SIRT in unresectable ICC	RECIST: 24	RECIST: 48		9.3
Hoffmann et al. (126)	2012	Retrospective	33	^{90}Y Resin Microspheres SIRT in unresectable ICC	RECIST: 36.4	RECIST: 51.5	RECIST: 9.8	22
Mouli et al. (127)	2013	Prospective Cohort	46	^{90}Y Glass Microspheres SIRT in unresectable ICC	WHO: 25 EASL: 73	WHO: 73 EASL: 27		Solitary: 14.6 Multifocal: 5.7
Camacho et al. (32)	2014	Prospective Cohort	21	^{90}Y Resin Microspheres SIRT in ICC refractory to standard chemotherapy	mRECIST: 27.5			16.3
Mosconi et al. (128)	2016	Case Series	23	^{90}Y Resin Microspheres SIRT in	RECIST: 15 mRECIST: 45			17.9

				unresectable/recurrent ICC				
Jia et al. (129)	2017	Retrospective	44	^{90}Y Resin Microspheres SIRT in unresectable and failed first-line chemotherapy ICC	mRECIST: 36.4	mRECIST: 45.5		9
Manceau et al. (130)	2018	Retrospective	40	^{90}Y Glass Microspheres SIRT with chemotherapy for inoperable ICC as first-line treatment	EASL: 96	0		28.6

2. Secondary Liver Disease

Beyond satisfactory results of ^{90}Y-SIRT application in primary malignant hepatic diseases such as HCC and ICC, the literature provides clinical evidence of the satisfactory application of ^{90}Y-SIRT in secondary liver disease. The following clinical trials provide clinical evidence of SIRT benefits in secondary hepatic disease, such as liver metastases from CRC, breast cancer, neuroendocrine tumors and ocular melanoma.

2.1. Prospective and Retrospective Studies of SIRT for Colorectal Cancer Liver Metastases (CRCLM)

To investigate the safety, RR, OS and PFS in patients with liver metastases treated by SIRT in CRC liver metastases, *Benson et al.* performed a prospective, multicenter phase II study, the first trial showing technical and dose reproducibility of ^{90}Y glass microspheres between centers. The authors showed that patients with liver metastases from colorectal cancer can be safely treated with ^{90}Y microspheres because treatment was well tolerated, with a median progression free survival of 2.9 months and median OS of 8.8 months, and with an acceptable toxicological profile. It was related some high-grade adverse events, as pain (12.8%), elevated alkaline phospatase (8.1%) or hyperbilirubinemia (5.3%).

For its side, *Lewandowski et al.* analyzed the safety, treatment characteristics and survival outcomes on SIRT for unresectable colorectal CRCLM refractory to standard of care therapy, using ^{90}Y-glass microspheres (132).

Some adverse effects were seen, such as grade 3 lymphocyte, bilirubin, albumin, ALP and AST toxicities, however in a few percentage (39 %, 11 %, 10 %, 8 % and 4 %, respectively), as well as grade 4 lymphocyte (5%) and ALP toxicities (3%). There was no occurrence of pneumonitis or other serious adverse effects such as gastrointestinal ulceration or REILD. Median OS for first ^{90}Y-SIRT treatment was 10.6 months. The authors mentioned the safety associated with ^{90}Y-SIRT and its important role in multimodality treatment of patients with liver metastases of CRC who have limited therapeutic options (132).

Some clinical trials prove safety and improvement in terms of RR of ^{90}Y-SIRT combined with first line chemotherapy as first line therapy for hepatic colorectal metastases.

In a phase 1 study, *Sharma et al.* demonstrated that SIRT with concomitant FOLFOX chemotherapy in patients with metastatic CRC was well tolerable. ^{90}Y-SIRT was applied 3-4 days after the first cycle of FOXFLOX. The chemotherapy regímen consists in oxaliplatin (30 to 85 mg/m2) administration to 20 patients for the first three cycles with full FOLFOX4 doses from cycle 4 until cycle 12 (133).

Chemotherapy treatment was continued until dose-limiting toxicity was achieved. As the primary end point was toxicity, the dose-limiting toxicity was grade 3 or 4 neutropenia, which was observed in 12 patients (60%). Grade 3 abdominal pain was observed in 5 patients (15%), microsphere-induced gastric ulcers were observed in 2 patients (10%). PR was achieved in 18 patients (90%) and SD observed in 2 patients (10%). Median PFS and TTP were 9.3 and 12.3 months, respectively. As expected, in patients without extrahepatic disease, the median PFS was superior, 14.2 months. The authors also assessed toxicity and maximum tolerated oxaliplatin dose during the first three cycles of chemotherapy and established it as 60 mg/m^2. (133)

It is difficult to establish a comparison in terms of the effectiveness of SIRT in combination with chemotherapy *per si*, since this is a phase 1 study and there is no randomization of patients to a chemotherapy group in this study.

Kosmider et al. also demonstrated SIRT effectiveness after first line conventional intravenous chemotherapy with 5-fluorourail/leucovorin or FOLFOX (5-fluorourail/leucovorin/oxaliplatin) in 19 patients with liver metastases of colorectal cancer. The median OS achieved for all patients was 29.4 months, and the group with no extra-hepatic disease had a better OS compared with patients with extra-hepatic disease (37.8 vs 13.4, respectively) (134). According to RECIST criteria, the ORR was 84%. Two patients (11%) with liver confined disease showed a CR, 14 patients (74%) showed PR and just 1 patient (5%) showed SD. Median PFS was 10.4 months and the median TTP was 15.8 months (134).

One treatment-related death from hepatic failure was reported, 7 patients with abdominal pain and fever in the first month and just one patient experienced an episode of febrile neutropenia after a FOLFOX chemotherapy with full-dose of oxaliplatin. However, no other patients experienced grade 3 or 4 toxicity (134).

^{90}Y-SIRT is also considered very effective and safe in combination with second- or third-line chemotherapy as adjuvant therapy in this clinical context.

In 30 patients with CRCLM which had previously received 5-fluorouracil based chemotherapy, *Lim et al.* reported, in 2005, an aceptable RR related with SS SIRT, with a with a PR in 10 patients (33%) and SD in 8 (27%). TTP was 5.3 months and the toxicity observed was acceptable, despite the detection of duodenal or gastric ulcers in 13% (135).

However, not only *Lim et al.* but also the authors of the studies described so far mentioned the need of phase III clinical trials to assess the efficacy of chemotherapy plus SIRT compared to chemotherapy alone (135) (134) (133).

So, randomized controlled trials have been performed to compare these therapeutic approaches, in terms of RR, mean survival and side effects.

FOXFIRE, SIRFLOX, and FOXFIRE-Global were randomized, phase 3 trials done in hospitals and specialist liver centers in 14 countries worldwide, including Portugal, with IPO Porto participation. These 3 studies aim to evaluate the efficacy of performing SIRT after chemotherapy with ^{90}Y-resin microspheres in patients with liver metastases of colorectal cancer (136). The recruitment period was from October 2006 until December 2014, being included 549 patients in chemotherapy group (FOLFOX) and 554 patients in SIRT plus chemotherapy group (FOLFOX plus SIRT). (136)

The results obtained and published in 2017 showed us that there is no difference in terms of median OS between FOLFOX and FOLFOX plus SIRT groups (23.3 and 22.6 months, respectively). Besides, the adverse effects were much more related in FOLFOX plus SIRT group. Serious adverse effects were related in 244 patients in FOLFOX group (43%) and in 274 of FOLFOX plus SIRT group (54%), the occurrence of neutropenia was higher in FOLFOX plus SIRT group, with 186 patients (37%) comparing with 137 (24%) of chemo alone group. Adverse effect-related deaths were 11 in FOLFOX group and 10 in FOLFOX plus SIRT group and, while 3 patients in the FOLFOX group die due to treatment-related problems, in FOLFOX plus SIRT, that number was higher, 8 patients (136).

So, SIRT addition to first line chemotherapy for the treatment of patients with unresectable liver metastases of colorectal cancer did not show any improvement in terms of for PFS or OS. Besides, it was demonstrated by these studies that adverse effects in patients when SIRT is performed were higher, so, since the OS is similar, both in chemotherapy alone and in SIRT after chemotherapy, it is not recommended its use as a complement to chemotherapy, because there is no need to possibly lead to a greater number of adverse effects without any proven advantage in terms of increasing the OS. However, further studies are needed in that subject (136).

Table 9: Prospective and Retrospective Studies of SIRT for unresectable CRCLM.

Author	Year	Design	N	Treatment	ORR (CR + PR) (%)	SD (%)	TTP (months)	OS (months)
Lim et al. {Lim, 2005 #199}	2005	Prospective	30	^{90}Y Resin Microspheres SIRT after failing initial 5-fluorouracil chemotherapy or secondly oxaliplatin or irinotecan	RECIST: 33 (PR)		5.3	
Sharma et al. (133)	2007	Prospective	20	^{90}Y Resin Microspheres SIRT after FOLFOX	RECIST: 90	RECIST: 10	12.3	
Kosmider et al. (134)	2011	Retrospective	19	^{90}Y Resin Microspheres SIRT after plus 5-fluorouracil and leucovorin	RECIST: 84 (CR: 11; PR: 74)	RECIST: 5		RECIST: 29.4

Benson et al. (131)	2012	Prospective phase II	151	^{90}Y Glass Microspheres SIRT				RECIST: 8.8
Lewandowski et al. (132)	2014	Prospective	214	^{90}Y Glass Microspheres SIRT in refractory cases to standard of care therapy				10.6

Table 10: FOXFIRE, SIRFLOX and FOXFIRE Global (136).

Intervention	Year	Design	Number of patients	Serious Adverse Event	Occurrence of Neutropenia	Adverse Effect-related Deaths	Treatment-related Deaths	Median OS (months)
FOLFOX	2007	Prospective phase III	549	244 (43%)	137 (24%)	11	3	23.3
FOLFOX + SIRT			554	274 (54%)	186 (37%)	10	8	22.6

2.2. Prospective and Retrospective Studies of SIRT for Breast Cancer Liver Metastases (BRCLM)

One of the most important clinical trials in BRCLM context was in 2007, in which *Bangash et al.* showed ^{90}Y-SIRT may be a viable therapeutic option in patients who have progressed or do not respond on first-line chemotherapy to unresectable chemoresistant breast cancer liver metastases (BRCLM) treatment. From 27 female patients, 9 showed PR and CP (39.1%) and SD and PD was observed in 12 and 2, respectively (52.1% and 8.8%) by CT follow-up images 90 days after treatment. 17 patients (63%) showed positive responses in PET/CT images. Median survival in ECOG 0 patients was 6.8 months, understandably higher value compared to ECOG 1,2 and 3 patients (2.6 months). In what tumor burden concerns, the median OS of patients with <25% was 9.4 months and from patients with <25% was 2.0 months (137).

Jakobs et al., in 2008, performed a study aiming to determine the safety and OS associated with a whole-liver SIRT using ^{90}Y-resin microspheres in patients with nonresectable BRCLM refractory to other therapeutic approaches (138). By RECIST criteria, it was related a PR in 61%, SD in 35% and PD in 4% in a follow-up 4.2 months after therapy. The median follow-up time was 14.2 months and the median OS was 11.7 months. The evidence of SIRT effect in these patients was shown by the decrease in tumor size, confirming one more time the acceptable toxicity profile and efficacy of a single-session of SIRT to whole-liver (138).

Cianni et al. in 2012, evaluated ^{90}Y-SIRT and its effects on the survival of patients with BRCLM refractory to other treatments. They demonstrated an high RR in these patients. By RECIST criteria, 29 patients had PR (56 %), SD was achieved in 18 patients (35 %) and 5 patients showed PD (10 %). Median OS obtained was 11.5 months and the authors concluded that patients with less than 25 % of hepatic involvement, ECOG performance status less than 1 and no evidence of EHD has an OS superior comparatively with patients low performance status (ECOG<2) or evidence of EHD (14.3 versus 8.2 months), like *Bangash et al.* was already concluded (139).

In 2014, *Saxena et al.* provides supportive evidence of ^{90}Y radioembolization safety and efficacy in patients with BRCLM. The median survival after ^{90}Y-SIRT was 13.6 months. *Follow up* images 1-month post-treatment showed a complete response to treatment in two patients (5 %), PR in 10 patients (26 %), SD in 15 patients (39 %), and PD in 11 patients (29 %). *Saxena et al.* related that RR to the treatment and performing chemotherapy after SIRT are associated with an improved survival (140).

Table 11: Prospective and Retrospective Studies of SIRT for unresectable BRCLM.

Author	Year	Design	N	Treatment	ORR (CR + PR) (%)	SD (%)	Median TTP (months)	OS (months)
Bangash et al. (137)	2007	Prospective phase II	27	^{90}Y Glass Microspheres SIRT	WHO: 39.1	WHO: 52.1		ECOG 0: 6.8 ECOG 1-3: 2.6 tumor burden <25%: 9.4 tumor burden >25%: 2
Jakobs et al. (138)	2008	Prospective	30	^{90}Y Resin Microspheres SIRT	RECIST: 61	RECIST: 35		RECIST: 23.6
Cianni et al. (139)	2013	Retrospective	77	^{90}Y Resin Microspheres SIRT in refractory cases to other treatments	RECIST: 56	RECIST: 35		RECIST: 11.5

Saxena et al. (140)	2014	Prospective	40	^{90}Y Resin Microspheres SIRT in BRCLM	RECIST: 26	RECIST: 39		RECIST: 13.6

2.3. Prospective and Retrospective Studies of SIRT for Neuroendocrine Tumor Liver Metastases (NETLM)

Many studies related a safe and efficient use of ^{90}Y resin and glass microspheres in of Radioembolization for Neuroendocrine Tumor Liver Metastases (NETLMs).

King et al., in 2008, evaluated the safety and efficacy of ^{90}Y-SIRT in unresectable NETLMs patients. Adverse effects were observed in 55% of the patients in 3 months, however, with little severity. Radiologic response was seen in half of patients submitted to the study, where CR was observed in 6 patients (18%) and PR in 11 patients (32%) and the mean OS was 29.4 ± 3.4 months (141).

Kennedy et al. related a median OS of 70 months, SD in 22.7%, PR in 60.5%, CR in 2.7% and PD in 4.9% in 148 patients with NETLMs. The authors, besides the acceptable responses rates, related a low toxicological profile too, proving the efficacy and safety of its application in whole liver and single or multiple fractionated lobe (72).

The use of glass and resin microspheres labeled with ^{90}Y in NETLMs was compared by *Rhee et al.*, in a multicenter open label phase II study (142).

The median radiation delivered to the hepatic lobes of the patients was greater when ^{90}Y-glass microspheres were used (117 Gy in right lobe and 108 Gy in left lobe) than when ^{90}Y-resin microspheres (50.8 Gy in right lobe and 44.5 Gy in left lobe). By RECIST criteria, PR and SD was achieved 6 months after treatment in 94% of the patients who underwent SIRT with ^{90}Y-resin microspheres and in 92% who underwent SIRT with ^{90}Y-glass microspheres. The median OS of patients in “resin-microspheres” group was superior relatively those in the “glass microspheres” group, 28 months vs 26 months, respectively (142).

Kalinowsky et al. showed the relevant effect of ^{90}Y-SIRT in liver metastasis volume reduction. Tumor reduction of 13% was observed in 9 patients. PR obtained was 66%, corresponding to 6 patients, 3 months after SIRT, SD was seen in 3 patients (33%) and TTP was 11.1 months. A survival rate at 1 year was total, and survival rates at 2 and 3 years was similar, 57% (143).

For its turn, *Cao et al.*, in 2009, exhibited a great radiologic response achieved in 58 NETLMs patients, in which 6 showed CR (10.3%), 14 showed PR and SD (24.1%) and 17 had PD (29.3%). OS rates at 1, 2 and 3 years were 86%, 58% and 47%, respectively and the median OS obtained was 36 months (144).

Saxena et al., in 2010, evaluated eventual prognostic variables that influenced radiologic response and OS in patients with unresectable NETLMs who underwent radioembolization and its impact in toxicological context. *Follow up* images showed a CR

in 7 patients (15%), PR in 19 (40%) and SD and PD in 11 patients (23%). The median OS was 35 months. Besides the low toxicological profile, *Saxena et al.* defined that a profile with low hepatic tumor burden, well-differentiated tumor, no extrahepatic disease and female gender showed more clinical benefit from SIRT (145).

For the same purpose, *Peker et al.* showed that the extent of tumor involvement is significantly related with the OS. In their patients' cohort, the authors obtained a median OS of 39 months, one-year survival rate of 71%- and two-year survival of 45%. By RECIST criteria, PR was achieved in 43%, CR in 3%, SD in 37% and PFS in 17%, 3 months after SIRT (146).

Fan et al. identified hepatic tumor burden similar or superior to 33% and islet cell histological subtype as factors associated with a great radiologic RR. In this study, CR was achieved in 3 patients (9%), PR in 6 patients (17%), SD in 21 (60%) and PD in 5 patients (14%). Median OS was 29.2 months and it was proved that SIRT is related with low rates of grade ≥3 toxicity (147).

More recently, *Do Minh et al.* performed a study to compare efficacy, survival outcome and prognostic factors between cTACE, DEB-TACE and ^{90}Y-SIRT for liver metastases treatment from gastro-enteropancreatic (GEP) NET (148).

Adverse events were recorded in 164 patients (85.4%), with rates of 85.2% after cTACE, 88.5% after DEB-TACE and 84.1% after ^{90}Y-SIRT, respectively. The overall cumulative 1-year survival was 80.9% after cTACE, 73.0% after DEB-TACE and 71.2% after ^{90}Y-SIRT. The overall cumulative 2 years-survival was 60.4% after cTACE, 38.3% after DEB-TACE and 49.4% ^{90}Y-SIRT. The overall cumulative 5 years survival was 28.2% after cTACE, 10.3% after DEB-TACE and 18.5% after ^{90}Y-SIRT (148).

Median OS obtained for the whole study cohort was 28.8months. For each of the techniques, median OS was superior in cTACE group (33.8 months) comparatively with DEB-TACE (21.7 months) and ^{90}Y-radioembolization (23.6 months). Once statistical analysis from the authors considered significantly differences between cTACE and ^{90}Y-radioembolzation and between cTACE and DEB-TACE but not between ^{90}Y-radioembolzation and DEB-TACE, patients who underwent cTACE are associated with a longer lasting life (148). *Do Minh et al.* also indicated that cTACE patients showed a significantly prolonged hepatic PFS compared to ^{90}Y-SIRT patients (21.6 vs. 11.2 months, respectively), suggesting the benefits of using cTACE as primary intra-arterial therapeutic option in this clinical context. (148)

Table 12: Prospective and Retrospective Studies of SIRT for unresectable NETLM.

Author	Year	Design	N	Treatment / Microsphere	ORR (CR + PR) (%)	SD (%)	Median TTP (months)	OS (months)
King et al. (141)	2008	Prospective	34	^{90}Y Resin Microspheres SIRT	RECIST: 50			RECIST: 29.4 +/- 3.4
Kennedy et al. (72)	2008	Retrospective	148	^{90}Y Resin Microspheres SIRT	RECIST: *60.5	RECIST: 22.7		RECIST: 70
Rhee et al. (142)	2008	Prospective phase II	22 20	^{90}Y Glass Microspheres SIRT ^{90}Y Resin Microspheres SIRT	RECIST: 54 RECIST: 50	RECIST: 38.5 RECIST: 43.7		RECIST: 22 RECIST: 28
Kalinowsky et al. (143)	2009	Prospective	9	^{90}Y Resin Microspheres SIRT	RECIST: 66	RECIST: 33	RECIST: 11	
Cao et al. (144)	2009	Prospective Multicenter	58	^{90}Y Resin Microspheres SIRT	RECIST: 27.5	RECIST: 27.5		RECIST: 36

Saxena et al. (145)	2010	Prospective phase II	48	^{90}Y Resin Microspheres SIRT	RECIST: 40	RECIST: 23		RECIST: 35
Peker et al. (146)	2015	Retrospective	30	^{90}Y Resin Microspheres SIRT	RECIST: 43	RECIST: 37		RECIST: 39
Fan et al. (147)	2016	Retrospective	38	^{90}Y Glass Microspheres SIRT	RECIST: 17	RECIST: 60		RECIST: 29.2
Do Minh et al. (148)	2017	Retrospective	44 122 26	^{90}Y Glass Microspheres SIRT cTACE DEB-TACE	RECIST: 0 WHO: 13.9 RECIST: 3.3 WHO: 15.6 RECIST: 4.3 WHO: 30.4	RECIST:88.9 WHO: 63.9 RECIST: 92.2 WHO: 50 RECIST: 91.3 WHO: 34.8		23.6 33.8 21.7

2.4. Prospective and Retrospective Studies of SIRT for Ocular Melanoma Liver Metastases (OMLM)

The first study regarding SIRT for OMLM was performed by *Kennedy et al.*, in 2009. A retrospective multicenter study was performed for patients with ocular melanoma who received SIRT, in which 1 patient had CR and 6 had PR. Toxicity was minimal and PET/CT at 3 months after SIRT revealed RR in all patients. They conclude that SIRT leads to a satisfactory RR in patients with hepatic metastases of OM with very few side effects. OS and 1-year survival rate were proven to be improved over best chemotherapy regimen. SIRT is also associated with a low incidence of acute toxicity and a descreased radiation liver damage (93).

Gonsalves et al. concludes that SIRT is safe and efficacy in the management of hepatic metastasis of uveal melanoma after immunoembolization or chemoembolization failure. The median OS was 10.0 months and the PFS of hepatic metastasis was 4.7 months. They also verified its safety and effectiveness in patients with limited pretreatment tumor burden, because patients who had a pretreatment tumor burden less than 25% had longer median OS and PFS (10.5 and 6.4 respectively) than patients who had a pretreatment tumor burden of 25% or greater (3.9 and 3.0 respectively) (92).

In 2012, *Klingenstein et al.* evaluated the OS, safety, and efficacy of metastatic uveal melanoma patients after SIRT as salvage therapy. By RECIST, PR was observed in 8 (62 %), SD in 2 (15 %) and PD in 3 (23 %) patients. Median OS time after ^{90}Y-SIRT was 7 months. Furthermore, they verified an acceptable tolerance by the patients (90).

In 2014, *Xing et al.* investigated OS, efficacy and safety of ^{90}Y-SIRT in patients with unresectable metastatic uveal and cutaneous melanoma that revealed refractory to systemic therapies. The authors concluded that ^{90}Y-resin microspheres were associated with longer survival from liver metastases than best supportive care. In a total of 58 patients, 28 underwent ^{90}Y-SIRT using ^{90}Y-resin microspheres and 30 patients received best supportive care. Median OS from diagnosis of liver metastases of melanoma in groups A was 19.9 months and in group B was and 4.8 months. In group A, median OS achieved from first ^{90}Y-SIRT procedure was 10.1 months and 6-and 12-month survivals were 69.2% and 34.6%, respectively (91).

Eldredge-Hindy et al. reported outcomes following ^{90}Y-SIRT for unresectable liver metastases from uveal melanoma and show favorable OS results in patients with unresectable liver metastases from uveal melanoma, with a PFS of 5.9 months and OS of 12.3 months after therapy. The study also mentioned that, by PET/CT imaging,

metabolic tumor volume and total glycolic activity are considered predictive functional tumor parameters, which could help in a more accurate patient selection and risk stratification (149).

Table 13: Prospective and Retrospective Studies of SIRT for unresectable OMLM.

Author	Year	Primary Location	Design	N	Treatment / Microsphere	ORR (CR + PR) (%)	SD (%)	OS (months)
Kennedy et al. (93)	2009	Ocular melanoma	Retrospective	11	^{90}Y Resin Microspheres SIRT	RECIST: 77	RECIST: 11	
Gonsalves et al. (92)	2010	Uveal melanoma	Retrospective	32	^{90}Y Resin Microspheres SIRT after failure in Immunoembolization or Chemoembolization.	RECIST: 6.3	RECIST: 56.3	RECIST: 10.0
Klingenstein et al. (90)	2012	Uveal melanoma	Retrospective	13	^{90}Y Resin Microspheres SIRT as salvage therapy	RECIST: 62	RECIST: 15	RECIST: 7.0 months
Xing et al. (91)	2014	Uveal (and cutaneous Melanoma)	Retrospective	15 13	^{90}Y Resin Microspheres SIRT refractory cases to systemic therapy	RECIST 1.1: 17.9	RECIST 1.1: 32.1	RECIST 1.1: 10.9 (uveal origin) RECIST 1.1: 12.4 (cutaneous origin)

Eldredge-Hindy et al. (149)	2016	Uveal melanoma	Prospective phase I	71	^{90}Y Resin Microspheres SIRT	RECIST: 8	RECIST: 52	RECIST: 12.3 months

IV. Clinical Evidence Trials for ^{166}Ho-microspheres SIRT

1. HEPAR I and HEPAR II

Since 2012, clinical trials have been performed to evaluate the potential use of ^{166}Ho as an alternative to ^{90}Y in SIRT.

The first clinical study was performed in 2012, The Holmium Embolization Particles for Arterial radiotherapy (HEPAR I), whose aim was to verify the safety and toxicity of radioembolization with ^{166}Ho (^{166}Ho-SIRT) in patients with liver metastases (103). For this purpose, they proceed to the administration of increasing doses of ^{166}Ho-microspheres to different cohorts in a total of 15 patients, escalating radiation doses of 20 Gy (n=6), 40 Gy (n=3) and 60 Gy (=3), to a maximum dose of 80 Gy in the last cohort (n=3) (103).

The grade of toxicity was rated according CTCAE v3.0. If there is no toxicity ≥ grade 3, the next cohort was treated according to the next radiation level. If in one patient CTCAE ≥ grade 3 is observed in a cohort, the cohort will be extended to six patients, which happened in the first cohort, because of the occurrence of a pulmonary embolism in one patient. If toxicity grade 3 or superior was observed in two or more patients in a cohort, the study was be terminated once level of maximum radiation is reached. The endpoint occurred in the 80 Gy cohort, reaching the dose-limiting toxicity in 2 of 3 patients, by revealing grade 4 thrombocytopenia and grade 3 leucopenia and hypoalbuminaemia. The maximum tolerated radiation dose on ^{166}Ho-SIRT in patients with liver metastases was 60 Gy (103).

As a complement of HEPAR I, another clinical trial was performed to evaluate ^{166}Ho-radioembolization efficacy in 38 patient's liver metastases refractory to systemic therapy and not able to perform surgical resection. This study is designated by HEPAR II (150).

The treatment was prepared considering the maximum tolerated radiation dose of HEPAR I, being that, aimed absorbed dose, 60 Gy or 3.8 GBq/kg of liver tissue, including the ^{166}Ho scout dose. The median absorbed dose to the liver was 51 Gy. After ^{166}Ho scout dose and administration, SPECT/CT and MRI were performed to quantify microsphere distribution. The patients were submitted to triphasic liver CT and PET/CT with ^{18}F-FDG each 3 months after the treatment, until 12 months (150).

This trial brought very satisfactory results, once disease control was achieved in 73% of the patients in first follow-up step, 3 months after ^{166}Ho-SIRT. The median OS was 14.5 months and the patients present an acceptable toxicity profile, in which 10 of 38 patients experiencing severe toxicity (26% of the patients). Besides, ^{166}Ho-SIRT can be quantified with high level of precision and accuracy by SPECT/CT images. (150)

These 2 studies were relevant to the CE mark approval of ^{166}Ho-SIRT use to unresectable liver tumors treatment, showing clinical evidence of the safe and efficient role in these patients (103) (150).

Table 14: HEPAR I and HEPAR II: design and main conclusions.

Author	Year	N	Tumoral Type	Intervention	Main Conclusions
HEPAR I (103)	2012	15	Liver Metastases	^{166}Ho-SIRT	Maximum tolerated radiation dose = 60 Gy
HEPAR II (150)	2015	38	Liver Metastases	^{166}Ho-SIRT	Median OS was 14.5 months; Acceptable toxicological profile; High accuracy and precision in quantification of ^{166}Ho by SPECT images.

2. Ongoing Clinical Trials Using 166Ho-radioembolization

2.1. HEPAR PLUS

Recent randomized clinical trials showed promissing results of peptide receptor radionuclide therapy (PRRT) as systemic therapy, mainly in long median survival rate obtained in patients with NET. Liver metastases are an essential factor for prognosis definition in patients with NET. Therefore, na additional radiation boost by ^{166}Ho-microspheres in liver metastases is expected to improve the prognosis of these patients (154).

Hepar Plus aims to verify the effect of addition of SIRT with ^{166}Ho-microspheres to PRRT with ^{177}Lu-DOTATATE in terms of complete and partial tumor response rate and toxicity associated. Biochemical response, QoL and dosimetry are secondary endpoints evaluated in this clinical trial (154).

2.2. SIM

The choice of the catheter has an important role in efficacy of radioembolization technique. It´s important that the catheter could deliver the most possible radiation and avoid any antireflux effect. Normally, a standard end-hole microcatheter is the chosen via to administration of microcatheter. However, more advance catheters are available and could fulfill the 2 requirements with more foresight (151).

The SIM Study evaluated 25 patients with unresectable chemorefractory liver dominant CRLM. Patients were divided in 2 groups: one group where administration of ^{166}Ho was performed with a standard end-hole microcatheter, and another group, where the administration was performed with an anti-reflux catheter. The primary aim of the study was a comparison of the T/N ratio between these two groups. The use of anti-reflux catheter increases T/N ratio, so its use can bring advantages (151).

Secondary endpoints include toxicological profile, tumor and healthy tissue absorbed dose, RR and OS and infusion efficiency access, as well as predictive value of ^{166}Ho scout dose for tumor response (151).

2.3. HEPAR Primary

HEPAR Primary Study started in 2017 and its primary aim was to verify the safety profile in 30 patients with unresectable HCC in advanced stages (BCLC Stage B or C). Secondary objectives will be assessed like the efficacy of ^{166}Ho use, tumor marker response, Quality of Life (QoL), biodistribution / dosimetry and hepatic function (152).

2.4. Hora Est

"Holmium radioembolization as adjuvant treatment to Radiofrequency Ablation for Early Stage HCC: a dose-finding study", or "HORA EST", is a clinical trial that evaluates patients that underwent ^{166}Ho-SIRT as an adjuvant treatment to percutaneous radiofrequency ablation (RFA).

HORA EST aims to find a treatment area dose in more than 90% of the patients considered for the study that could deliver to the target tumoral area a radiation absorbed dose of ≥ 120Gy. Furthermore, HORA EST had secondary objectives as accessing toxicological profile, local tumor recurrence, TTP, PFS and QoL (153).

Table 15: Ongoing ^{166}Ho-SIRT clinical trials: design and main conclusions.

Author	Beginning of the study	N	Tumoral Type	Intervention
HEPAR PLUS (154)	2014	30	Neuroendocrine liver metastases	^{166}Ho-SIRT after PRRT with ^{177}Lu-DOTATATE
SIM (151)	2016	25	Colorectal liver metastases	^{166}Ho-SIRT with standard end-hole microcatheter vs ^{166}Ho-SIRT with anti-reflux catheter
HEPAR Primary (152)	2017	30	HCC BCLC Stage B or C	^{166}Ho-SIRT
HORA EST (153)	2018	20 *	Early Stage HCC	RFA after ^{166}Ho-SIRT

*Estimated Enrollment

V. Comparison of the 3 Techniques Used in Radioembolization

It is known that three possible SIRT techniques are nowadays available, each of them with their specificities.

In table 16, main physical characteristics of ^{90}Y and ^{166}Ho are presented and it is possible to verify differences between them, mainly in terms of physical half-life and gamma radiation emission. As a complement, the characteristics of the three microsphere types available are mentioned in table 17. It is essential to make a detailed comparison between the three procedures, thus understanding which of them combines the most advantageous characteristics for the therapeutic approach of a given clinical indication.

Within ^{90}Y-microspheres, the most relevant difference between SS and TS is the activity per sphere. SS have a much higher specific activity than TS (2500 Bq per microsphere vs 50 Bq per microsphere), which means that it is necessary a low number of glass microspheres to have the same activity delivered than the resin microspheres. So, a smaller number of microspheres are administrated per GBq of ^{90}Y activity of TS than SS. In a vial of 3GBq, SS has 40-80 million of microspheres, comparing with TS, which have only 1.2 million. Resin microspheres have approximately less than a half of glass microspheres density (1.6 vs 3.3), which implies a lower specific gravity in SS, however, the diameter range of resin microspheres is 30% superior than glass microspheres (20-30 vs 20-60 µ).

The higher number of microspheres per vial, together with the biggest range in diameter of them, leads us to understand that SS present a higher embolic effect comparing with TS and, thus, SS are more adequate for patients with large lesions. However, it can result in a slowed antegrade hepatic arterial flow, once bigger microspheres require slow injections and angiographic control too. Since a larger number of microspheres are infused, flow stasis effects occur more often when resin microspheres are used, which could lead to an incomplete delivery of the prescribed activity. TS, due to its lower diameter of microspheres associated and consequent lower embolic power, have an important role in patients when prevention of vascular stasis and reflux is essential.

Shelf-life is also distinct between the two 90Y-SIRT procedures, in that SS have approximately 1 day and TS have 12 days. This unconformity implicates that in SS infusion, approximately the same amount of microspheres per GBq will be administered. In TS, the number of microspheres administered per GBq will increase due to the physical decay of ^{90}Y (time interval left between preparation and administration).

By its side, ^{166}Ho-microspheres have a mean diameter of 30 µm, where 97% are into the range of 15-60 µm. They have a diameter range near to the resin microspheres (20-60 µm), although slightly higher. Its specific activity (activity per microsphere) varies

from 67 to 400 Bq, since the activity ordered is different and personalized for each patient. However, QS presents an intermediate value between the SS (50 Bq) and TS (2500 Bq). Although having approximately the same maximum beta particle mean range in soft tissue, 2.5 mm, the reach of beta particles of ^{90}Y is until 11 mm, slightly higher in comparison with ^{166}Ho, which is until 9 mm.

In what density concerns, ^{166}Ho-microspheres have a value of density of 1.4 g/cm^3, near to plasma, having the lowest density in comparison with ^{90}Y resin and glass microspheres (1.6 g/cm^3 of resin microspheres and 3.3 g/cm^3 for glass microspheres), being associated to a lower risk of stasis and backflow during the infusion.

The physical half-life of ^{166}Ho is relatively lower compared to ^{90}Y (26.8 and 64.1 hours, respectively), which means that it´s necessary a higher activity of ^{90}Y-microspheres (almost 3 times) to achieve an equivalent absorbed dose in comparison with ^{166}Ho-microspheres. The shorter half-life also justifies the fact of the delivery of radiation in target local be faster in ^{166}Ho-microspheres than in ^{90}Y-microspheres. Using QS, 90% of the radiation is delivered 4 days after injection, meanwhile, using SS or TS, approximately the same amount of radiation is delivery only 11 days after it.

Among all the advantages of ^{166}Ho-SIRT, the biggest advantage consists in the possibility of performing the scout dose using the same radiopharmaceutical that will be used in therapy.

The possibility of carrying out pre-therapeutic evaluation with a small amount of ^{166}Ho-microspheres allows the assessment of the intrahepatic distribution of particles and extrahepatic shunts in a much more reliable way compared to ^{90}Y- SIRT, in which a different radiopharmaceutical (^{99m}Tc-MAA) is used in pre-therapeutic evaluation.

In ^{90}Y-SIRT, several studies already mentioned show the effectiveness of using ^{99m}Tc-MAA for pre-therapeutic evaluation in ^{90}Y-radioembolization, however, being a different chemical element (^{99m}TC vs ^{90}Y) and different particles (MAA vs microspheres), it is expected that dosimetry planning with ^{99m}Tc will not fully translate the therapeutic procedure with ^{90}Y-microspheres, or at least it will not translate as accurately as in the case of the ^{166}Ho-microspheres. So, ^{99m}TC-MAA use in ^{90}Y-SIRT can lead to over or under-estimation of the ^{90}Y-microspheres activity to be managed in therapeutic phase.

^{166}Ho high energy beta emission represent its therapeutic role, the destruction of the tumor tissue, while the emission of low gamma radiation allows the acquisition of images of the microspheres by SPECT/CT and, once Holmium and Erbium are lanthanides, MRI images can be performed too, because of paramagnetic property of these compounds.

The possibility of MRI acquisition in ^{166}Ho-SIRT is a factor that greatly supports this technique. MRI provides images with high soft-tissue contrast, high resolution, and high anatomic reference. In ^{166}Ho-scout image for dosimetry planning, the addition of MRI to SPECT/CT provides images with high sensitivity and spatial resolution, allowing a more reliable activity calculation and, therefore, an even more personalized therapeutic approach. MRI in dosimetry planning after ^{166}Ho-scout dose administration in combination with the high sensitivity and spatial resolution images of SPECT/CT allows a more reliable activity calculation, and a consequent much more personalized treatment.

It was already mentioned in this dissertation that MRI provides breathing-motion artifact correction, which is one of the most SPECT/CT acquisition problems, and, therefore, ^{166}Ho-SIRT shows superior image capabilities either in the pre-therapy images, to perform the dosimetry planning, or in the post-treatment and follow-up images, for calculating and evaluating T/N) using this multimodal image technique in comparison to the imaging acquired with ^{90}Y-SIRT.

Table 16: ^{90}Y and ^{166}Ho physical characteristics.

Isotope	Yttrium-90	Holmium-166
Physical half-life (hours)	64.2	26.8
Beta emission (MeV)	Maximum energy of 2.26 and a mean energy of 0.94	Maximum energy of 1.85 (50%) and 1.77 (48.7%)
Gamma Emission (KeV)	No gamma emission	81 (62%)
Radiation Delivered	Until 94% of the radiation delivered in the first 11 days	More than 90% of the radiation delivered in the first 4 days
Range of Beta Particule	Maximum range of 11 mm with a mean of 2.5 mm	Maximum range of 8.7 mm with a mean of 2.5 mm

Table 17: Sir-Spheres (SS), TheraSphere (TS) and QuiremSpheres (QS): main characteristics associated to the three SIRT techniques available (87) (79) (52) (76) (74).

Commercial Name	SS	TS	QS
Composition and radiolabelling	Resin with bound yttrium by ion exchange of sodium by yttrium	Glass with yttrium in matrix by neutron activation in a nuclear reactor	PLLA with holmium by neutron activation in a nuclear reactor
Approval	Approved by FDA in 2002 for the treatment of colorectal metastases together with intrahepatic floxuridine	Approved by FDA in 1999 for treatment of unresectable HCC	Approved by CE in April 2015 for treatment of unresectable liver tumors
Density (g/mL)	1.6	3.3	1.4
Diameter (mean/range) (µm)	32 (20-60)	25 (20-30)	30 (15-60)
Number of spheres in 3GBq (million)	40-80	1.2-8	40
Activity per microsphere (Bq)	50	2500	67-400
Amount of mg per dose (mg)	1370	110	600

Scout dose	^{99m}Tc-MAA	^{99m}Tc-MAA	^{166}Ho-microspheres
Image techniques	SPECT / PET	SPECT / PET	SPECT / MRI
Activity Available (GBq)	3	3 to 20, with step of 0.5	Personalized for each patient
Embolic Effect	Moderate	Mild	
Specific Gravity	Low	High	
Handling for dispensing	Possible	Not possible	
Spliting one vial for two administrations	Possible	Not possible	Not possible
Necessity for contrast medium guidance	Yes, if necessary	No	Yes, if necessary

VI. Clinical Practice - Factors that Influence Lung Shunt

1. Introduction

The review analysis let us to understand the relevance of the pre-therapeutic phase for SIRT effectiveness. Shunt dose administration, ^{99m}Tc-MAA in ^{99}Y-SIRT or ^{166}Ho-scout in ^{166}Ho-SIRT, allows to simulate intra and extra-hepatic distribution pattern of the microspheres that will be administered in the therapeutic phase. Microspheres extrahepatic distribution is an undesirable factor and the therapy will be more effective the less it is, since the greater the amount of microspheres in the extrahepatic locations, the smaller the amount of microspheres in the intrahepatic space for the intended purpose. In addition, microspheres migration to other tissues or organs, such as G.I. tract and, mainly, lungs, can lead to problems concerning radiation toxicity due to deposition and irradiation of microspheres in non-target tissues. Therefore, hepatopulmonary shunt/lung shunt (LS) calculation is mandatory in SIRT and, in addition to be an effectiveness predictive factor, it is also a therapy selection factor, since patients who reveal shunt greater than 20% cannot carry out SIRT.

Therefore, the aim of this clinical practice is to determine whether there are factors related to the microspheres used in the treatment or inherent in the patient or their pathology in question that could influence the LS obtained, as a complement to the bibliographic review carried out in this dissertation.

For this purpose, we conducted a retrospective analysis of the last 80 patients considered to underwent SIRT in IPO Porto. An identity (ID) was assigned by the Nuclear Medicine Service of IPO Porto to each of the 80 patients considered for this study. Therefore, in order to guarantee data protection, the database was developed in a completely anonymous way, in which the clinical information provided is associated only with the ID. The name of patients remains confidential and the association between this and IDs is exclusive of nuclear medicine service of IPO Porto. From the 80 patients considered, 5 patients were excluded from the data analysis, 4 by missing data and 1 by revealing a LS of 21,5% in pre-therapeutic phase, superior to the maximum acceptable value (20%). So, from the 80 patients who started the procedure, only 75 are eligible for data analysis (Figure 13).

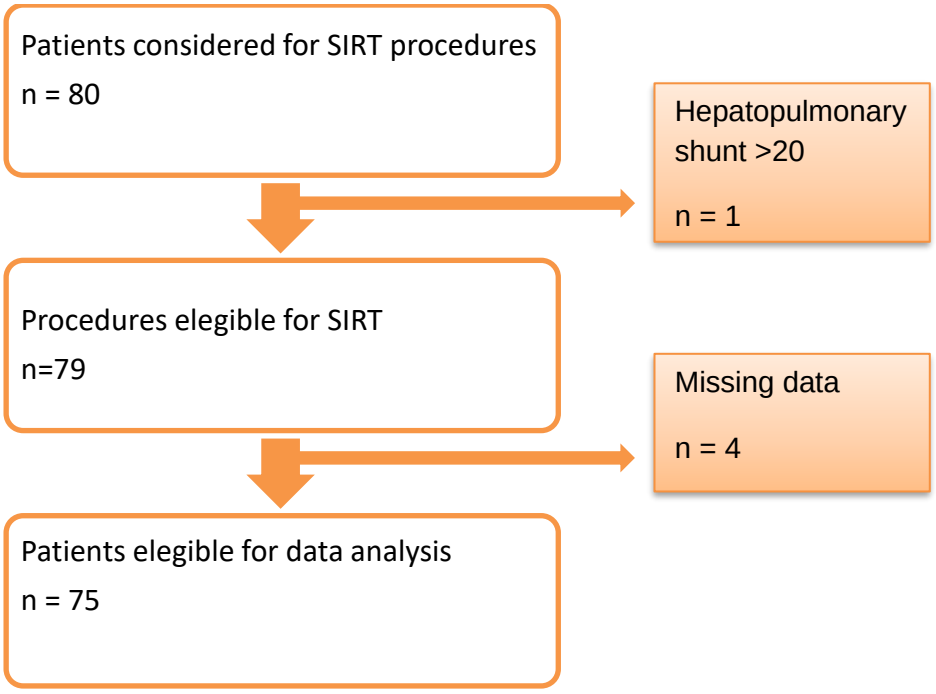

Figure 13: Inclusion flowchart of patients data analysis.

Baseline characteristics of the patient cohort, including age, gender, weight, height, body surface area (BSA), type of hepatic disease, tumor primary location, time interval between shunt and therapy, type of microspheres used and, obviously, the percentage of shunt, are presented in table 18.

Table 18: Baseline characteristics of IPO Porto patients who underwent SIRT.

Baseline characteristics	Data
Elegible SIRT patients (n)	75
Gender	
Male	53 (70.7%) *
Female	22 (29.3%)
Age (y)	65 (30-91) **
Weight (kg)	71 (45-107)
Height (cm)	167 (149-189)
Body Surface Area (cm^2)	1,83 (1.37-2.23)
Hepatic Disease	
Primary	46 (61.3%)
Metastatic (Secondary)	29 (21.3%)

Tumor Type	
Hepatocellular carcinoma (HCC)	29 (38.7%)
Intrahepatic Cholangiocarcinoma (ICC)	17 (22.7%)
Cholangiocarcinoma (CC)	1 (1.3%)
Colorectal cancer (CRC)	18 (24%)
Neuroendocrine tumor (NET)	8 (10.7%)
Gastrointestinal stromal tumor (GIST)	1 (1.3%)
Choroid plexus carcinoma (CPC)	1 (1.3%)
Interval (d)	21 (7-54)
Microspheres	
SIR-Spheres (SS)	52 (69.3%)
TheraSphere (TS)	7 (9.3%)
QuiremSpheres (QS)	16 (21.3%)
Shunt (%)	5.96 (1.0-16)

* value of the qualitative variable and respective percentage

**median value of the quantitative variable and respective range

The majority of the cohorts are male patients, 53 patients, and 22 are female representing 70.7% and 29.3% of total, respectively. The median age of the patients is 65 years-old, being the younger 30 and the older 91. The medium BSA from among patients is 1.83, in which the minimum value is 1.37 and maximum is 2.23. BSA calculation was based on collected data of patients´ weight and height. From 75 patients assessed, 46 were diagnosed with primary hepatic disease, 29 with HCC and 17 with ICC. The remaining 30 patients had metastatic liver disease, 8 patients from NET, 1 from cholangiocarcinoma (CC), 18 from CRC and 1 from gastrointestinal stromal tumor (GIST). The time interval between pre-therapeutic phase and therapy of the patients is also included, and its median value is 21 days, ranging between 7 and 54 days. ^{90}Y-SIRT is the most representative SIRT procedure in our database, representing 78.6% of total SIRT procedures considered. This high percentage turns out to be explainable since ^{166}Ho-SIRT is quite recent and only introduced in IPO Porto clinical practice in 2019, meanwhile ^{90}Y-SIRT is performed since 2011. 52 patients underwent ^{90}Y-SIRT using SS (69.3%), meanwhile 7 patients using TS (9.3%). A smaller number of patients underwent ^{166}Ho-SIRT, 16 patients, which represents 21.3% of total SIRT procedures. The shunt percentage of each patient was recorded. The minimum shunt percentage value observed was 1 and the maximum was 16. The medium value of the cohort is 5.96.

Considered these data, we can verify if the shunt percentage is influenced by any of the other characteristics mentioned in the baseline.

2. Materials and Methods

Statistics analysis of the collected data was performed using SPSS for Windows, version 26.0, a commercial statistical software package. Quantitative variables “shunt”, “age”, “weight”, “height”, “BSA” and “interval” and qualitative variables “gender”, “hepaticdisease” and “tumortype” were includes in this study.

The first step was to verify that our data follows a normal distribution. For that purpose, Komolgorov-Smirnov test for normality of shunt data distribution was performed. Considering an hypothesis test, where H0: the data follows a normal distribution and H1: the data does not follow a normal distribution, since p-value of the Komolgorov-Smirnov test is less than 0.05, H0 is rejected and the hypotheses of data normal distribution is rejected (Table 19). In addition, Q-Q plot shows that distribution of the observed values does not present a shape close to that of the normal line (Figure 14).

Table 19: Kolmogorov-Smirnov test to test normality of shunt distribution (adapted from SPSS).

	Kolmogorov-Smirnov		
	Statistic	Gl	Sig.
Shunt (%)	0.157	75	0.000

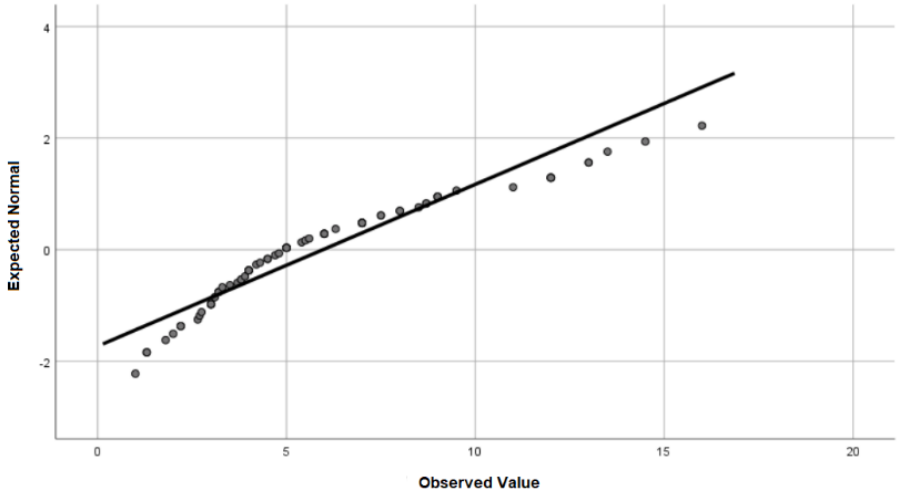

Figure 14: Normal Q-Q Plot for normal data of shunt (adapted from SPSS).

Thus, since the data do not follow a normal distribution, non-parametric tests will be used to assess whether there is an association between shunt and the other variables considered in study. In order to analyze the association between shunt and quantitative variables, the spearman rank correlation (SRC) test was performed. In qualitative variables, Wilcoxon-Mann-Whitney (MWU) test was used to analyze if there is difference in the median percentage of shunt between the groups in tested variables. For both, we will perform a hypothesis test. In spearman rho correlation test, considering H0: there is no correlation between variables and H1: there is correlation between variables, we will verify the p-value of correlation coefficient obtained for each comparison. In MWU test, we will consider H0: there are no significant differences between groups and H1: there are significant differences between variables in order to assess the p-value for the comparison between groups.

3. Results

3.1. Shunt and Quantitative Variables

To assess the strengh of association between shunt and the remaining quantitative variables, an analysis of the correlation between the quantitative variables considered for this study was performed. This analysis aims to calculate the SRC

coefficient in each of the tested associations. If this is statistically significant ($p < 0.05$), we can assume that there is correlation between the variables under study.

Therefore, the analysis was carried out according to the bivariable correlation model of the variables "shunt", "age", "weight", "height", "BSA" and "interval".

Table 20: SRC test to evaluate correlation between shunt and the other quantitative variables (adapted from SPSS data analysis).

		Age	Interval	BSA	Height	Weight
Spearman´s Rho for Shunt (%)	Correlation Coefficient	-0.052	-0.033	-0.331 **	-0.199	-0.343 **
	Sig. (2-tailed)	0.660	0.779	0.008	0.117	0.006

** Correlation is significant at the 0.01 level (2-tailed).

By table 20 analysis, we can verify a significant SRC ($p < 0.01$) between the variables shunt and BSA ($p = 0.008$) and shunt and weight ($p = 0.006$). We also found that there is no significant correlation between shunt and height ($p = 0.117$; $p > 0.01$). Since BSA is calculated from the weight and height variables, we assume that the significant interaction that occurs between shunt and BSA is by the influence of weight on the shunt. This analysis also allows us to assess that, apart from height, age and interval do not have a statistically significant correlation with shunt ($p = 0.660$ and $p = 0.779$, respectively).

SRC coefficient obtained is negative for weight and, consequently, for BSA. It is possible to conclude that variables ratio is negative (negative SRC coefficient) and an increase in shunt value is related to a decrease in weight and BSA value, as we can observe in scatterplots of BSA and weight distribution for shunt in figure 15. However, the scatterplot show that this association is quite weak, since R^2 value is close to zero for BSA ($R^2 = 0.061$) and weight ($R^2 = 0.096$).

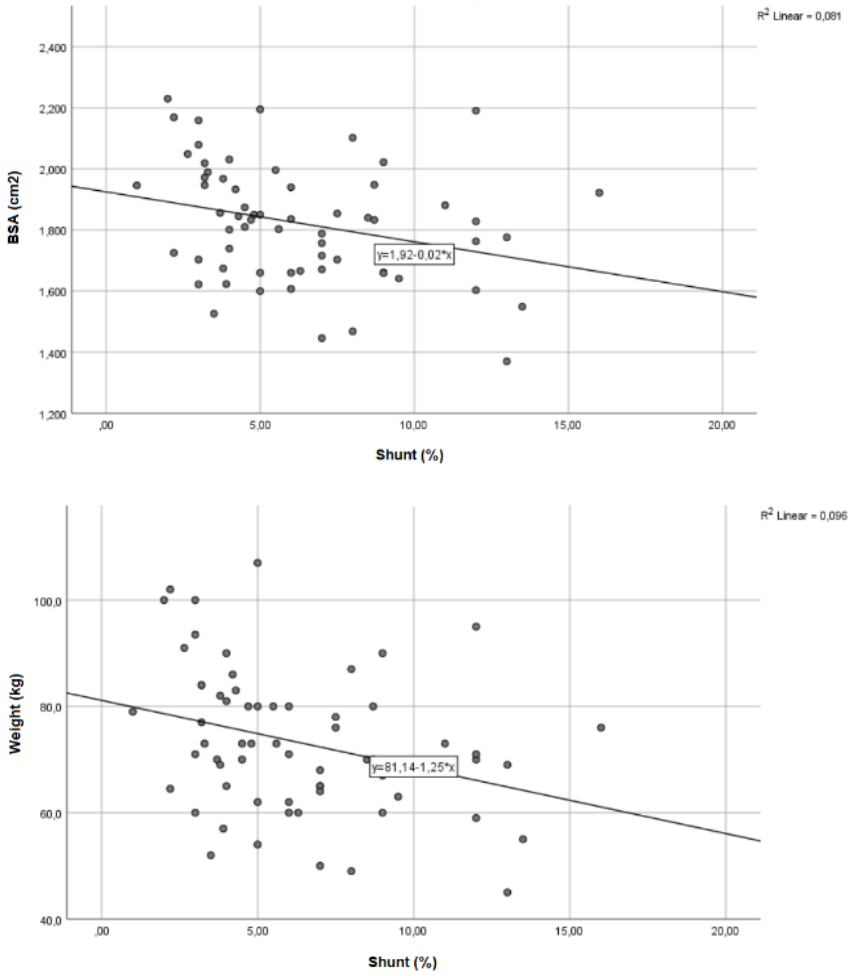

Figure 15: Scatterplots of BSA vs shunt and weight vs shunt (adapted from SPSS data analysis).

3.2. Shunt and Qualitative Variables

To assess the strengh of association between shunt and the qualitative variables considered, it is required to perform the MWU test (Wilcoxon rank-sum test), in order to compare if there is significant differences in value of shunt between the groups for each qualitative variable.

3.2.1. Gender

The box plot in figure 16 shows the distribution of shunt values for female and male groups and practically similar median values in both. Male group has a greater amplitude, also derived from their higher percentage in the cohort. To verify whether the

differences between the male and female groups are statistically significant, it was performed MWU test and, the 2-tailed p-value obtained was 0.917 (table 21). Considering the p-value of 0.05, we cannot reject the hypothesisthat the percentage of shunt obtained is similar in both groups. These results support the proposition that there is no significant difference in shunt percentage between male and female groups.

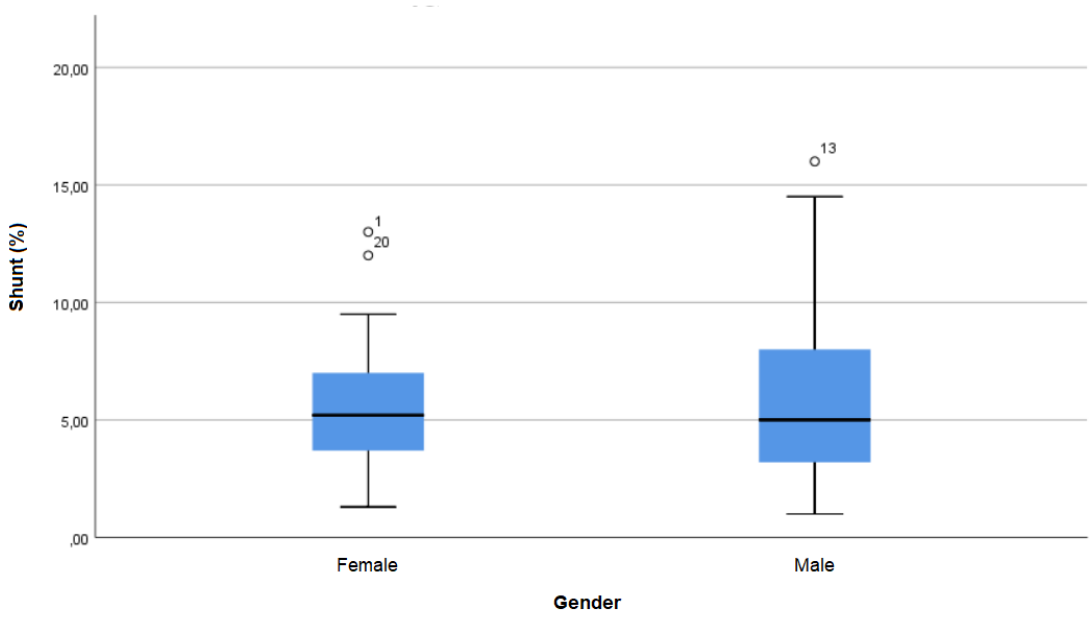

Figure 16: Box plot of distribution of shunt data in male and female groups (adapted from SPSS data analysis).

Table 21: MWU test for comparison between male and female groups (adapted from SPSS data analysis).

	Shunt (%)
Mann-Whitney U	574.000
Wilcoxon W	2005.000
Z	-0.105
Asymp. Sig. (2-tailed)	0.917

3.2.2. Hepatic Lesion

Box plot analysis of shunt distribution in primary (HCC) and metastatic/secondary (CRC, NET, CC, CPC and GIST) disease allow to verifying a different median value between groups. The higher shunt value of the patients is an outlier value in the primary hepatic disease group (ID=13). However, the median value reveals to be superior in the metastatic hepatic disease group (figure 17).

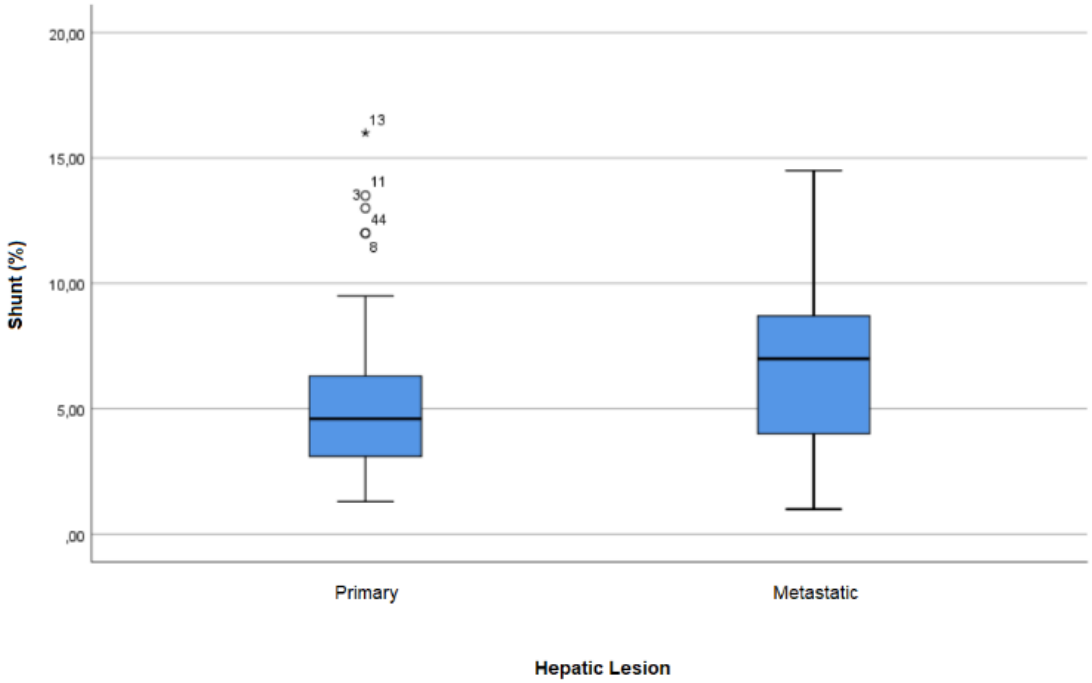

Figure 17: Box plot of distribution of shunt data for primary and metastatic hepatic lesion (adapted from SPSS data analysis).

In order to verify if the visual discrepancies values in shunt distribution between groups are statistically significant, MWU was performed, showing no statistically significant differences between both groups, once the p-value obtained is superior to 0.05 ($p = 0.077$).

Table 22: MWU test for comparison between primary and metastatic disease groups (adapted from SPSS data analysis).

	Shunt (%)
Mann-Whitney U	504.500
Wilcoxon W	1585.500
Z	-1.769
Asymp. Sig. (2-tailed)	0.077

3.2.3. Tumor Type

Our patient cohort had several primary liver pathology locations, from HCC and HCC to CRC, NET, CPC and GIST metastasis. Figure 18 presents the box plot that shows shunt distribution for the different pathologies. In cases of CPC, GIST and CC, as there is only one patient for each one of the pathologies, the exact value of shunt reveale+d by the patient characterize the tumor type group in box plot.

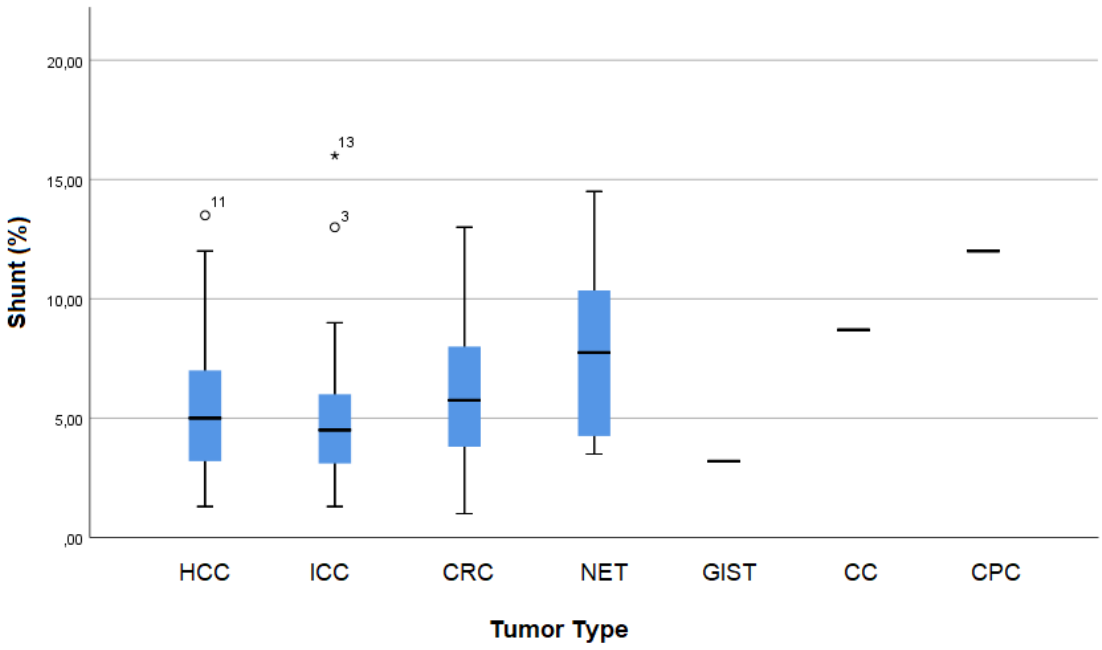

Figure 18: Box plot of distribution of shunt data in tumor type groups (adapted from SPSS data analysis).

After verifying that there are no relevant differences in shunt distribution between primary and metastatic liver disease, we will verify whether there are differences between the different groups of tumor type. For statistical purposes, the CPC, GIST and CC groups were not included in MWU tests due to the small sample in these groups (n = 1).

So, we performed MWU test for comparison between HCC and ICC groups (a), HCC and CRC groups (b), HCC and NET groups (c), ICC and CRC (d), ICC and NET (e) and CRC and NET (f).

Since no statistically significant difference s were obtained between primary and metastatic groups, it is expected that no relevant differences will be obtained in MWU test between the HCC and CRC (b), HCC and NET (c), ICC and CRC (d) and ICC and NET (e) groups. The p-value obtained for all these four comparisons was inferior to 0.05: p(b) = 0.430, p(c) = 0.96, p(d) = 0.330 and p(e) = 0.116, showing no statistically significant differences between the groups of primary and metastatic liver diseases.

MWU test was also carried out to compare shunt value in groups of primary hepatic disease, HCC and ICC (a) groups, and in groups of metastatic disease, CRC and NET (f) groups. The p-value obtained by MWU U test in (a) and (f) was no statistically significant too [p(a) = 0.317 and p(f) = 0.317; p > 0.05]. We can then conclude that there are no significant differences in shunt values between groups of primary hepatic disease and between the two statistically measurable groups of metastatic liver disease.

Table 23: MWU test for comparison between HCC and ICC groups (a), HCC and CRC groups (b), HCC and NET groups (c), ICC and CRC (d), ICC and NET (e) and CRC and NET (f) (adapted from SPSS data analysis).

	Shunt (%)					
	HCC and ICC (a)	HCC and CRC (b)	HCC and NET (c)	ICC and CRC (d)	ICC and NET (e)	CRC and NET (f)
Mann-Whitney U	224.500	225.000	71.000	123.500	41.000	54.000
Wilcoxon W	377.500	660.000	506.000	276.500	194.000	225.000
Z	-0.501	-.789	-1.663	-0.974	-1.573	-1.001
Asymp. Sig. (2-tailed)	0.616	0.430	0.096	0.330	0.116	0.317

3.2.4. Microspheres

Box plot of figure 19 presents LS distribution in the three types of microspheres used in SIRT. We found that SS group is the one with the greater amplitude in LS values, including patients with the highest and the lowest percentage of LS verified in the study. TS group is the one with the smallest amplitude, a fact that is justified by the disparate number of patients included in each group, 52 patients in SS and 7 in TS. However, despite the discrepancy in the number of patients, there is no such discrepancy at the median level in both groups, being even higher in the SS. On the other hand, QS group includes 16 patients and has a median lower than the TS and SS.

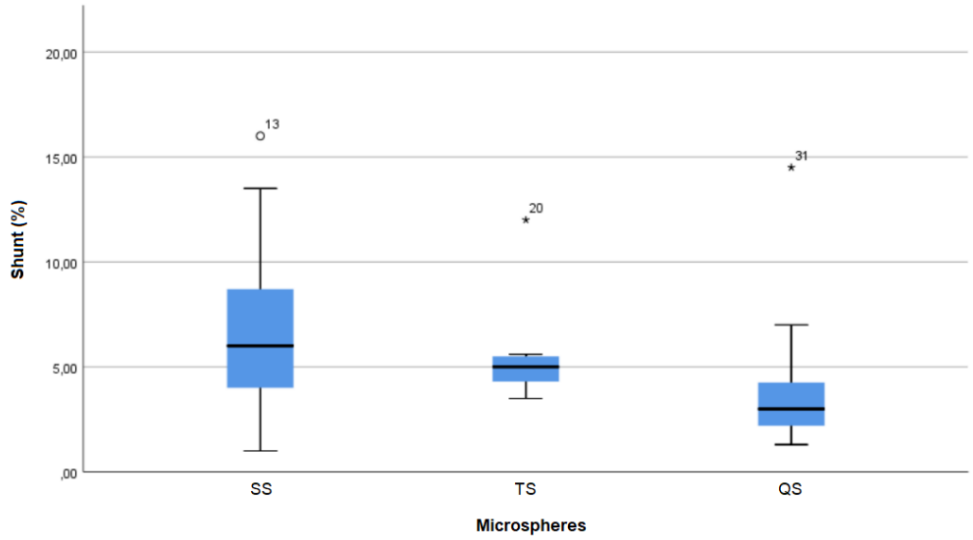

Figure 19: Box plot of distribution of shunt data in SS, TS and QS (adapted from SPSS data analysis).

In order to assess whether the type of microsphere used influences the percentage of shunt and complement the observational analysis made to the box plot, MWU test was used to check for any differences in shunt distribution for the 3 groups of microspheres used in SIRT. MWU test was performed for each group of 2 variables, SS and TS (a), SS and QS (b) and TS and QS (c). Statistically significant differences were obtained in (b) ($p = 0.000$; $p < 0.01$) and (c) ($p = 0.022$; $p < 0.05$). In (a), p-value obtained was superior to 0.05 ($p = 0.526$), showing that there are no significant differences in shunt distribution between groups analyzed.

Table 24: MWU test for comparison between SS and TS groups (a), SS and QS groups (b) and TS and QS groups (c) (adapted from SPSS data analysis).

	Shunt (%)		
	SS and TS (a)	SS and QS ** (b)	TS and QS * (c)
Mann-Whitney U	155.000	174.500	22.500
Wilcoxon W	183.000	310.500	150.500
Z	-0.633	-3.495	-2.241
Asymp. Sig. (2-tailed)	0.526	0.000	0.022

*Differences are significant at the 0.05 level (2-tailed)
**Differences are significant at the 0.01 level (2-tailed)

4. Data Analysis

The distribution data from the patients who underwent SIRT at IPO Porto do not present a normal distribution, as was verified by the histogram, Q-Q plots and the $p < 0.05$ obtained from the Kolmogorov-Smirnov normality test. Thus, non-parametric tests were chosen to carry out both the correlation assessment between the shunt and quantitative variables and differences in shunt distribution between groups of qualitative variables. These tests have less power compared to parametric tests, being much more conservative since they do not find so many differences when they really exist.

The non-parametric tests allowed us to verify that there is an interaction of weight, BSA, and type of microspheres used in the percentage of shunt obtained. The correlation between weight and shunt and, consequently, between BSA and shunt, is statistically significant. SRC coefficient shows that there is a negative and extremely tenuous relationship between the variables, thus, the increase in shunt is related to a decrease in weight and BSA.

Regarding the type of microspheres, we know that radiopharmaceutical used for shunt research is not the same for the 3 different procedures. Shunt calculation in ^{90}Y-SIRT is performed using ^{99m}Tc-MAA. As SS and TS are ^{90}Y-resin microspheres and ^{90}Y-glass microspheres, respectively, it is understandable that we obtained not significant differences obtained in shunt values between the two groups, since the same radiopharmaceutical is used in LS for SS and TS. The main objective in this phase is to

assess if there are significant differences in shunt values between the groups of ^{90}Y-microspheres and the group of ^{166}Ho-microspheres.

In ^{166}Ho-SIRT, shunt determination is performed with a small amount of ^{166}Ho-microspheres, similar to QS administered in therapeutic phase. Analyzing the differences in shunt between the SS and QS and TS and QS, MWU test provides a statistically significant evidence in shunt value for both comparisons, showing that there are significant differences in the percentage of shunt between the groups. Thus, there are significant differences in the percentage of shunt obtained with ^{99m}Tc-MAA in relation to the scout dose with ^{166}Ho-microspheres, and the value of shunt obtained with ^{166}Ho-microspheres is significantly lower, as we can observe in box plot.

This clincal practice corroborates the biggest advantage inherent to QS procedure over SS and TS, which is the scout dose. The use of the same radiopharmaceutical for LS calculation and for therapeutic phase allows an extremely reliable prediction of intra and extrahepatic microspheres distribution. Despite all the clinical evidence indicating the safety and reliability of ^{99m}Tc-MAA shunt assessment in SS and TS use, the distribution pattern will present some discrepancies and cannot be compared to ^{166}Ho-microspheres scout dose use in the use of QS. In ^{90}Y-SIRT, we are using different particles (MAA and microspheres), with a different number, size, density and morphology, as well as different isotopes (^{99m}Tc and ^{90}Y) in the pre-therapeutic and therapeutic phase. The results obtained show that the percentage of shunt obtained in patients who underwent ^{166}Ho-SIRT is lower than that obtained in patients who underwent ^{90}Y-SIRT. LS is an undesirable event, since microspheres deposition in the lungs decreases the effectiveness of SIRT and can damage pulmonary tissue. As LS obtained is inferior in QS group, we can take the advantage of using QS use over SS or TS.

Although we had a very representative sample of patients (n = 80), we would certainly have more reliable results if the number of patients who underwent SIRT with QS was superior. However, the use of QS is still a recent procedure and ^{90}Y-microspheres (mainly by SS) are still the most required type of microspheres for this purpose in IPO Porto. This retrospective analysis included 16 patients in QS group, a number that is not very representative but that which is the possible given the time-line of this study. To assess more representative sample of patients in the QS groups, more time would be necessary.

The fact that it was not possible to have access to activity administered data, either in the pre-therapeutic phase or in the therapeutic phase, is a negative aspect of this study. Data about the activity administered to each patient would allow us to assess whether there would be a correlation between activity administered and percentage of

shunt obtained and if the differences observed between SS/TS and QS groups would be related to a small ^{166}Ho-microspheres scout dose activity in comparison to ^{99m}Tc-MAA.

VII. Conclusion and Future Perspectives

The review analysis and retrospective clinical practice of this dissertation reinforce, above all, evidence of the safe and effective applicability of SIRT in several clinical contexts, mainly in HCC and CRC metastases.

In addition, it is proven that ^{166}Ho-microspheres is a valuable alternative to ^{90}Y-glass or resin mcirospheres in SIRT. This recent technique has clear advantages over existing ^{90}Y-microspheres techniques, mainly due to the introduction of ^{166}Ho-scout in the pre-therapeutic phase, thanks to the possibility of acquiring MRI acquisition in post-therapeutic phase and image processing software Q-Suite.

Given its recent past, prospective studies have been carried out to further investigate the role of ^{166}Ho-microspheres in SIRT, in order to improve this therapeutic option, mainly to optimize the dosimetry model and image processing.

Despite the benefits that are already recognized, prospective clinical trials as HEPAR Primary are essential to evaluate RR and overall long-term survival in ^{166}Ho-SIRT, to verify if they are significantly higher when ^{166}Ho-microspheres are applied compared to ^{90}Y-microspheres.

Furthermore, application of the dual isotope imaging in shunt evaluation, using ^{166}Ho-scout combined with ^{99m}Tc-labelled colloid, must be explored. ^{166}Ho-microspheres simulates microspheres distribution into target tissue and ^{99m}Tc-labelled colloid allow non-target liver tissue delineation. This tool can be an asset in much more reliable and personalized dosimetry planning.

The combination of SIRT with other therapeutic approaches in the treatment of liver tumors is also an option that has been increasingly explored. Prospective clinical trials are being performed to evaluate the improvement in RR and OS by combination therapies use, as HEPAR PLUS to assess ^{166}Ho-SIRT role combined with ^{177}Lu-DOTATATE for liver metastases of NET patients, or HORA EST to evaluate the combination of RFA and ^{166}Ho-SIRT in HCC patients.

VIII. Appendixes

Appendix I - Liver cancer epidemiology

Table A.I 1: Estimated number of incident cases and deaths, liver, males, all ages. Adapted from (1).

Population	Incidence	Mortality
Eastern Asia	343 523	312 228
South-Eastern Asia	65 407	65 238
North America	29 900	22 889
South-Central Asia	29 027	27 060
Northern Africa	19 912	19 570
Southern Europe	17 702	14 800
Western Europe	17 300	15 896
Central and Western Europe	13 737	13 581
South America	13 565	12 738
Western Africa	10 778	10 747

Table A.I 2: Estimated number of incident cases and deaths, liver, females, all ages. Adapted from (1).

Population	Incidence	Mortality
Eastern Asia	123 804	115 704
South-Eastern Asia	23 603	23 191
South-Central Asia	14 983	13 752
North America	11 951	11 450
South America	10 683	10 235
Central and Eastern Europe	9 047	9 164
Northern Africa	8 023	7 935
Southern Europe	7 324	7 196
Western Europe	6 359	6 741
Western Africa	5 796	5 609

Table A.I 3: Estimated age-standardized incidence and mortality rates in 2018, liver, males, all ages (1).

Population	Incidence	Mortality
Eastern Asia	26.8	24.2
Micronesia	25.6	19.8
South-Eastern Asia	21.0	20.9
Northern Africa	20.8	20.4
Polynesia	14.4	10.6
Melanesia	14.2	13.1
Western Africa	11.1	11.1
Southern Europe	10.9	8.3
North America	10.1	7.1
Middle Africa	9.4	9.5

Table A.I 4: Estimated age-standardized incidence and mortality rates in 2018, liver, females, all ages (1).

Population	Incidence	Mortality
Melanesia	8.9	8.3
Eastern Asia	8.7	8.0
Northern Africa	7.8	7.7
South-Eastern Asia	6.6	6.5
Central America	6.0	5.5
Western Africa	5.7	5.6
Micronesia	5.4	4.9
Polynesia	4.1	4.5
Middle Africa	3.9	3.9
Caribbean	3.8	3.7

Appendix II - ECOG performance status

Table A.II 1: General health status assessment by ECOG performance status.

Status	Definition of Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair for more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix III - Child-Phug classification

Table A.III 1: Liver function assessment by Child-Phug classification.

Measure	1 point	2 points	3 points
Ascites	Absent	Slight	Moderate
Serum Bilirubin	<2.0	2.0-3.0	>3.0
Serum Albumin	>3.5	2.8-3.5	<2.8
Prothrombin Time	<4	4-6	>6
Encephalopathy grade	---	1-2	3-4

Appendix IV - Response criteria for target lesions

Table A.IV 1: Clinical endpoints definition according to WHO, EASL, RECIST 1.1 and mRECIST criteria.

	WHO	EASL	RECIST 1.1	mRECIST
Complete Response (CP)	The disappearance of all target lesions (26)	complete disappearance of all known disease and no new lesions determined by two observations not less than 4 weeks apart (30)	the disappearance of all target lesions for a period of at least one month (155)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (27)
Partial Response (PR)	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the	>50% reduction in total tumor load of all measurable lesions determined by two observations not less than 4 weeks apart (30)	At least 30 % decrease in the sum of the longest diameter of measures lesion, taking as reference the baseline sum of the longest diameter (155)	At least a 30% decrease in the sum of diameter rs of target lesions, taking as reference the baseline sum diameters (27)

	baseline sum longest diameter (26)			
Stable Disease (SD)	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started (26)	does not qualify for CR/ PR or progressive disease (30)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since the treatment started (155)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. The sum must also demonstrate an absolute increase of at least 5 mm (27)
Progressive Disease (PD)	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or	>25% increase in size of one or more measurable lesions or the appearance of new lesions (30)	>20% increase in the sum of longest diameter of measured lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (155)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study (27)

	the appearance of one or more new lesions (26)			

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