A Phase II Trial Assessing the Safety and Efficacy of Sorafenib in Combination with Yttrium^{90} Radioembolization in Patients with Advanced Hepatocellular Carcinoma.

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Abstract

In a phase II trial we investigated the safety, tolerability and efficacy of sorafenib in combination with ytrium^{90} radioembolization in advanced hepatocellular carcinoma (HCC). 26 patients with advanced HCC were recruited and were treated with sorafenib continuously and ytrium^{90} radioembolization 6 to 8 weeks after the beginning of sorafenib. The most common adverse events were constitutional symptoms such as fatigue (23.1%), and weight loss (23.1%) as well hand-foot skin reaction (19.2%), and abdominal pain (23.1%). When looking at grade 3 and 4 events, diarrhea (11.5%), hand-foot skin reaction (15.4%) and abdominal pain (15.4%) were the most frequent. Overall, the type and rate of adverse events observed in our study did not differ widely from those seen with sorafenib or Y90 radioembolization alone.

Overall median survival was 395 days (12.97 months) and survival rate at 1 years was 65.4%. Alcoholic cirrhosis, the absence of macroscopic vascular invasion or extrahepatic disease, and decrease in AFP with sorafenib were associated with prolonged survival.

The proposed regimen was associated with a 21% increase in survival when compared to sorafenib alone and may also confer a survival advantage when compared to yttrium^{90} radioembolization.

Dans cette étude de phase II, la sécurité, la tolerabilité et l'efficacité de sorafenib combiné avec la radioembolization yttrium^{90} sont investiguées.

26 patients avec un carcinome hépatocellulaire avancé ont été recrutés et ont reçu sorafenib en continue ainsi que la radioembolization ytrium90 entre 6 à 8 semaines après le de but du sorafenib.

Les effets secondaires les plus fréquents sont des symptômes systémiques tels que la fatigue (23.1%), la perte de poids (23.1%), le syndrome pieds-main (19.2%) ainsi que la douleur abdominale (23.1%). La diarrhée (11.5%), le syndrome pieds-mains (15.4%) et la douleur abdominale sont les effets secondaires de grade 3 ou 4 les plus

fréquents (15.4%). De manière générale, le type et la fréquence des effets secondaires observés dans cette étude ne diffèrent pas grandement de ceux obtenus avec un traitement par sorafenib ou radioembolization seul.

La survie médiane est de 395 jours (12.97 mois) et le taux de survie à 1 an est de 65.4%. La cirrhose d'origine alcoolique, l'absence d'invasion vasculaire macroscopique ainsi que la baisse de l'AFP avec sorafenib sont associés avec une prolongation de la survie. Le régime de traitement proposé dans cette étude est associé avec une augmentation de la survie de 21%.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common and deadliest cancers worldwide. In Canada, its incidence is rising along with the associated mortality. Most patients tend to present with advanced stage disease for which treatments are extremely limited. In 2007-2008, sorafenib became the first approved systemic treatment for advanced hepatocellular carcinoma. Around the same time, loco-regional treatments such as yttrium^{90} radioembolization were brought back to clinical practice. Despite those advances, the prognosis for patients diagnosed with advanced hepatocellular carcinoma remains poor. This study aims at investigating the safety and tolerability of sorafenib in combination with yttrium^{90} radioembolization in patients with advanced HCC as well as gather early efficacy data for this regimen.

Hepatocellular Carcinoma

a. Epidemiology

i. Incidence and Mortality

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer representing 85-90% of the primary liver cancer burden worldwide (1). In 2008, an estimated 748,300 new cases and 695,900 deaths occurred worldwide. The prognosis is poor with a ratio of mortality to incidence of 0.93. (2) In men, it is the fifth most frequently diagnosed cancer and the second leading cause of cancer-related death globally. In women, it is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death. In almost all populations, males have

higher liver cancer rates than females, with male: female ratios usually averaging between 2:1 and 4:1(1, 3).

There is considerable regional heterogeneity in the incidence of liver cancer worldwide and 85% of the disease burden is found in developing countries(4). The highest age adjusted incidence rates (>20 per 100,000) are reported in East and Southeast Asia (North and South Korea, China, Vietnam) and sub-Saharan Africa (Cameroon and Mozambique). Southern Europe, including Italy, Spain and Greece, has medium-high incidence rates (5-20/100,000), North America intermediate incidence (5-9/100,000), while South and Central America, as well as the rest of Europe are low-incidence areas (<5 per 100,000) (5, 6). China alone accounts for more than 55% of all cases worldwide, with age-standardized incidence rates of 37.9 in male and 14.2 in female (6).

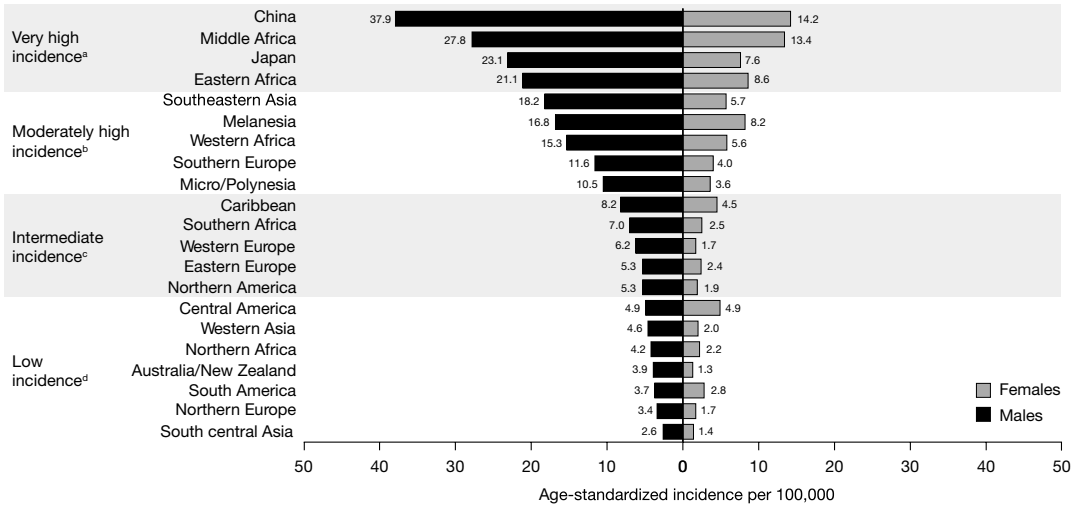

Figure 1. Global variation in liver cancer incidence rates. Reproduced from Parkin DM, Bray F, Ferlay J et al. Global cancer statistics, 2002. CA Cancer J Clin (7)

In Canada, in 2012, HCC accounted for about 1% of all new cancer diagnoses and death with an estimated 2000 new cases. Age-standardized incidence was

4/100,000 (male, 7/100,000; female, 2/100,000) and a male to female ratio of approximately 3:1. (8)

ii. Etiology

Major risk factors for hepatocellular carcinoma are Hepatitis B Virus (HBV) infection, Hepatitis C Virus (HCV) infection, alcoholic liver disease, non-alcoholic fatty liver disease, aflatoxin B1 exposure as well as the rarer hereditary hemochromatosis, alpha1-antitrypsin deficiency, hereditary tyrosinemia and Wilson's disease. HCC is unique in that, most of these risk factors lead to chronic liver disease and cirrhosis, which is detected in 90% of HCC cases and is therefore the largest single risk factor. The risk of developing HCC in patients with cirrhosis varies based on the underlying condition and the stage of the cirrhosis. The highest 5-year cumulative risks are seen in patients with HCV (17-30%), hemochromatosis (21%), HBV (10-15%), and alcoholic cirrhosis (8%). (1, 4, 6, 9)

Globally, chronic HBV infection is the most frequent underlying cause of HCC and accounts for approximately 50% of all cases worldwide, 60% in developing countries and about 23% in developed countries. It is also the cause of almost all childhood cases. The highest incidences rates of HCC are reported in regions where hepatitis B virus infection is endemic like in Southeast Asia and sub-Saharan Africa where over 8% of the populations is chronically infected with the virus. Indeed, the increased HCC risk associated with chronic HBV infection particularly applies to areas where HBV is transmitted from mother to newborn or from siblings at an

early age resulting in a chronic infection in up to 90% of patients. (1, 4). Chronic HBV infection carries a lifetime risk of HCC of 10 to 25%(6). Risk is furthered increased by male gender, family history of HCC, increased duration of infection, exposure to aflatoxin, alcohol abuse, smoking, co-infection with HCV or hepatitis D virus, high level of viral replication, and HBV genotype C infection (1, 6, 10). HBV can cause HCC by two different mechanisms: a direct and an indirect. The indirect mechanism of inflammation leads to chronic liver disease and cirrhosis in which prolonged immune reaction and increased hepatocyte turnover contribute to oncogenesis. In the direct mechanism, viral integration into the genome of the infected cell causes oncogene activation, insertion mutation, chromosomic alteration and genome rearrangements (9). In the majority of HBV related HCC cases (70-90%), liver cirrhosis is present. (4, 10)

Chronic Hepatitis C virus (HCV) infection is associated with 33% of HCC cases in developing countries and 20% in developed countries. Chronic HCV infection increases the risk of HCC 15 to 20 times, when compared to non-infected individuals, and it takes on average about 30 years after the initial exposure to HCV to develop HCC. The risk of developing HCC is especially high among those patients who develop cirrhosis and is also increased in patients who became infected at an older age, are male, are co-infected with HIV, and have a heavy alcohol intake (>50g/day) (1, 4).

Alcohol consumption especially if heavy (defined as ingestion of > 50 to 70g/day)

and HCC risk increases in a liner fashion when intake is superior to 60g per day. Alcohol does not appear to have a direct carcinogenic effect but rather increases the risk of cirrhosis which itself is a risk factor for HCC. There is also a strong synergistic effect between heavy alcohol consumption and HBV or HCV (1, 6).

Aflatoxin (AFB_1) is a mycotoxin produced by the *Aspergillus* fungus, which is classified as a potent carcinogen by the International Agency for Research on Cancer (11). It grows on many substrates, including corn, peanuts, and soybeans especially when stored in warm, and humid conditions. It is especially prevalence in Eastern Asia and Sub-Saharan Africa. AFB_1 is metabolized into an active compound, which can bind to DNA and produce mutations. A characteristic mutation of the p53 gene ($p53\ 249^{ser}$) is observed in up to 60% of all HCC diagnosed in area of high aflatoxin exposure (1, 6). A strong synergistic effect exists between aflatoxin and HBV since aflatoxin and HBV increase the risk of HCC 4 and 7 folds respectively but the two combined produce a 60 fold increase in the risk of developing HCC (12).

In Western countries, 30 to 40% of all patients with HCC do not present with any of the previously described risk factors. However, epidemiological studies have revealed that they have features suggestive of non-alcoholic steatohepatitis (NASH) including a high prevalence of obesity and diabetes. Diabetes has been shown to be significant risk factor for HCC. In one large, US based, cohort study including 173,643 patients with and 650, 620 patients without diabetes, HCC incidence was found to be more than doubled in patients with diabetes. (13)

In Canada, the most common etiology associated with HCC is HCV. Indeed in 2000, chronic infection with hepatitis C had an incidence rate of 61.0 per 100 000 people compared to 3.2 per 100 000 for chronic HBV. (14)

iii. Trends

The incidence of HCC is increasing in the Western World including in the US, the UK, Japan, Spain and Australia (1). In the United States, the incidence of HCC has more than tripled in the past two decades and HCC due to Hepatitis C virus infection is now the fastest-rising cause of cancer related death (1, 4, 6, 15). Other factors such as the increase in obesity and diabetes rates also contribute to this trend.

Furthermore, despite a general decline in cancer mortality rate for most cancer sites, mortality for HCC is increasing and is the fastest growing case of cancer related death in men. (1)

In Canada, similar trends are observed. Between 1984 and 2000, the age-adjusted incidence rate increased by 38% in both genders. Over the same period, mortality increased by 48% for men and 39% for women. Between 1998 and 2007, the incidence rate of liver cancer continued to increase by 3.6% per year, and the mortality rate by 2.2% per year in males. In females, the incidence rate increased by 2.4% per year. (14, 16)

In Canada, hepatitis C is the primary risk factor for HCC and is mostly responsible for the reported increased in incidence.(14) As seen in the US, the rise in obesity and

diabetes prevalence may also play a role. The incidence of HCC in Canada is expected to continue to rise given the large group of people infected with HCV and it is also expected to affect younger age cohorts. In one study, age-adjusted incidence rates were projected to increase by 73% in males and 28% in females from 1996 to 2015. (17) Some of the observed increase may also be explained by the rise in immigration from world regions where risk factors for liver cancer, such as hepatitis B virus infection and exposure to aflatoxins, are prevalent. (16)

b. Advanced Hepatocellular Carcinoma

i. Staging

The need for accurate prognostic data as well as comparable clinical trial populations has driven the development of prognostic and classification algorithms. Numerous systems, most of them linking pathological, biochemical or clinical parameters to survival, have been proposed including the Okuda, the CLIP, and the Taipei integrated. (18)

First published in 1999, the Barcelona Clinic Liver Cancer (BCLC) staging not only classifies patients according to tumour burden, underlying liver dysfunction and patient symptoms but it also links each stage to specific interventions (19).

Since then, the BCLC has been validated in multiple studies and has become the most widely used and preferred staging system. It has also been updated to incorporate new validated therapeutics. (18, 20)

In 2010, the American Hepato-Pancreato-Biliary Association second expert consensus conference on HCC concluded that no single staging system is applicable to all patients with HCC. However, the consensus recommended the use of the

Barcelona Clinic Liver Cancer (BCLC) classification in patients who are not candidates for liver transplantation or resection. (21)

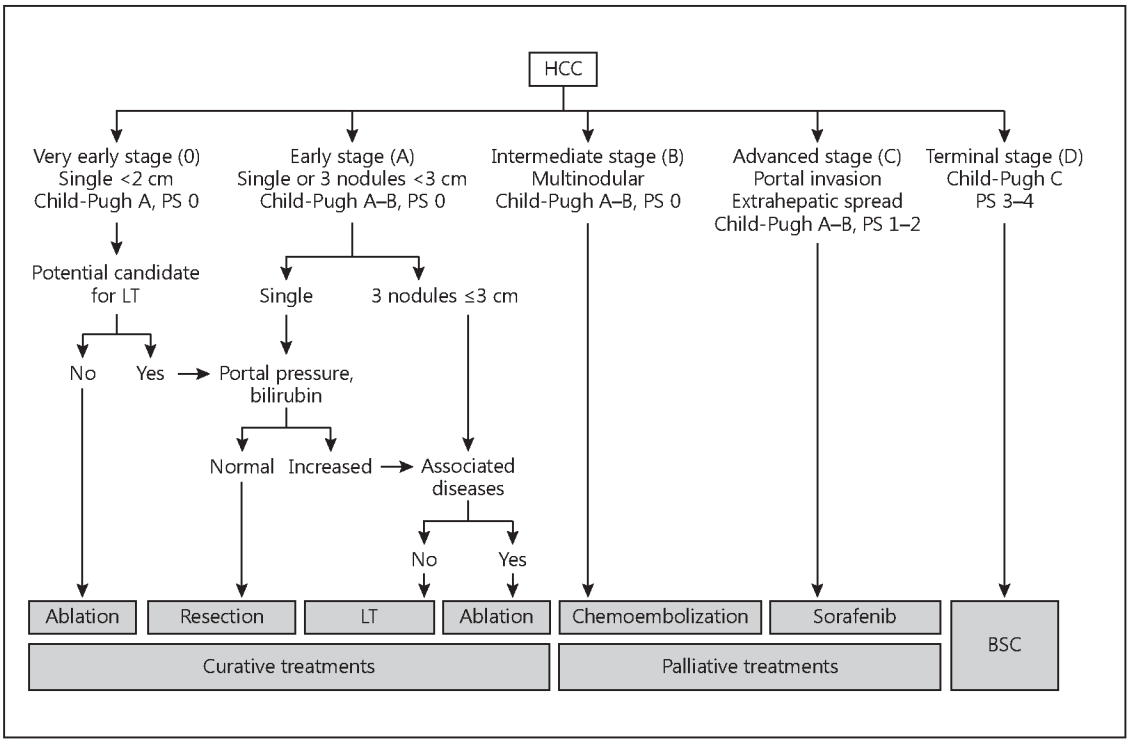

Figure 2. The BCLC staging and treatment strategy – Reproduced from Forner A, Bruix J. The size of the problem: clinical algorithms. Digestive diseases. 2013;31(1):95-103. (18)

We will focus on the advanced stage disease since it is the population selected for this study. According to BCLC classification, advanced stage (C) is characterized by portal invasion, extrahepatic spread or mild symptoms (performance status of 1 or 2) with a Child-Pugh liver function score of A or B. It is associated with a survival of 4-10 months if left untreated. (18, 22)

ii. Treatments

At the time of diagnosis less than 20% of patients with HCC are eligible for potentially curative treatments such as surgical resection, liver transplant, or local ablation. For the remainder, treatment focuses mostly on transarterial

chemoembolization (TACE) and sorafenib depending on the stage of the disease. External beam radiation and systemic chemotherapy play a limited role in HCC. According to the BCLC staging and treatment algorithm, TACE is reserved for patients with stage B disease, and experimental treatments and now sorafenib for patients with BCLC stage C. We will review treatment for advanced HCC (BCLC-stage C) only since it is the focus of this study.

In a meta-analysis including 503 patients, TACE was shown to have "a beneficial survival effect"(23) compared to conservative management in patients who were not candidate for surgical management but had disease limited to the liver. (23, 24) However, TACE was shown to be associated with complications, liver decompensation and extensive necrosis in patients with portal vein thrombosis and is therefore not recommended in this subgroup. (23, 25)

For patients with BCLC stage C disease or patient who progressed and were ineligible for TACE, multiple systemic chemotherapy agents have been evaluated, but to this day there is no evidence that systemic chemotherapy improves overall survival in any subset of HCC patients. Prior to the introduction of sorafenib in 2006, doxorubicin both as a single agent and in combination with other drugs was the most commonly used chemotherapeutic agent. Its use was controversial given the conflicting results obtained in various randomized controlled trials. (26)

Other frequently used chemotherapeutic agents included 5-fluorouracil, gemcitabine, and cisplatin. Combinations of these agents have been shown to be

more effective than single agents in the treatment of advanced HCC, although minimal improvements in survival have been observed. (26, 27)

Presently sorafenib is the recommended first line therapy for BCLC – stage C disease as well as for patients who are ineligible for other therapies or are progressing after TACE and is licensed in Canada for that use.

Worldwide, the role of Yttrium-90 radioembolization in the treatment of HCC is still being investigated and varies according to treatment availability, cost, as well as physicians and institutions preferences. In Canada, Therasphere was licensed in February 2005 as a class III medical device for the treatment of hepatic neoplasia. It has also received the US Food and Drug Administration Humanitarian Device Exemption in 1999 for use in radiation treatment or as a neoadjuvant to surgery or transplantation in patients with unresectable HCC. SIR-Spheres are not presently licensed in Canada. (28) To date, there are no reported randomized control trials investigating the use of radioembolization in advanced HCC but numerous series provide information on its safety and potential efficacy in this study population.

2. Sorafenib

a. Molecular and biological characteristics

Sorafenib tosylate (BAY43-9006, Nexavar; Bayer, West Haven, CT) is an oral multikinase inhibitor with demonstrated anti-angiogenic and anti-proliferative effects. It acts by inhibiting the serine-threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors (VEGF) 1, 2, 3 and platelet-derived growth factor receptor. Both these pathways

have been implicated in the pathogenesis of HCC. (29)

b. Clinical data: Sorafenib in advanced HCC

In 2006, the results of a multicenter, uncontrolled phase II study of sorafenib in advanced hepatocellular carcinoma were published showing tolerability and possible efficacy. This study recruited 137 patient with measurable, histologically proven, inoperable HCC who had not received any prior systemic treatments and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, Child-Pugh scores of A or B and a life expectancy of at least 12 weeks. It also required patient to have elevated alphafetoprotein (AFP) level and adequate hematologic, hepatic and renal function. In this study, 61% of patients were over 65 years of age, 71% were male, 50% had an ECOG performance status of 0 and 50% of 1. Furthermore, 72% of patient had a Child-Pugh score of A. Patient received sorafenib 400 mg BID but were allowed 2 dose reductions for drug related toxicities (200 mg BID and 200 mg daily).

Drug related adverse events were classified and graded using the National Cancer Institute [Bethesda, MD] Common Toxicity Criteria v2.0. The most common drug-related adverse events were dermatologic (hand-foot skin reaction 5.1%), constitutional (fatigue 9.5%) and gastrointestinal (diarrhea 8.0% and anorexia 1.5%). No grade 4 events were observed. Best response achieved was stable disease (for 16 weeks or more) in 46% of patient, partial response in 3% and minor response in 8%. 48% had progressive disease by radiological assessment. Median overall survival with sorafenib treatment was 9.2 months with a median time to progression of 5.5 months. (30)

On the basis of those results, the SHARP (Sorafenib HCC Assessment Randomized Protocol Trial) trial, a large phase 3, multicenter, double-blind, randomized, placebo controlled clinical trial, assessing the safety and efficacy of sorafenib in patients with advanced HCC was conducted.

The SHARP trial population included patients with pathologically confirmed hepatocellular carcinoma who had not received any prior systemic or molecularly targeted therapy and who were not eligible for or had failed surgical or locoregional therapies. Patients also had to have an ECOG performance status of 2 or less, a Child-Pugh score of A, a life expectancy of 12 weeks or more and adequate hematologic, hepatic and renal function. (29)

602 patients underwent randomization (299 in the sorafenib group and 303 in the placebo group). The median age was 64.9 and 66.3 in the sorafenib and placebo group respectively. 87% of the patients were male, 97% had a Child-Pugh score of A, and 54% had an ECOG performance status of 0. 38% and 39% had an ECOG of 1 and 8% and 7% an ECOG of 2. The sorafenib and placebo group respectively included 18% and 17% of BCLC stage intermediate (stage B) and 82 and 83% of advanced stage (stage C) patients. Macroscopic vascular invasion, extrahepatic spread or both were present in 70% of the study population. 50% had no undergone any prior treatment while the other half had failed surgical or locoregional therapy.

Patients were randomized in a 1:1 ratio to received 400 mg BID of sorafenib orally or matching placebo. Treatment interruptions and up to two dose reductions using a pre-established protocol (first to 400 mg once daily and then to 400 mg every 2 days) were permitted for drug- related adverse effect. (29)

In 2007, the SHARP trial was terminated early given the positive results obtained at the second interim analysis. Indeed, sorafenib was found to confer a survival advantage of 3 months over placebo (HR: 0.69, p=0.00058). "This significant survival benefit represented a 31% relative reduction in the risk of death »(29) in the first year. The median overall survival was 10.7 months in the sorafenib arm versus 7.9 months with placebo. In subgroup analysis, the overall survival benefit remained significant except in patients with extrahepatic disease at the time of enrolment. (HR: 0.85 95% CI [0.64-1.14]). In the sorafenib group, time to radiological tumour progression (TTP) was also increased by 2.7 months (2.8 vs. 5.5 months) (HR: 0.58, p <0.001). On the other hand, time to symptomatic progression was not significantly different between the 2 groups (HR: 1.08, p=0.77)

As seen in the phase II trial, the most common adverse events reported were gastrointestinal, constitutional and dermatologic with diarrhea, weight loss, hand-foot skin reaction, alopecia, anorexia and voice changes being significantly more frequent in the sorafenib group. Of the Grade 3 and 4 adverse events only diarrhea (8% vs. 2 %) and hand-foot skin reaction (8% vs. <1%) were statistically significantly more frequent in the sorafenib group.

The rate of discontinuation due to adverse event was similar in both groups (38 % in sorafenib vs. 37% in placebo group). (29)

In 2007-2008, sorafenib became the first approved systemic treatment for patients with advanced HCC in Europe and various countries including the United States, and

Canada. Since then, sorafenib has emerged as the primary treatment for advanced HCC and to this day, remains the only systemic treatment shown to improve the outcome of this patient population. (29)

In order to further improve outcomes of patients with advanced HCC, trials of combination therapy involving sorafenib and targeting multiple signalling pathways are being conducted (clinicaltrial.gov). mTOR inhibitors are of particular interest since the mTOR pathway has been found to be aberrantly up regulated in around 50% of HCC samples and is thought to play a critical role in the pathogenesis of HCC (31, 32)

In a phase I trial of sorafenib combined with everolimus, biologically effective everolimus concentration could not be achieve at the maximum tolerated dose and further testing of this regimen has been abandoned. (33) Another phase I trial of sorafenib combined with temsirolimus demonstrated that this regimen had an acceptable safety profile and might have some efficacy. A Phase II is presently underway. (34)

Reports on series of patients treated with sorafenib in combination with other locoregional are also emerging. In one retrospective study involving 290 patients with advanced HCC and comparing sorafenib as a monotherapy to sorafenib with other locoregional treatments (including TACE or external beam radiation), no difference was found in the safety and tolerability of the two regimen. Median overall survival was increased in the sorafenib with other locoregional treatments arm reaching 8.5 months versus 5.5 months with sorafenib alone. (35)

A search on clinicaltrial.gov for studies involving sorafenib for patients with advanced HCC revealed that numerous clinical trials involving sorafenib in combination in gentamicin, transarterial chemoembolization, radioembolisation, and radiotherapy are also underway.

3. Yttrium 90 radioembolization

a. Clinical data

Historically, the use of radiotherapy in the treatment of HCC has been limited given the radiosensitive nature of normal hepatic tissues (36) and the risk of radiation induced liver disease (also called radiation hepatitis) which is the most clinically significant complication of radiation to the liver from an external source. (37) In order to deliver higher doses of radiation in a selective manner, arterially delivered devices have been developed taking advantage of the hypervascular nature and particular vascularization of HCC. Indeed, contrary to healthy hepatic tissue which relies mostly on the portal vein for its vascular supply, intrahepatic malignancies draw most of their blood supply from the hepatic artery, having up to 3 times more arterial supply than surrounding hepatic tissue. (38, 39).

Radioactive elements are injected through a selected hepatic artery and are consequently trapped in the tumoral microvasculature due to arteriolar capillary blockage. This technique, called radioembolization, allows for the delivery of high radiation doses in a highly selective fashion thereby offering efficacy and lowering the risk of Radiation Induced Liver Disease. (40)

The use of Yttrium-90 radioembolisation for cancer dates back to 1969 when Nolan and Grady observed 76 patients with incurable cancers (including 2 patients with HCC) who underwent an intra-arterial injection of Yttrium-90 oxide(41). This experience was followed by a study of 15 patients with primary and metastatic tumour to the liver who underwent bremsstrahlung scans post whole liver treatment with injection of Y-90 microspheres.(41)

In 1992, Shepherd et al. published the data of a dose escalation phase I trial of Yttrium-90 in 10 patients with HCC. Radioembolisation was done in 2 phases including a planning and a treatment phase. During the planning the presence of extrahepatic shunting was assessed using technetium-99m microsphere. If significant shunting to extrahepatic organs was found, the treatment phase wouldn't take place. This study not only helped refined the technique by showing the need for proper assessment of peritumoral vasculature and potential shunts but it also provided further safety data as well as some early efficacy data. "In 8 of the 10 patients, there was a significant concentration of Y-90 in localized tumour masses with tumour-to-liver perfusion ratios from 1.0:1-10.0:1." Post-treatment, All patients achieved stable disease for a median duration of 10 weeks (range, 5-64 weeks). The median survival was 18 weeks (range: 2-150 weeks) with 3 patients living longer than 1 year. No hepatic or hematologic complications were seen. One patient had a duodenal ulcer 2 weeks post treatment, which required surgical intervention. (42)

Multiple small trials of Yttrium-90 in HCC followed showing promising results in patients with HCC (43). Yan et al. conducted a study on 18 patients with HCC using 35 microns nondegradable 90-Y glass microsphere. Patients received 2442-5550 MBq. The mean absorbed dose was 30.33 Gy in healthy liver tissue and 88 Gy in tumour tissues. Mean tumour to healthy liver tissue ratio was 3:1with the highest being 14:1. “Fourteen patients were still alive after half a year's follow-up and 6 of these 14 were still alive after 1 year.” (44)

In 1994, another study done by Lau et al. using Y90 resin microspheres on 18 patients with inoperable HCC showed more positive survival data. In this trial, patient also underwent a two-step procedure (treatment planning followed by radioembolisation). The planning phase included selective hepatic angiography (HAG) with technetium 99m labeled macroaggregated albumin scan (Tc-MAA) for assessment of the lung shunting and of the tumour to normal (T/N) tissue ratio. Radioembolisation was only administered in patients found to have lung shunting of Tc-MAA less than 15%, no significant shunting to the gastrointestinal region, no multiple and complicated arterial blood supply to the liver on HAG, T/N ratio of Tc-MAA of more than 2 in the planning phase. The median survival was 30.6 weeks. Patients who received radiation doses greater than 120 Gy lived significantly longer: 55.9 weeks vs. 26.2 weeks ($P = 0.005$)(45). In a follow-up study by the same authors, 71 patients were included. Median survival was 9.4 months (range 1.8 to 46.4 months). Treatment was well tolerated and there was no bone-marrow toxicity, or clinical evidence of radiation hepatitis or pneumonitis. Estimated radiation doses delivered to tumour tissues ranged from 83 to 748 Gy (median 225

Gy) in the initial treatment and the highest cumulative dose reached was 1580 Gy. Two patients later underwent surgical resection and were found to have complete histological remission. Lower pre-treatment level of alpha-fetoprotein and higher tumour-to-normal uptake ratio of yttrium-90 microspheres were associated with prolonged survival. Furthermore, treatment was found to be effective in large tumours as well as postoperative recurrence and repeated treatments of residual or recurrent tumours could offer further palliation and prolonged of survival (46, 47)

In 2000, Dancey et al. published more safety and efficacy data on Yttrium 90 radioembolisation for HCC. 22 patients were enrolled but only 20 (9 with Okuda stage I, and 11 with Okuda stage II disease) were included in the efficacy analysis. Median survival was found to be 54 weeks and median time to tumour progression 44 weeks. Radiation dose >104 Gy (P = 0.06), tumour-to-liver activity uptake ratio >2 (P = 0.06), and Okuda stage I (P = 0.07) were associated with prolonged survival. The most common serious adverse events were elevations in liver enzymes and bilirubin and upper GI ulceration. (48)

In 2004, Carr et al reported the results of a study conducted on 65 patients with biopsy proven inoperable HCC. At baseline 50.8% of patients had bilobar tumour invasion, 15.4% of patients had over 50% tumour replacement of the liver and 27.7% had major portal vein thrombosis.

Median radiation dose was 134 Gy. Median survival was 649 days and 302 days for Okuda I (65%) and Okuda II (35%) respectively. Most common adverse events were lymphopenia in 75% of patient, transient elevation of liver enzymes (38.5%),

abdominal pain (13.8%), worsened ascites (12.3%) and cholecystitis (3%).(49) That same year, Salem et al. reported on the use of Y90 radioembolisation in patients with advanced HCC and portal vein thrombosis. All 15 patients developed increased bilirubin post treatment but only 2 had grade 1 or 2 and one grade 3 toxicity. There were no procedure related complications in this series. (50)

Also in 2004, Geschwind et al. reported data on 80 patients from a database of 121 patients who are received Y90. The patients included had unresectable HCC with ECOG score of 0-2, lymph node–limited extrahepatic HCC metastases, adequate pulmonary, hematologic and renal function. Patients were excluded if they had concurrent malignancy, HCC of the infiltrative type, bulky disease representing at least 70% tumour replacement of liver, tumour representing at least 50% replacement of liver with an albumin level <3.0 g/dL, prior intra-arterial liver-directed treatment, prior external beam radiation, evidence of any uncorrectable flow to the gastrointestinal tract observed on angiography or technetium-99 macroaggregated albumin scan, or a significant lung shunt. Up to two treatments per liver lobe were performed. Patients received either a fixed dose protocol of 100 Gy or a nominal fixed dose of 135-150 Gy. 44% of the patients had bilobar disease, 16% had >50% liver replacement by tumour. 90% had Child Pugh A and 10% Child Pugh B liver function. 68% were Okuda stage I. The Kaplan–Meier estimated median survival times were 628 days for Okuda stage I patients and 384 days for Okuda stage II patients. In this study, Child Pugh A liver function, AFP below 400ng/ml and tumour replacement < 50% were associated with prolonged survival. Grade 3 and over adverse events were mostly hepatic (28%) with increase serum bilirubin and

ascites being the most common. 13% of patient had pain. There was one fatal event of liver failure and 2 patients had cholecystitis. (51)

In 2005, Goin et al. reported data from the same database this time including all 121 patients treated between 1986 and 2003. Of the 121 patients, 51% were under 65 years of age, 77% were male, 98% had a diagnosis of HCC, 55% had bilobar disease, 25% had over 50% of the liver replaced by tumour, 25% had portal vein thrombosis. 80%, 19% and 1 % had Child Pugh scores of A, B, and C respectively. 57% were Okuda stage I, 39% Okuda stage II and 4 % Okuda stage III. This study did not report on overall median survival but rather tried to establish risk variables associated with poor outcome. High risk variables were defined as Infiltrative or bulk disease, poor liver function, non HCC, as well as lung shunt of > 30Gy. Median survival in patients with a high-risk variable was 108 days versus 466 days for patients who had none. (HR : 6.0/95%CI: 3.6–10.1/P < .0001).(52)

That same year, Salem et al. reported on a phase II study of 43 patients with unresectable HCC. 65% of patients were male, 53% had bilobar disease, 8% had over 50% liver involvement, and 20% had portal vein thrombosis. 65, 30, and 5% had ECOG score of 0,1, and 2 respectively. 30% had extrahepatic disease. Median survival for Okuda stage I and II patients was 24.4 and 12.5 months respectively and 20.5 and 13.8 months for Child-Pugh A and B/C. High-risk characteristics as defined in Goin et al (2005)(52), presence of ascites, ECOG performance status > 0, presence of extrahepatic disease, > 25% tumour burden, infiltrative disease, main portal vein thrombosis and alphafetoprotein >400 ng/mL were associated with poorer

outcome. Grade 3 or 4 adverse events were seen in 22 out of 23 patients with post-treatment information. 96% of patients had grade 3 or 4 lymphopenia, 14% had increased total serum bilirubin, 7% had ascites, 5% had elevated aminotransferase levels and 2% had fatigue (40).

In 2006, Kulik et al. presented clinical data on 35 patients with unresectable HCC treated with glass Y90 microsphere with the intent of downstaging to surgical resection, radiofrequency ablation of liver transplantation. 66% (23 of 34) of patients were successfully downstaged and 8 patients underwent liver transplantation and 1 surgical resection following treatment with radioembolisation. All patients were treated on an outpatient basis and the most common adverse events were fatigue and flu-like symptoms. One case of grade 3 toxicity was reported (bilirubin elevation). This study concluded that Y90 radioembolisation could be safely performed on an outpatient basis and should be further investigated for downstaging patients with HCC who are initially ineligible for potentially curative treatment modalities. (53)

That same year, Sangro presented data on 24 patients with HCC who were not candidate for surgery or other locoregional treatments. Patients were excluded if they had portal vein thrombosis and/or invasion and if they had extrahepatic disease (except abdominal lymph nodes). Median overall survival was 7 months.

In 2007, a panel of experts from the radioembolisation brachytherapy oncology consortium concluded that « there is sufficient evidence to support the safety and effectiveness of yttrium-90 (Y90) microsphere therapy in selected patients. »(54)

In 2008, Kulik et al. published data on 108 patients from 2 centers with unresectable

HCC with the purpose of comparing Y-90 radioembolisation in patients with portal vein thrombosis (PVT) and those without. 34% of patients had portal vein thrombosis, 17% had tumour burden greater than 50% of the liver. 63.58% of patients had Okuda stage I disease. Partial response rate using the WHO criteria was 42.2% and with EASL modification of WHO, response rate increase to 70%. 34.7% had stable disease while 23.1% had disease progression. Median survival was significantly longer in patients without portal vein thrombosis 467 days versus 304 days in patients with segmental PVT and 133.5 days in patients with main PVT. This study was followed by Woodall et al., which showed no difference between rate of complication between patients with and without PVT following treatment with Yttrium 90. (55)

In 2009, a structured meta-analysis of radioembolization in various cancers was published. 14 studies providing treatment outcome and involving a total of 425 patients with HCC were identified (38). Resin microsphere were found to have a higher rate of adverse event than glass (0.89 vs. 0.78 (p=0.02)). Median survival from time of treatment ranged from 7.1 to 21.0 months while median survival from

time of diagnosis or recurrence ranged from 9.4 to 24.0 months. (see table 1)

Study	Number (*n*)	Results									
		Tumor response on CT								Median survival (months)	
		CT performed in	Response measured at (months post ^{90}Y-RE)	RECIST[a]	CR (%)	PR (%)	SD (%)	AR (%)	PD (%)	From diagnosis (or reoccurrence)	From ^{90}Y-RE
Resin microspheres											
Lau et al. (1994) [31]	18	18	2	–	0	44	44	89	11	NR	7.1
Lau et al. (1998) [32]	71	71	2	–	0	27	65	92	8	9.4 (range 1.8–46.4)	NR
Lim et al. (2005) [19]	5	4	2	Yes	0	25	50	75	25	NR	NR
Sangro et al. (2006) [33]	24	21	2	–	NS	NS	NS	88	12	NR	7.1 (95% CI 2.1–12)
Jakobs et al. (2007) [24]	5	5	2–3	Yes	0	NS	NS	100	0	NR	NR
Glass microspheres											
Houle et al. (1989) [34]	7	7	NR	–	0	0	29	29	71	NR	NR
Andrews et al. (1994) [11]	1	1	2	–	0	0	0	0	100	NR	NR
Dancey et al. (2000) [35]	22	19	2–3	–	5	16	58	79	21	NR	12 (range 2–42)
Carr et al. (2004) [36]	65	65	3	–	3	28	40	71	29	Okuda I 12 (95% CI 2–42) Okuda II 10 (95% CI 6–20)	NR
Geschwind et al. (2004) [30]	100	NR	NR	NR	NR	NR	NR	NR	NR	NR	Okuda I 21.0 Okuda II 1.0
Liu et al. (2004) [37]	11	11	1–1.5	–	9	72	0	82	18	NR	NR
Salem et al. (2005) [38]	43	43	Varying	–	NS	NS	NS	79	21	Okuda I 24 (95% CI 18–28) Okuda II 12 (95% CI 9–17)	NR
Kulik et al. (2006) [40]	35	34	6 (0.8–16)	–	NS	NS	NS	88	12	NR	NR
Sato et al. (2006) [39]	19	19	5 (1.5–14)	–	NS	NS	NS	79	21	NR	NR

CR complete response, *PR* partial response, *SD* stable disease, *AR* any response (= CR + PR + SD), *PD* progressive disease, *NR* not reported, *NS* not specified
[a]Response measured and presented according to RECIST criteria [41]

Table 1 – Tumor responses and median survival after radioembolization in patients with HCC. Reproduced from Vente et al. (38)

Vente's meta-analysis marks a transition in radioembolization research. Up until that point, most published literature on radioembolization in HCC consisted of small retrospective studies involving less than 45 patients. The patients included were extremely diverse in terms of clinical stage of disease and radioembolization technique was not completely standardized. (38) In studies published in 2010 and after, patients were clinically staged at baseline using BCLC staging algorithm, Child-Pugh and ECOG scores. Standardized protocols for patient assessment, dose

calculation and treatment delivery were in place. (56, 57) Radioembolization had gone from "a procedure relying on local expertise to a routine procedure yielding predictable results in properly trained centers"(56).

1st Author	Year Published	Type of Study	n	Device	Inclusion Criteria	Exclusion Criteria
Kwok (58)	2014	Retrospective	30	resin	Inoperable HCC including BCLC stage B or C and BCLC stage A who refused or progressed on TACE	
Mazzaferro (57)	2013	Prospective	52	glass	patients with liver cirrhosis and HCC confined to the liver and not eligible to conventional curative treatments	• ECOG 2 • Extrahepatic spread • Tumour burden > 50%
Sangro (25)	2011	Retrospective	325	resin	« patients with HCC who were not suitable for radical therapies (e.g., resection, liver transplantation, local ablation) and were not considered good candidates for transarterial therapies or systemic therapy based on clinical judgment »	
Hilgard (55)	2010	Observational cohort	108	glass	nonresectability of HCC and BCLC C tumour stage OR BCLC A and B who are not eligible for selective TACE ECOG 0-2 Child Pugh ≤ 7	extrahepatic spread (except abdominal LN < 2 cm and lung nodules < 1 cm)
Salem (56)	2010	Retrospective	291	glass	« The decision to treat patients with Y90 as part of this study was made by consensus at our weekly multidisciplinary HCC conference »	extrahepatic disease - non" liver dominant"

Table 2 – Studies investigating the use of radioembolization in HCC published since 2010 and their characteristics.

In 2010, Hilgard et al reported on the treatment outcome of 108 patients. Inclusion criteria were nonresectability of HCC, BCLC C tumour stage, liver function with a Child- Pugh score 7 points or less, and an ECOG performance status of 0, 1, or 2. « Patients with BCLC A and B were also included if they were not eligible for selective TACE. »(58)

The most commonly reported adverse events were fatigue (61%), abdominal pain (56%) and lymphopenia (71%). A case of radiation cholecystitis was observed. 70% of patients had a bilirubin elevation following treatment but in the majority of cases

the bilirubin went back to baseline within 4-6 weeks. Median survival in patients BCLC stage B was 16.4 months, Child Pugh A score 17.2 months and Child Pugh B score 6 months. Patients with portal vein thrombosis had a median survival of 10.0 months while those without 16.4 months. (58)

That same year, the largest prospective cohort of patients with HCC treated with radioembolization was published and included 291 patients. « The decision to treat patients with Y90 as part of this study was made by consensus at our weekly multidisciplinary HCC conference ». 12% of patients underwent treatment with the intent to downstage the tumour and undergo curative therapy. The most commonly encountered toxicities were fatigue (57%), pain (23%) and nausea/vomiting (20%). "Grades 3–4 bilirubin toxicities were noted in 19% of patients »(59). Mortality at 30 days post treatment was 3%. Median survival in patients with BCLC stage B was 17.2 month versus 7.3 in patients with stage C but no extrahepatic disease and 5.4 in BCLC stage C with extrahepatic disease. (59)

In 2011, Sangro et al. presented the results of a large multicentric European study. 325 patients "with HCC who were not suitable for radical therapies (e.g., resection, liver transplantation, local ablation) and were not considered good candidates for transarterial therapies or systemic therapy based on clinical judgment »(25). The most commonly encountered adverse events were mild and included fatigue in 54.5% of patients. Mortality from all causes was reported to be 0.6% and 6.8% at 30 and 90 days post treatment. Median overall survival was 12.8 months but included patients with various BCLC stage. Median survival for patients with BCLC stage B and C was 16.9 and 10.0 months respectively. Key prognostic factor included ECOG

score, extrahepatic disease, BCLC stage, tumour burden and baseline hepatic function. (25)

In 2013, Mazzaferro presented the result of a phase II study of Y90 radioembolization in 52 intermediate and advanced patients with HCC. This study included patients with liver cirrhosis, HCC confined to the liver and who are not eligible to conventional curative treatments. They were excluded if they had an ECOG of 2 or above and if they had extrahepatic spread including lymph nodes above 1.5 cm. 82.7% had Child Pugh score A and 17.3% a score of B. 32.4% were BCLC B and 67.3% BCLC stage C. Median overall survival was reported to be 15 months, 18 months for BCLC stage B patients, and 13 months for BCLC stage C. The most common clinical toxicities (grade 3 and above) encountered were anorexia in 15.4% of patients and ascites in 9.6%. The most common laboratories abnormalities were bilirubin elevation in 27% of patients and lymphopenia in 15.4%. Furthermore 36.5% of patients suffered from at least one episode of liver decompensation and in 27.3% of patients this led to death. The safety profile remained the same even in the presence of portal vein thrombosis. (60)

Kwok et al. published a retrospective study comparing 30 patients who received Y90 radioembolization to 16 patients who did not. The two groups did not differ in terms of clinical or disease characteristics. Mean age was 65 years old in both groups. This study included patients with ECOG score of 0 to 2, BLCL stage A, B and C and patients with Child-Pugh scores of A or B. In the treatment group, patients with BCLC stage C, portal vein invasion and less than 3 nodules had a statistically significant survival benefit. Median survival was calculated from the date of study

planning (the date patients received their Technetium-99m-macroaggregated albumin scan). Median survival for the treatment group was 10.6 month with Child Pugh A, 3.5 months with Child-Pugh B, 14.5 month with BCLC stage B, 5.2 months with BCLC stage C, 14.5 months in the absence of portal invasion and 5.2 in its presence. Reported adverse events included radioembolisation induced liver diseases in 13% of patients as well as abdominal pain in 16% of patients. (61)

Overall the tolerability and safety of radioembolization in patients with HCC and cirrhosis is well established. The most commonly reported adverse events across all series are summarized in table 3 and include fatigue (54-61%), abdominal pain (23-56%), nausea and vomiting (6.7-32%), and transient lymphopenia (15.4-71%) (56, 57, 62). The serious complications resulting from excessive microspheres being delivered to organs other than the liver that had been previously reported in the 2009 meta-analysis have become rarer attesting to the increased expertise and standardization in delivering the procedure. (38, 56) (56, 57)

	Kwok (58)		Mazzaferro (57)		Sangro (25)		Hildgard (55)		Salem (56)	
	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)	All grades (%)	Grade ≥3 (%)
Fatigue	-	-	-	5.8	54.5	2.5	61	0	57	-
Nausea/Vomiting	6,7	-	-	9.6	32.0	0.3	-	-	20	-
Abdominal pain	16,7	-	-	5.8	27.1	1.5	56	0	23	-
Fever	10	-	-	3.8	12.3	0	-	-	3	-
Ascites	-	-	-	9.6	-	-	3	0	-	-
Anorexia	-	-	-	15.4	-	-	-	0	15	-
GI Ulceration	-	-	-	0	3.7	1.8	0	-	0	-
Lymphopenia	-	-	-	15.4	-	-	71	71	-	-
Bilirubin Elevation	-	-	-	26.9	36	-	67	23	74	19
ALT Elevation	-	-	-	-	15.1	-	53	0	63	5
Alkaline Phosphatase Elevation	-	-	-	19.2	-	-	-	0	79	4
Albumin Decrease	-	-	-	17.3	19.0	-	-	-	95	18
Liver Decompensation	13	-	-	36.5	-	-	-	-	-	-

Table 3 – Type and frequency of adverse events in studies investigating the use of radioembolization in HCC published since 2010

Liver related side effects are a potentially lethal and serious complication of radioembolization especially in patients with compromised liver function, portal vein thrombosis and large tumour burden. Table 4 summarized the incidence of liver related side effects in published series on radioembolization in patients with HCC. 20-40% of patients experience hepatic dysfunction post radioembolization; however, in most this is transient and mostly managed on an outpatient basis.

Autor, [Ref.]	Material	Interval (days)	Patients	Ascites (%)	Total Bilirubin Grade >3 (%)	Transaminases Grade >3 (%)	Other liver-related SAEs
Lau *et al.*, [13]	Resin	n.r.	71	n.r.	n.r.		4% liver failure (not RILD)
Dancey *et al.*, [8]		n.r.	22	n.r.	22*	22*	2 potential treatment-related deaths
Geschwind *et al.*, [81]	Glass	0-90	80	7*	16*	6*	1 treatment-related death 1 encephalopathy SWOG grade 3
Carr, [7]	Glass	0-180	65	12	38*		
Salem *et al.*, [15]	Glass	0-90	43	7	14**	5**	
Goin *et al.*, [82]	Glass	0- >90	121	n.r.	n.r.		5% treatment-related death
Sangro *et al.*, [17|	Resin	0-90	24	n.r.	12**		2 treatment-related deaths
Kulik *et al.*, [12]	Glass	0-180	82 cirrhotics	18**	40**		4% encephalopathy CTC grade 3
			26 non-cirrhotics	4**	4**		0% encephalopathy
Hilgard *et al.*, [31]	Glass	0- >90	108	0**	23**	0*	3% encephalopathy CTC grade 3
Kooby *et al.*, [68]	Resin	0-30	27	n.r.	n.r.		22% hepatic dysfunction
Salem *et al.*, [16]	Glass	0-90	291	n.r.	14**	20**	
Sangro *et al.*, [33]	Resin	0-90	325	n.r.	5**	3**	

Interval, days after radioembolization; SAE, serious adverse events; n.r., not reported; RILD, radiation-induced liver disease. *CTC (>3 times the upper normal limit). **SWOG (>200% increase from baseline). (See above-mentioned references for further information.)

Table 4 - "Liver-related side effects report after radioembolization in HCC patients." Reproduced from Sangro et el. (57)

On the other hand, efficacy and treatment outcome has been difficult to assess since most studies include a mixed population of patients with HCC. In table 5 the survival data obtained from the 5 most recent series published on radioembolization in patients with HCC is summarized. The heterogeneity of the patient population in each series is apparent. Furthermore inclusion and exclusion criteria varied significantly across studies (see table 2) as did the analysis and presentation of survival data.

When looking at survival for patient with BCLC stage B disease, survival from the time of first radioembolization treatment ranged from 14.5 to 18 months. When this category was further divided according to Child Pugh score, patients with BCLC stage B and Child Pugh A had a median survival ranging from 17.3 to 18 months while those with a Child Pugh B score had a survival ranging from a mere 3.6 months to 13.5 months. In patients with BCLC stage C disease, which defines advanced HCC, median survival ranged from 5.2 months to 13 months. Patients with portal vein thrombosis had a median survival of 5.2 to 16.4 months.

Number of patients	Median in months	Kwok (58)		Mazzaferro (57)		Sangro (25)		Hildgard (55)		Salem (56)	
Overall		-	-	52	15	325	12.8	108	16.4	-	-
Child Pugh A		25	10.6	-	-	268	14.9	84	17.2	116	17.2
Child Pugh B		5	3.5	-	-	57	10.0	24	6	122	7.7
ECOG 0		9	>58.6	-	-	176	16.9	-	-	-	-
ECOG 1-2		21	5.7	-	-	145	9.9	-	-	-	-
BCLC A		4	>31.9			52	24.4			48	26.9
Child Pugh A		-	-	-	-	47	30.9	-	-	27	20.5
Child Pugh B		-	-			5	19.4			21	29.1
BCLC B		13	**14.5**	17	**18**	87	**16.9**	51	**16.4**	83	**17.2**
Child Pugh A		-	-	15	18	82	18.4	-	-	48	17.3
Child Pugh B		-	-	2	NC	5	3.6	-	-	35	13.5
BCLC C		13	**5.2**	35	**13**	183	**10.0**			107	**7.3**
Child Pugh A		-	-	28	16	137	9.7	-	-	41	13.8
Child Pugh B		-	-	7	6	46	10.0			66	6.4
Portal Vein Thrombosis -		18	14.5	17	18	249	15.3	75	10.0	-	-
Portal Vein Thrombosis +		12	**5.2**	35	**13**	73	**10.2**	33	**16.4**	-	-
Extra hepatic disease		-	-	-	-	28	7.4	-	-	45	5.4

Table 5 – Survival data from studies investigating the use of radioembolization in HCC published since 2010.

Radioembolization is gaining consensus as a treatment of choice for specific patients population including patients with portal vein thrombosis in whom it has been shown to have a more favourable safety profile than transarterial chemo-embolization in that population. (56, 57, 63-65) It is also well tolerated in elderly patients (62).

b. Commercial Devices

Yttrium-90 has evolved into two commercially available radioembolisation devices: glass microspheres called TheraSphere® (MDS Nordion, Toronto, Canada) and resin microspheres called SIR-Spheres® (Sirtex Medical, Sydney Australia). Both are loaded with yttrium 90 (Y-90), a pure beta emitter that has the advantage of having a short half-life of 2.67 days and decays to stable zirconium-90. It also has a short tissue penetration with an average range of local radio-therapeutic effect of 2.5 mm in tissue (0.94 mega-electron volt (MeV) per beta particle) and a maximal range of

less than 1cm. The two devices differ in their size, the amount and method of isotope loading, their gravity and activity delivered per sphere.(57) TheraSphere are intra-arterial, minimally embolic, 20-30 micron particle insoluble glass microspheres loaded with Yttrium-90. It has a higher specific activity (2,500Bq) and a lower number of spheres (1.2 million / 3 GBq) as compared to the alternate resin microspheres treatment and thereby may carry lower risks of toxicity. (38, 43)

4. Combining Sorafenib and TheraSphere

a. Reasoning

While sorafenib is now first line therapy in advanced HCC, the survival benefit of less than 3 months it confers remains modest. Numerous investigators have therefore proposed that combined therapies be the focus of research (38). Combination trials aiming at improving clinical efficacy are presently underway with sorafenib + systemic chemotherapy, sorafenib + TACE and sorafenib + radiation or radioembolization.

Sorafenib with radioembolization is of special interest for both biological and clinical reasons and there is reason to believe that this combination might have a synergic effect. Originally, anti-angiogenic agents were thought and found to lower the efficacy of other drugs and radiation since they would interfere with the delivery of the treatment to the tumour. However, the clinical picture that some of the combination trials have shown seems to contradict this belief. (66) On a molecular and cellular level, 4 mechanisms appear to be involved in the synergy that this

combination creates: targeting of the mechanism of radioresistance, the vascular effect, the oxygen effect and the cell cycle. (67)

The cell cycle effect of sorafenib was observed in an in vitro study where after exposure to sorafenib, cells were more likely to be in the G1-S phase, which is the most radiosensitive.(67)

At the vascular level, VEGF, which is one of the kinases inhibited by sorafenib, is a key mechanism involved in the carcinogenesis of HCC and it has also been implicated in the mechanism of tumour progression after radiotherapy. Indeed, irradiation caused an increased transcription and expression of the VEGF gene, which was associated with rapid tumour progression surrounding the field of irradiation. (67)

The oxygen effect also plays an important role. Hypoxic cells are 2 to 3 times more resistant to ionizing radiation than normoxic cells. Anti-angiogenic agent and particularly VEGF inhibitors help reduce the hypoxia present in the tumour by "normalizing" the tumour vasculature at least transiently and allowing more oxygen to be delivered to the core of the tumour. By doing so it renders the cells more sensitive to radiation. (67-70) This concept was particularly emphasized in a large reviews where evidence that anti-angiogenic agents could transiently normalize the abnormal vasculature of solid tumours were presented (71, 72)

At the clinical level, the combination of sorafenib and radioembolization is of particular interest since both of them have to shown to be safe and tolerable in patients with advanced HCC including elderly and patients with portal vein thrombosis. Both of them have also demonstrated a survival benefit in patients with

BCLC stage C disease. Another interesting aspect raised by Girard et al. is the fact that sorafenib offers survival and progression free survival but did not really show a strong tumour response. Radioembolization and radiation on the other hand, offered strong local tumour response. The combination might allow for good primary tumour response along with microscopic and extrahepatic disease control. (67)

Various in vivo and in vitro studies have shown promising results and sorafenib has been shown to enhance radiation efficacy in various type of cancer including HCC, colorectal cancer, head and neck squamous cell carcinoma and breast cancer. (73-78).

The ideal timing for the administration sorafenib and radioembolization is not known. In one study measuring the VEGF level in patients receiving sorafenib, lower plasma VEGF level 8 weeks after beginning treatment were shown to correlated with increased survival. Furthermore, it offers some information regarding plasma trend in response to sorafenib. "In this study, plasma VEGF concentrations increased from pre-treatment levels within 4 weeks of starting sorafenib in 47 of 63 patients (74.6%). This was followed by a decrease in plasma VEGF levels at 8 weeks in 68.1% of patients. » (79)

Based on this early pre clinical and clinical data, we designed our study to try to create a vasculature normalization window with sorafenib and increase radiation-induced regression with Y-90.

b. Clinical data

Only in the past year has clinical data regarding the use of Y90 radioembolization in combination with sorafenib become available. Of the 3 studies published to date, 2 have investigated the use of sorafenib post radioembolization and only one reports on the use of sorafenib peri-radioembolization. (66, 80, 81)

Chow et al. conducted a multicenter phase II study of sequential use of radioembolization using resin microspheres and sorafenib in inoperable HCC. Patients with ECOG 2 or main trunk portal vein thrombosis were excluded from the study. Sorafenib was initiated 14 days post-radioembolization. 29 patients were included. 97% of patients experienced at least one toxicity. Overall 57% of patients required sorafenib interruption, 39% required dose reduction and 4 % were permanently discontinued. The most commonly encountered adverse events were hand-foot syndrome, rash and alopecia. Hand-foot syndrome was also the most common adverse event grade 3 or above. Overall median survival for patients BCLC stage B was 20.3 months and 8.6 months for BCLC stage C. (80)

In June 2014, results of the European multicenter trial SORAMIC assessing the safety and toxicity of radioembolisation plus sorafenib in advanced HCC were published demonstrating that this combination treatment was “as-well tolerated as sorafenib alone”. This study was conducted using radioembolisation with resin microspheres followed by sorafenib and included patients who were ineligible for other

treatment, a Child Pugh score of B7 or less and ECOG of 0 or 1. Sorafenib treatment was started on day 3 after the last radioembolization procedure. (81)

In both of the previously cited studies, patients only started sorafenib after radioembolization had been performed. To this day, only Rana et al. have published data on patients with advanced HCC receiving radioembolization sorafenib treatment was initiated. In this retrospective study of 10 patients, all patients were BCLC stage C and 9 out of 10 continued sorafenib post radioembolization with resin microspheres. Sorafenib therapy had been initiated since a median time of 43 days (range 9–905 days). Overall survival from time of initiation of sorafenib therapy was 61 weeks. Survival was improved in patients with Child Pugh score of A (42 vs. 12 weeks median overall survival) but was unchanged by the presence of portal vein thrombosis, metastatic disease or prior therapy. The rate of toxicity was 70% with 30% of patients experiencing an adverse event of grade 3. The most commonly observed adverse events were diarrhea, abdominal pain and fatigue overall while ascites was the most commonly observed grade 3 toxicity. (66)

5. Methods

a. Patients

The target study population consisted of 26 consecutive eligible patients over 18 years of age with a diagnosis of HCC as defined by the AASLD (American Association for the Study of Liver Diseases) guidelines for cirrhotic subjects. (Appendix Figure A1)(82) To be eligible, patients had to meet criteria for advanced HCC according to

the BCLC (Barcelona Clinic Liver Cancer) staging system (Appendix Figure A2) (23) or to have had disease progression after other locoregional treatments. An ECOG (Eastern Cooperative Oncology Group) performance status of 2 or less (appendix Table A1), a Child Pugh liver function score of A to B (Appendix Table A2), a life expectancy of 12 weeks or more, and adequate renal, and hematologic functions (Appendix Table A3) were also required. Patients who had previously received locoregional, surgical or systemic cancer treatment were not excluded.

Patients were excluded if they had Child-Pugh scores of C, ECOG statuses of 3 or 4, extensive extrahepatic disease, presented with liver tumours of more than 50% of liver volume, significant pulmonary disease (COPD), cardiac disease (NYHA class I, active coronary disease and uncontrolled hypertension), active infection or HIV, recent GI bleeding (less than 30 days), organ allograft, major surgery within 4 weeks of entry, use of biological response modifiers such as granulocyte colony-stimulating factor (G-CSF) 3 weeks prior to entry, and autologous bone marrow transplant.

Patients were enrolled from the McGill University Health Centre Hepatocellular Carcinoma Clinic from January 2008 to December 2008.

The study was approved by the institutional ethics review board and overseen by a safety committee. The safety committee was constituted of 3 experts in the field of oncology who were chosen by the ethics review board. They held biannual meeting to review clinical data and were notified of any mortality or serious adverse event.

b. Patient Pre-treatment Evaluation

All patients underwent pre-treatment evaluation including medical history, baseline physical examination, ECOG evaluation, laboratory work up (alpha fetal protein, virology for HBV and HCV as appropriate, renal, hematological and liver function test) and imaging (CT-scan imaging of the abdomen and pelvis as well as any other imaging required to assess for the presence of distant metastasis given the medical history and examination). Patients were classified according to the TNM (tumour-lymph nodes-metastasized) system – 6th edition (Appendix Figure A3) for liver cancer and the BCLC (Barcelona Clinic Liver Cancer) algorithm. (Appendix Figure A2).

c. Treatment

All patients began sorafenib (initial dose 400 mg po BID, taken orally in 200mg tablets) and then underwent weekly liver function, hematology, biochemistry and AFP (alpha fetoprotein) measurement and biweekly medical consultation for a period of at least 6-8 weeks prior to radioembolization.

During this period, patients also underwent the preparation procedure for Yttrium-90 radioembolization. This procedure was performed according to the manufacturer's standard treatment protocol. It included mapping hepatic and mesenteric angiography to determine vascular anatomy, hepatic arterial anatomy of the whole liver, arterial supply to the tumour, and optimal catheter placement.

A Technetium 99m (Tc99m) MAA (macro-aggregated albumin) scan was also performed to evaluate and measure pulmonary and gastro-intestinal shunting.

When necessary, coil embolization of non-target vessels was performed to allow for selective and safe infusion. Calculation of total and lobar liver volumes were performed to allow for dose determination. Radiation dose was calculated using the manufacturer's guidelines and instructions for use. Target dose was 120 Gy. Patients with elevated hepatopulmonary shunt leading to exposure of the lungs of >30 Gy in a single session of >50 Gy in repeated sessions or with risk of deposition of microspheres in extrahepatic abdominal locations did not receive radioembolization.

After a 6 to 8 weeks period of the sorafenib regimen, radioembolization was performed as an outpatient procedure and under conscious sedation in the interventional radiology suite of the McGill University Health Center - Hospital Royal Victoria. Treatment administration was performed according to the manufacturer's guidelines and following the previously established care protocol in place at our institution. The Y-90-containing microspheres were delivered to the tumour at the lobar or segmental level via a catheter placed into the right or left hepatic artery. Proper catheter positioning into the hepatic vasculature was verified by angiography prior to treatment administration.

Sorafenib treatment (400mg po BID) resumed 24 hours after radioembolization and continued until unacceptable side effect, death or lack of clinical benefit was observed.

After radioembolization, patients underwent biweekly liver function, hematology, standard biochemistry and AFP (alpha fetoprotein) measurement and monthly medical consultation. After 3 months of follow-up and based on patients' health status, the frequency of these tests was decreased to monthly blood work (liver function, hematology, biochemistry and AFP tests) and medical consultation. Follow up CT scans were obtained 3 weeks post Yttrium-90 radioembolisation and then every 3 months.

If a patient had bilobar disease, a second Yttrium-90 radioembolization was performed to treat the second lobe. Repeat treatment cycles were performed when the initial treatment effect was sub-optimal or when the tumour burden could not be safely targeted in one session. A minimum delay of 6 weeks was observed between treatments.

Sorafenib treatment interruption and dose reductions for drug related adverse effects were done following the regimens used in the SHARP trial except that there was no limitation in the number of dose reduction or interruption permitted. (See Appendix Table A4) If dose reduction was required the following pre-established reduced doses were used.

Full dose: 400mg (2X200mg) taken orally twice daily

1st reduction: 400 mg (2X200mg) orally every day

2nd reduction: 400 mg (2X200mg) every other day

Once adverse event had resolved or was sufficiently improved, dose re-escalation was attempted.

d. Outcomes and Assessments

The primary outcome of the study was safety and tolerability. Adverse events were recorded at each visit in all patients recruited into the study. Patients were encouraged to report symptoms and any change in health. Adverse events were graded using the NCI Common Terminology Criteria for Adverse Events version 3.0. The secondary outcome was overall survival. Overall survival was measured from the day patients began sorafenib treatment until the date of death from any cause. Other outcomes included survival according to HCC etiology, Child-Pugh score, BCLC staging, presence of macroscopic vascular invasion and/or extrahepatic disease and trend in serum AFP levels.

e. Statistical Analysis

Outcomes were assessed according to the intention-to-treat principle. A Kaplan Meier analysis was used in the calculation of all survival outcomes.

6. Results

a. Patients

From January to December 2008, 26 patients were enrolled into the study. All are included in the intention-to-treat analysis.

The patients' demographics and baseline characteristics are highlighted in Table 1. The mean age was 65.04 years old but ranging from 35 to 81. 88.5% of patients were male. The two most common etiologies observed were alcoholic cirrhosis in 30.8% and hepatitis C in 23.1% of patients. Most patients had an ECOG status of 1 (46.2) while 25% had an ECOG of 2 and 25% an ECOG of 0. 73.1 % and 26.9% of patients had a Child-Pugh score of A and B respectively. The majority of patients (84.6%) were BCLC stage C – advanced hepatocellular carcinoma and 50% had macroscopic vascular invasion or extrahepatic spread. 61.5 % of patient had an elevated AFP at baseline with values ranging from 62 to 35,173 μg/L.

15.3% of patient had received prior treatment for their disease including radiofrequency ablation, chemoembolization, surgery and external beam radiation. None of the patient had previously received systemic treatment.

Demographic and Baseline Characteristics of the Patients		
Age -yr (min-max)	65	(35-81)
Sex - no.(%)		
Male	23	(88,5)
Female	3	(11,5)
Cause of disease - no. (%)		
Alcohol	8	(30,8)
Hepatitis C	6	(23,1)
Hepatitis B	5	(19,2)
Cryptogenic	3	(11,5)
NASH	3	(11,5)
Unknown	1	(3,8)
ECOG performance status - no (%)		
0	7	(26,9)
1	12	(46,2)
2	7	(26,9)
Child Pugh Score - no (%)		
A	19	(73,1)
B	7	(26,9)
BCLC Stage - no (%)		
B (intermediate)	4	(15,4)
C (advanced)	22	(84,6)
Macroscopic vascular invasion, extrahepatic spread or both		
Absent	13	(50,0)
Present	13	(50,0)
Alpha-fetoprotein		
Elevated - no (%)	16	(61,5)
Median in µg/L	3456.88	(62-35173)
Previous treatment – no (%)		
Total	4	(15.3)
Chemoembolization	1	(3.8)
Radiofrequency ablation	2	(7.7)
Other (Surgery & External beam radiation)	1	(3.8)

Table 6 - Demographic and Baseline Characteristics of all Patients Enrolled

b. Treatment Compliance

Of the 26 patients enrolled only 20 did received radioembolization for reasons highlighted in table 7.

Cause for ineligibility for Y90 treatment	Number of Patients
Withdrew consent	1
Significant shunting found on Tc99m MAA scan	2
Unacceptable adverse event prior to Y90 radioembolization	2
Patient loss to follow-up	1

Table 7 - Cause of ineligibility for Y90 treatment

Of the 20 patients who received radioembolization, 75% received one treatment and 25% received two treatments. Of the 5 patients who received a second treatment, 3 had treatment of the other lobe of the liver while two had repeat treatment to the same lobe.

c. Safety

The overall incidence of adverse event in the study was 100% with 38.46% of patients experiencing a grade 1 adverse event, 61.54% a grade 2, 58.84% a grade 3 and 7.69% a grade 4.

65% of reported adverse events were grade 1 or 2 in severity and only 3.33% were grade 4.

As highlighted in Table 8, constitutional symptoms such as fatigue (23.1%), and weight loss (23.1%) as well hand-foot skin reaction (19.2%), and abdominal pain (23.1%) were the most commonly reported adverse events. When looking at grade 3 and 4 events, diarrhea (11.5%), hand-foot skin reaction (15.4%) and abdominal pain (15.4%) were the most frequent.

Only 2 grade 4 events were reported and consisted of worsening of cirrhosis and pulmonary embolism.

The rate of treatment discontinuation due to adverse events was 23.1% (6 patients). 61.9% of patients required a dose reduction of sorafenib and 38.1% required a treatment interruption. Dermatological adverse events, especially hand-foot skin reaction were the most common cause of both treatment interruption and dose reduction.

Sorafenib Dose Intervention -no (%)		
Patient with dose reduction	13	(61,9)
Patient with drug interruption	8	(38,1)
Treatment ended	5	(23,8)

Adverse Events					
	Any Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Overall Incidence - % of patients experiencing	100	38.46	61.54	53.84	7.69
Adverse Event – no (%)					
Constitutional Symptoms					
Fatigue	6 (23.1)		4	2 (7.7)	
Weight loss	6 (23.1)		6		
Dermatologic events					
Dry Skin	1 (3.8)		1		
Hand-Foot skin reaction	5 (19.2)		1	4 (15.4)	
Rash	2 (7.7)	1	1		
Alopecia	3 (11.5)	3			
Other (Itching)	1 (3.8)	1			
Gastrointestinal events					
Diarrhea	3 (11.5)			3 (11.5)	
Constipation	3 (11.5)	1	1	1 (3.8)	
Ascites	4 (15.4)		2	2 (7.7)	
Abdominal cramps	1 (3.8)		1		
Dysphagia	2 (7.7)	1	1		
Abdominal pain	6 (23.1)		2	4 (15.4)	
Anorexia	1 (3.8)		1		
Laboratory Abnormalities					
Anemia	1 (3.8)		1		
Thrombocytopenia	1 (3.8)	1			
INR	1 (3.8)			1 (3.8)	
AST/ALT/Bilirubin	1 (3.8)			1 (3.8)	
Vascular (PE)	1 (3.8)				1 (3.8)
Liver dysfunction/Worsening of cirrhosis	3 (11.5)		2		1 (3.8)
Bleeding	3 (11.5)	1	1	1 (3.8)	
Voice changes	1 (3.8)	1			
Leg Edema	3 (11.5)	3			
Hypertension	1 (3.8)		1		
TOTAL	**60**	**13**	**26**	**19**	**2**

Table 8 – Sorafenib Treatment Adjustments and Adverse Events

d. Survival

Survival was calculated from the day sorafenib was initiated.

Overall survival analysis was performed on July 20, 2010. At the time 21 deaths had occurred. Overall median survival was 395 days or 12.97 months with a 95% confidence interval of 358.02 to 431.98 days or 11.76 to 14.19 months. Survival rate at 1 year was 65.4%.

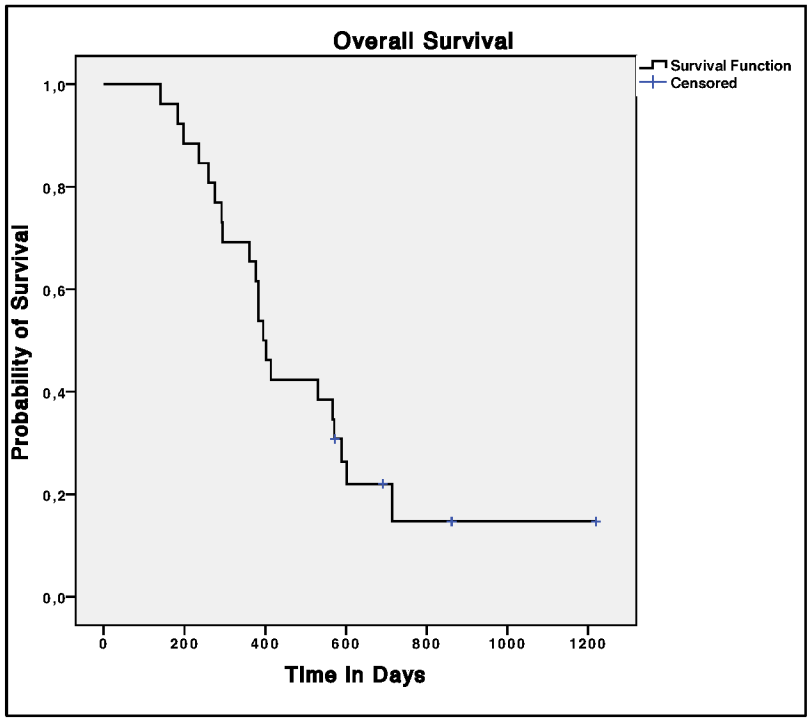

Figure 3 - Kaplan-Meier Analysis of Overall Survival

When looking at survival according to Child-Pugh score, patients with a score of A and B had a median survival of days 395 days (12.97 months) and 402 days (13.02 months) respectively.

Survival also varied according to etiology. Patients who had alcoholic cirrhosis had a median survival of 571 days (18.76 months) while those with hepatitis C cirrhosis and cirrhosis from other etiologies including NASH had a median survival of 383

days (12.58 months) and 292 days (9.59 months) respectively. Median survival for patients with hepatitis B could not be calculated given the small number of patients in this subgroup. (Figure 4)

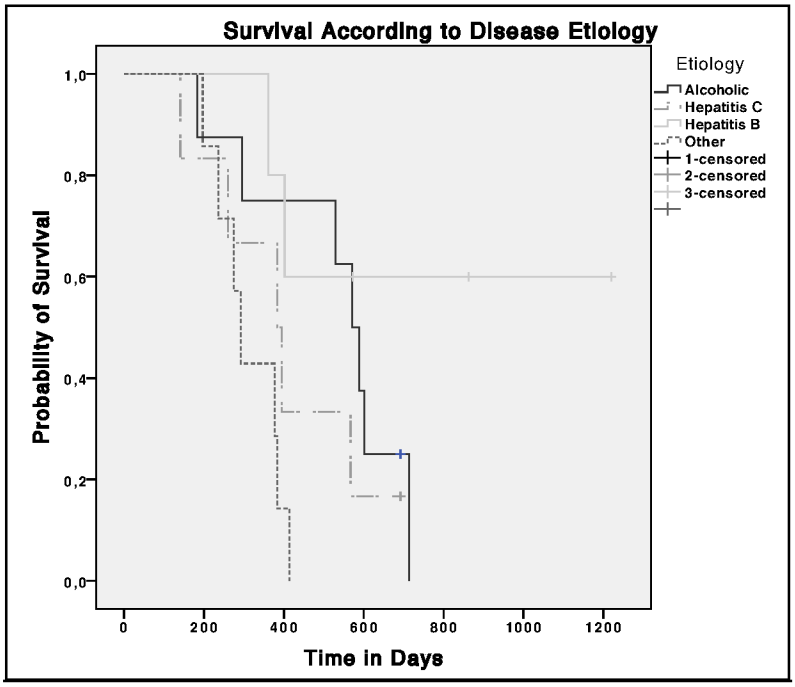

Figure 4 - Kaplan-Meier Analysis of Survival According to Disease Etiology.

Survival was significantly affected by the presence of macroscopic vascular invasion or extrahepatic disease at baseline. Median survival in patients who did not present those characteristics was 589 days (19.35 months) vs. 383 (12.58 months). (Figure 5)

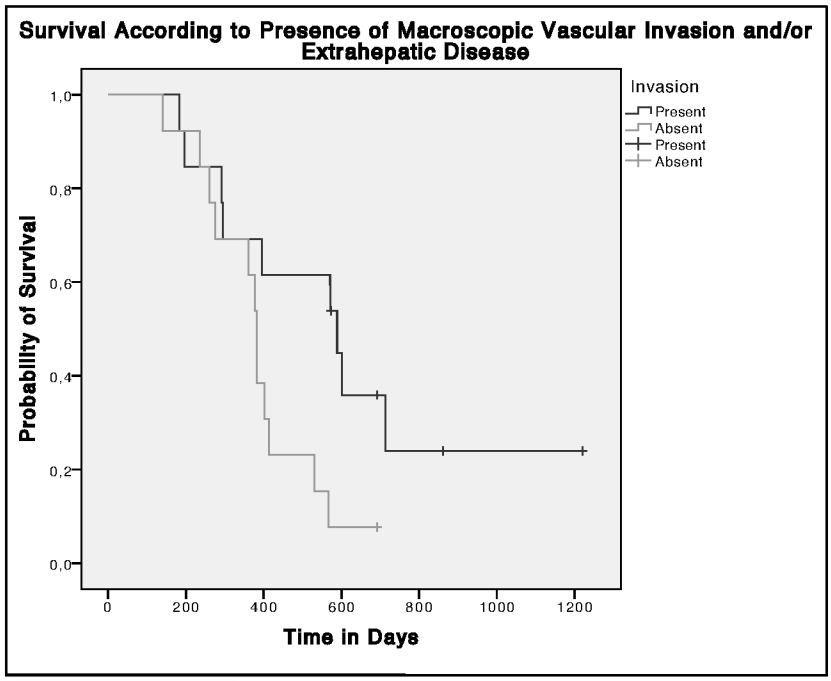

Figure 5 - Kaplan-Meier Analysis of Survival According to the Presence of Vascular Invasion and/or Extrahepatic Disease at Baseline.

Of the 26 patients enrolled in the study, only 16 had elevated serum AFP at baseline. Among those, 8 experienced a decrease in AFP with sorafenib alone and their serum AFP continued to decrease after radioembolization. Another 7 patients did not have a decrease in AFP with sorafenib alone but had a decrease in AFP post radioembolization. Only 1 patient had a rising AFP despite sorafenib and radioembolization.

Median survival varied with AFP trend. Patients who had a decrease in AFP with sorafenib alone had a median survival of 402 days (13.21 months) compared to 236 days (7.75 months) in those who had not. (see Figure 6)

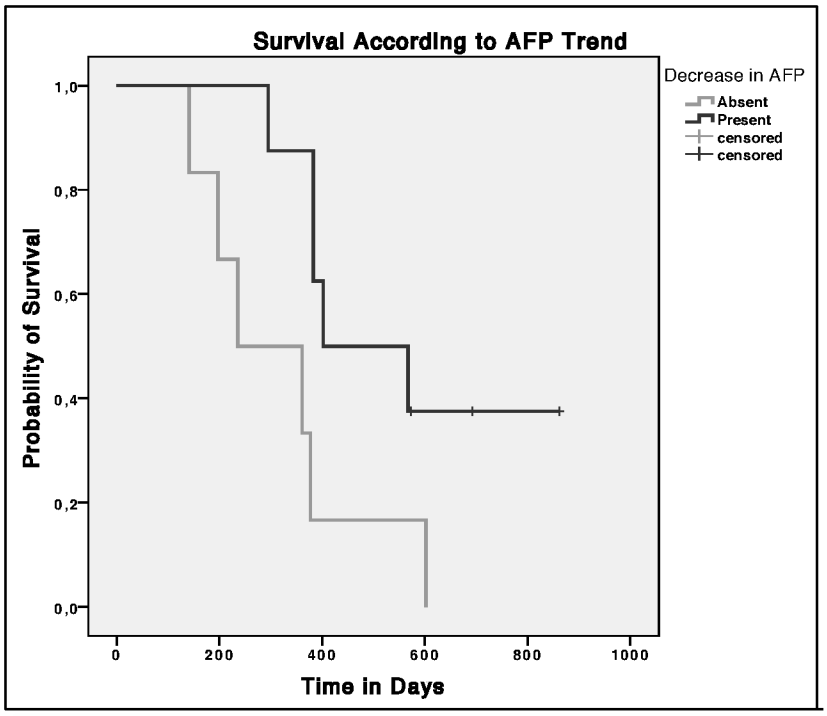

Figure 6. Survival According to serum AFP Response to Sorafenib

Kaplan-Meier analysis of survival according to BCLC staging could not be performed given the small number of patients with stage B disease.

Cause for ineligibility for Y90 treatment	Median survival in months
Overall survival	12.97
Survival according to Child-Pugh score	
Child-Pugh A	12.97
Child-Pugh B	13.02
Survival according to disease etiology	
Alcoholic cirrhosis	18.76
Hepatitis C	12.58
Other	9.59
Survival according to the presence of macroscopic vascular disease and/ or extrahepatic disease	
Present	12.58
Absent	19.35
Survival according to AFP trend	
Decrease in AFP with sorafenib	13.21
No decrease in AFP with sorafenib	7.75

Table 9 – Survival data obtained in this study

Discussion

For advanced HCC, sorafenib, a multi tyrosine kinase inhibitor is the recommended first line therapy and remains the only treatment with a proven survival benefit. However, the survival advantage it confers remains modest and further treatment are being investigated. One of the strategies consists in using sorafenib in combination with other treatment modalities. Locoregional treatments are of particular interest since sorafenib predominantly results in delayed tumour progression by inhibiting tumour cell proliferation rather than shrinking tumours. On the other hand, locoregional treatments such as external beam radiation, TACE and radioembolization are associated with a high rate of complete or partial radiological response. Combining the two treatment modalities might allow to good primary tumour curbing along with microscopic and extrahepatic disease control. Given the potential radiosensitizing properties of sorafenib and clinical results obtained in advanced HCC with radioembolization, this combination appears promising. We therefore conducted phase II study sorafenib in combination with radioembolization in patients with advanced HCC. As discussed above, we designed our study and treatment regimen based on pre-clinical and early clinical data, showing the potential for radiosensitization and vasculature normalization with sorafenib.

The main objective of this study was to assess the safety and tolerability of sorafenib combined with radioembolization in patients with advanced hepatocellular carcinoma. As previously mentioned, this is a particularly challenging population given the unique combination of advanced malignancy and underlying liver disease.

In order to be able to compare the safety profile of sorafenib alone versus sorafenib in combination with Y90 radioembolization, we chose to reproduce the inclusion criteria used in the SHARP trial (29) except that

- We did not require pathological diagnosis but instead used the clinical criteria of the AASLD (American Association for the Study of Liver Diseases) guidelines for cirrhotic subjects (82) which is used in clinical practice.
- We defined advanced disease according to the BCLC staging system as opposed to by eligibility for other treatment.
- We did not exclude patients who had received previous systemic treatment.
- We did not exclude patients with a Child Pugh score of B.
- We also did not require patients to have at least one untreated lesion that could be measured using Response Evaluation Criteria in Solid Tumours.

We compared the demographics and baseline characteristics of patients in the sorafenib group of the SHARP trial to those of patients in this study using a 2 sample Z test (See table 10). The only statistically significant differences between the two populations were:

- the proportions of patients with ECOG scores of 0 and 2. Indeed, in our study fewer patients had an ECOG of 0 while more had an ECOG of 2 compared to the sorafenib group in the SHARP trial.
- the proportion of patients with Child-Pugh score of B was higher in our study. ($p < 0.0001$)

- the proportion of patients with macroscopic vascular invasion, extrahepatic spread or both was lower in our study. (p = 0.0354)

Demographic and Baseline Characteristics of the Patients	Sorafenib group - SHARP trial		This study		p-value
Age -yr (min-max)	64.9		65	(35-81)	
Sex - no.(%)					
Male	260	(87,0)	23	(88,5)	
Female	39	(13,0)	3	(11,5)	
Cause of disease - no. (%)					
Alcohol	79	(26,0)	8	(30,8)	0.5943
Hepatitis C	87	(29,0)	6	(23,1)	0.5228
Hepatitis B	56	(19,0)	5	(19,2)	
Cryptogenic	-	-	3	(11,5)	
NASH	-	-	3	(11,5)	
Unknown	49	(16,0)	1	(3,8)	
ECOG performance status - no (%)					
0	161	(54,0)	7	(26,9)	**0.008**
1	114	(38,0)	12	(46,2)	0.4192
2	24	(8,0)	7	(26,9)	**0.0016**
Child Pugh Score - no (%)					
A	284	(95,0)	19	(73,1)	**<0.0001**
B	14	(5,0)	7	(26,9)	**<0.0001**
BCLC Stage - no (%)					
B (intermediate)	54	(18,0)	4	(15,4)	0.7395
C (advanced)	244	(82,0)	22	(84,6)	0.7395
Macroscopic vascular invasion, extrahepatic spread or both					
Absent	90	(30,0)	13	(50,0)	**0.0354**
Present	209	(70,0)	13	(50,0)	**0.0354**
Alpha-fetoprotein					
Elevated - no (%)	-	-	16	(61,5)	
Median in ug/L	-	-	3456.8	(62-35173)	
Previous treatment – no (%)					
Total	57	(19,0)	4	(15.3)	0.6426
Chemoembolization	86	(29,0)	1	(3.8)	
Radiofrequency ablation	17	(6,0)	2	(7.7)	
Other (Surgery & External beam radiation)	-	-	1	(3.8)	

Table 10 - Comparing our Study Population to the Sorafenib Group in the SHARP trial.(29)

In terms of tolerability for the sorafenib portion of the treatment. The rate of dose reduction, interruption and treatment termination compared to the sorafenib group of the SHARP trial are highlighted in table 11. There was a significantly higher rate of dose reduction in our study (26% vs. 61.9%).

Sorafenib Dose Intervention -%	SHARP trial- Sorafenib Group	This Study	p-value
Patient with dose reduction	26,0	61,9	0.0001
Patient with drug interruption	44,0	38,1	0.5607
Sorafenib discontinuation	38,0	23,8	0.1501

Table 11 - The rate of dose reduction, interruption and treatment termination compared to the sorafenib group of the SHARP trial

Adverse Events									
		SHARP Trial			Our Study			p-value	
		Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any grade	Grade 3 or 4
Overall Incidence - % of patients experiencing		80			100	53.84	7.69	**0.0116**	
Adverse Event - no									
Constitutional Symptoms									
	Fatigue	22	3	1	6	2	0	**0.0065**	**0.0218**
	Weight loss	9	2	0	6	0	0	**<0.0001**	0.6755
Dermatologic events									
	Dry Skin	8	0	0	1	0	0	0.7302	-
	Hand-Foot skin reaction	21	8	0	5	4	0	**0.0289**	**0.001**
	Rash	16	1	0	2	0	0	0.624	0.7659
	Alopecia	14	0	0	3	0	0	0.1347	-
	Other (Itching)	5	1	0	1	0	0	0.4316	0.7659
Gastrointestinal events									
	Diarrhea	39	8	0	3	3	0	0.8172	**0.017**
	Constipation	14	0	0	3	1	0	0.1347	**0.0007**
	Ascites	22	6	<1	4	2	0	0.1521	0.0744
	Abdominal cramps	-	-	-	1	0	0	-	-
	Dysphagia	-	-	-	2	0	0	-	-
	Abdominal pain	8	2	0	6	4	0	**<0.0001**	**<0.0001**
	Anorexia	14	<1	0	1	0	0	0.8416	-
Laboratory Abnormalities									
	Anemia	-	-	-	1	0	0	-	-
	Thrombocytopenia	-	-	-	1	0	0	-	-
	INR	-	-	-	1	1	0	-	-
	AST/ALT/Bilirubin	-	-	-	1	1	0	-	-
Vascular (PE)		-	-	-	1		1	-	-
Liver dysfunction/Worsening of cirrhosis		11	2	1	3	0	1	0.0597	0.2093
Bleeding		7	1	0	3	1	0	**0.0096**	**0.0291**
Voice changes		-	-	-	1	0	0	-	-
Leg edema		16	3	0	3	0	0	0.2013	0.6067
Hypertension		5	2	0	1	0	0	0.4316	0.6755

Table 12 - Adverse Events in our study compared to sorafenib group in SHARP trial.

Fatigue, hand-foot skin reaction and abdominal pain were significantly more common in both its mild and more severe grades in our study. The frequency of bleeding was also significantly higher in our study but remained a rare event.

Gastro-intestinal manifestations such as diarrhea and constipation grade 3 and 4 were also more common in our study but not significantly so. (See table 12)

When comparing the type and frequency of adverse events seen in this study to those documented in the largest and most recent series on radioembolization in HCC.

The higher ECOG and Child Pugh scores in our population might easily explain those differences. Furthermore, abdominal pain is a well-documented side effect of Y90 radioembolization and constipation might have been secondary to narcotic usage.

Comparing the type and frequency of adverse events observed in this study to those reported in radioembolization series in HCC and summarized in table 3, it appears that the addition of sorafenib did not have any impact on the safety and tolerability of radioembolization.

Overall, the type and rate of adverse events observed in our study did not differ widely from those seen with sorafenib or Y90 radioembolization alone and lower rates of discontinuation and interruption were seen even thought this did not reach statistical significance.

When looking at survival, we compare the results of this study to the survival in the sorafenib group in the SHARP trial and to the survival reported in patients with

advanced HCC in the most recent radioembolization series (Previously summarized in table 5).

In the SHARP trial, median survival was calculated from the date of randomization and was 10.7 months in the sorafenib group and 7.9 months in the placebo arm. In this study, overall survival was calculated from the day of sorafenib initiation and was 12.97 months. This represents a 21% increase in survival. At 1 year patients in our study had a 65% chance of being alive versus 44% in the sorafenib group in SHARP. Furthermore it should be noted that the two populations were not completely identical since patients with poor prognostic factors including ECOG 1 and 2 and Child Pugh score B were overrepresented in out study compared to the SHARP trial.

Using radioembolization in patients with BCLC stage C disease, median survival was calculated from the time of first radioembolization treatment and ranged from 5.2 months to 13 months. Those results are difficult to compare to those obtained here since in this study radioembolization took place about 6 weeks after sorafenib was initiated and survival started being recorded. There is also a significant difference in the patient populations since our study not only included 15% of patients with BCLC- stage B but also patients with extrahepatic disease. Given the range of median survival obtained in previously published studies (5.2 to 13 months) and the median survival of 12.7 months in this study, it is possible that sorafenib in combination with radioembolization offers a survival advantage to patients with advanced HCC when compared to radioembolization alone.

In our study, AFP trend in response to sorafenib was found to correlate with increased survival as previously observed (83-85).

Our study was designed to try to take advantage of the potential synergic effect of sorafenib and radioembolization. As previously described, the study published in 2014 by Tsuchiya et al. (79)showed that VEGF plasma level was initially increased prior to dropping in patients with HCC talking sorafenib. This supports our belief that sorafenib should be started prior to radioembolization and that a minimum delay of 6 weeks should be observed between treatment initiation and radioembolization in order to take full advantage of the anti-angiogenic properties of sorafenib. This strategy is further supported by unpublished data collected during this study showing normalization of vasculature on angiogram after treatment with sorafenib. Indeed all patients in our study who received radioembolization had to undergo two serial angiograms. The first one during the planning phase of treatment which occurred within 2-4 weeks of sorafenib initiation and another at the time of radioembolization about 6 weeks after sorafenib initiation. The collection and analysis of this data is ongoing.

Conclusion

In the treatment of advanced HCC, sorafenib in combination with radioembolization does not appear to carry more toxicity than sorafenib alone. The most commonly encountered adverse events were fatigue, abdominal pain, and Hand-Foot syndrome. Median survival with this treatment combination was 12.97 months; a

21% increase from the sorafenib arm of the SHARP trial despite the increased prevalence of poor prognostic factors in our study population. In this study, sorafenib was initiated first and followed by radioembolization approximately 6 weeks after in order to take advantage of the biological mechanism of sorafenib action and its potential role as a radiosensitizer. Further investigation of this treatment regimen is warranted.

Appendices

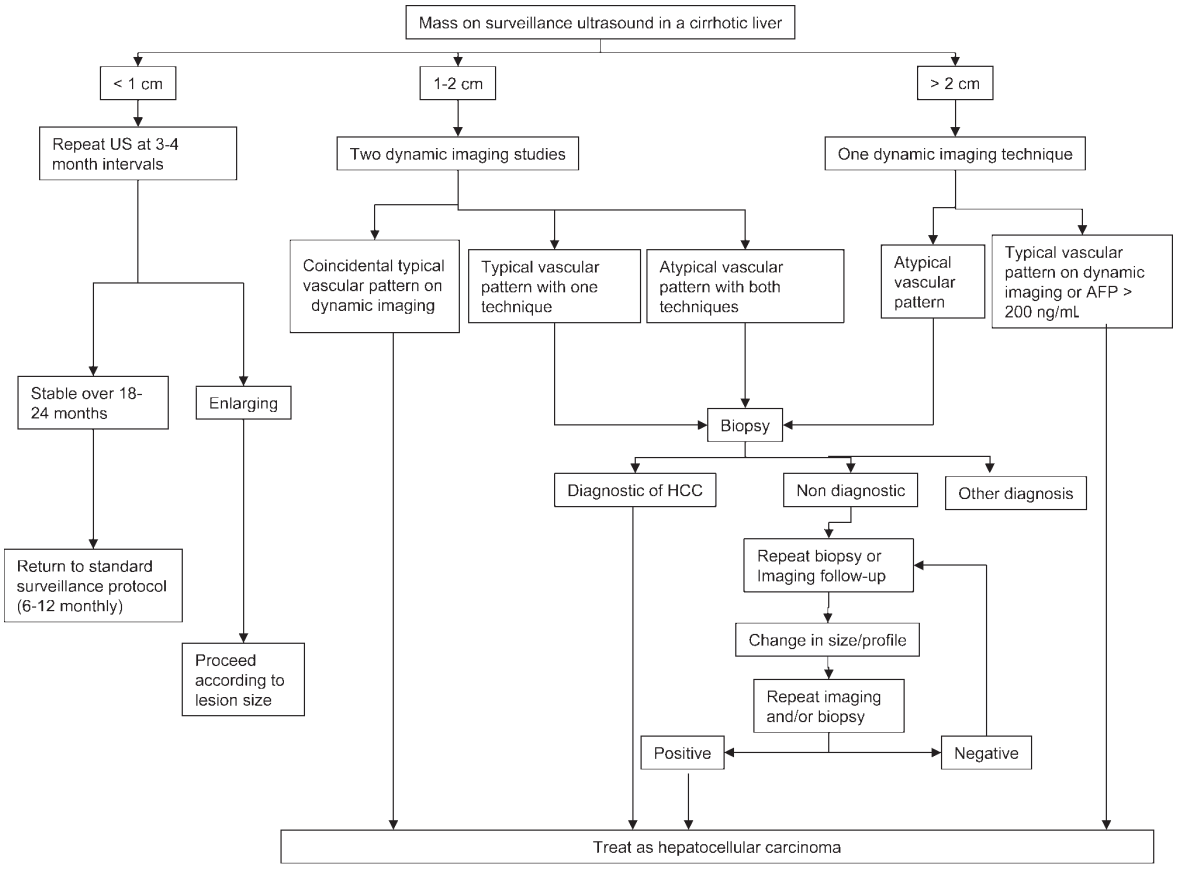

Figure A1. Suggested algorithm for investigation for a nodule found on ultrasound during screening or surveillance*. Reproduced from Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208-36. (82)*

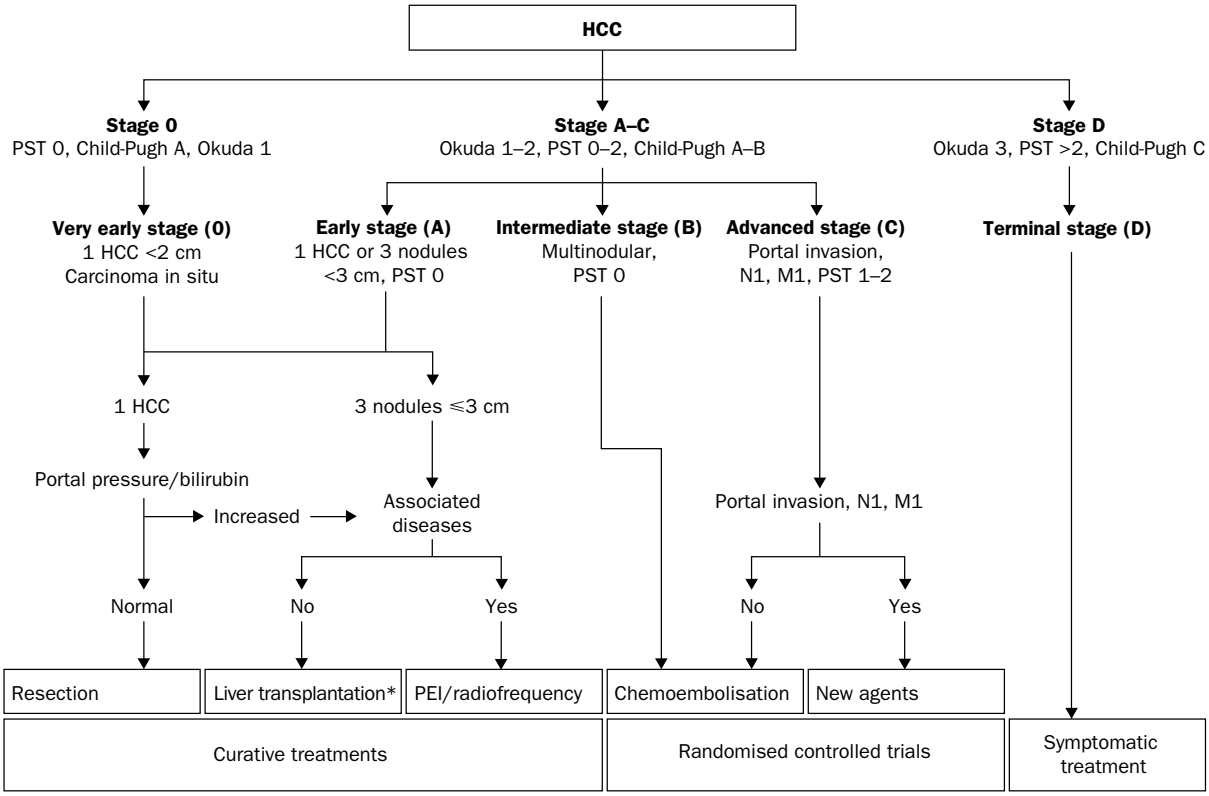

Figure A2. Barcelona-Clinic Liver Cancer staging classification and treatment schedule*. Reproduced from Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362(9399):1907-17. (23)*

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
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, e.g., light house work, office work
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 more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Table A1. Definition of ECOG performance status*. As published in Am. J. Clin. Oncol: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. (28)*

Measure	Score*		
	1 point	2 points	3 points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time, sec (seconds prolonged)	<4	4–6	>6
Encephalopathy grade†	None	1–2	3–4

* Child–Pugh A: 5 or 6 points; Child–Pugh B: 7–9 points; Child–Pugh C: >9 points

Table A2. Child-Pugh Classification*. Reproduced from Llovet J, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90 and adapted from Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646-9. (86)*

Hematology - Hemoglobin - Platelets - International normalized ratio - Prothrombin time	 $\geq$ 8.5 g/dL $\geq$ 60 X 10^9/L < 2.3 < 6 seconds above control
Renal: serum creatinine	< 1.5 times the upper limit of the normal range

Table A3. Hematological, and renal function criteria for patient eligibility.

DEFINITION OF TNM

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Solitary tumor without vascular invasion
T2 Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
T3 Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
T4 Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
Stage IV	Any T	Any N	M1

Figure A3. TNM staging for liver cancer – 6th edition*- Reproduced from American Joint Committee on Cancer Cancer Staging Manual 6th edition – 2002 – p133.*

Table B1. Sorafenib dose delay and modification guidelines for non-dermatological toxicities		
Grade	Dose delay	Dose modification
Hematologic toxicities		
Grade 0-2	Treat on time	No change
Grade 3	Treat on time	Decrease one dose level
Grade 4	Delay* until ≤grade 2	Decrease one dose level
Non-hematologic toxicities (except skin toxicity)†		
Grade 0-2	Treat on time	No change
Grade 3	Delay* until ≤grade 2	Decrease one dose level‡
Grade 4	Off protocol therapy	Off protocol therapy

* If no recovery after 30-day delay, treatment will be discontinued unless patient is deriving clinical benefit

† Also excludes nausea/vomiting that has not been premedicated, and diarrhea

‡ If more than two dose reductions are required, treatment will be discontinued

Table B2. Sorafenib dose delay and modification guidelines for dermatological toxicities*			
Grade		During a course of therapy	Dose for next cycle
Grade 1		Maintain dose level	Maintain dose level
Grade 2	1st appearance	Interrupt until resolved to grade 0–1	Maintain dose level
	2nd appearance	Interrupt until resolved to grade 0–1	400 mg every day
	3rd appearance	Interrupt until resolved to grade 0–1	400 mg every 2 days
	4th appearance	Discontinue treatment permanently	
Grade 3	1st appearance	Interrupt until resolved to grade 0–1	400 mg every day†
	2nd appearance	Interrupt until resolved to grade 0–1	400 mg every two days
	3rd appearance	Discontinue treatment permanently	

* Patients experiencing hand–foot skin reaction should have their signs and symptoms graded according to the following system: grade 1: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort, which does not disrupt normal activities; grade 2: painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities; grade 3: moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. Other skin toxicities will be graded according to CTCAE v3.0 Common Terminology Criteria for Adverse Events version 3.0.

† For patients who require a dose reduction for grade 3 rash or hand–foot skin reaction, the dose of study drug may be increased to the starting dose after one full cycle of therapy has been administered at the reduced dose without the appearance of rash or hand–foot skin reaction grade ≥1.

Table A4. Sorafenib dose modification for non-dermatological and dermatological toxicities. *Reproduced from Llovet J, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90. (87)*

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