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Y90 Radioembolization for Locally Advanced Hepatocellular Carcinoma with Portal Vein Thrombosis: Long-Term Outcomes in a 185-Patient Cohort

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ABSTRACT

We report survival outcomes for advanced stage hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) treated with radioembolization (Y90). **Methods:** With IRB approval, we searched our prospectively acquired database for Y90 patients treated between 2003-2017. Inclusion criteria were patients who had HCC with tumor PVT. Patients with metastases were excluded. Laboratory data were collected at baseline and 1 month post-Y90. Toxicity grades were reported according CTCAE v 4.0, long-term survival outcomes were reported and stratified by Child-Pugh (CP). Overall survival (OS) was calculated using Kaplan-Meier. Multivariate analysis was conducted using Cox-proportion hazards. A subanalysis for patients with high alpha-fetoprotein (AFP) (>100 ng/dl) was conducted. **Results:** 185 patients with HCC PVT had Y90. Seventy-four (40%) were CP-A, 51 (28%) were CP-B7 and 60 (32%) were ≥CP-B8. New albumin, bilirubin and alkaline phosphatase grade 3/4 toxicities were 3%, 10%, and 0% for CP-A, 14%, 12% and 6% for CP-B7, and 23%, 32% and 3% for ≥CP-B8. Median OS for CP-A patients was 13.3 months (95%CI: 8.7-15.7). CP-B7 and CP≥B8 patients exhibited median OS of 6.9 months (95%CI: 5.3-10.1) and 3.9 months (95%CI: 2.9-5.0), respectively. Significant OS prognosticators on univariate analysis were albumin, bilirubin, ascites, tumor ≤5 cm, focality, distribution, infiltration, ECOG, AFP, and PVT extent. Multivariate analysis showed bilirubin, no ascites, tumor ≤5 cm, solitary lesion, baseline AFP <100 ng/dL, and ECOG to be prognosticators of OS. Of 123 patients with high AFP (>100 ng/dl), 12 patients restored normal AFP levels (<13 ng/dl) and exhibited median OS of 23.9 months (CI: 20.1-124.1). At 1-month, AFP responders showed better OS 8.5 vs 4.8 for non-responders (P=0.018); at 3-month AFP responders had OS 13.3 vs 6.9 in non-responders (P=0.21). **Conclusions:** Y90 radioembolization can serve as a safe and effective treatment for advanced stage HCC patients with tumor PVT. OS outcomes are affected by baseline liver function, tumor size and AFP level.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most common malignancy worldwide with a marked increase in prevalence in the United States within the past 50 years (*1,2*). It is the most common primary liver malignancy and second most common cause of cancer-related mortality worldwide (*3*). Due to co-morbidities, underlying liver function, tumor size, and late stage presentation, only 10% of HCC patients can receive curative treatments (*4*).

An estimated 7-15% of HCC patients present with infiltrative disease (*5*). Most of those patients present with portal vein thrombosis (PVT), therefore they are not typically considered candidates for possible curative treatments (resection, transplantation) given that the presence of PVT significantly increases the chances of extrahepatic spread and decreases overall survival (*6*). Y90 radioembolization has previously been found to be a safe and promising treatment for the treatment of HCC patients with PVT. Since the treatment is microembolic, it maintains the hepatic vasculature intact (*7*).

There are several treatment options for HCC patients with PVT. The current standard of care for these patients is sorafenib (*8*). Regorafenib also has been proven to provide a survival benefit for HCC patients who progressed during Sorafenib treatment (*9*). Other systemic treatments such as erlotinib have failed to provide improved survival when added to sorafenib (*10*). Although contraindicated for patients with PVT, transarterial chemoembolization is still used (*11-13*).

This study reports on the largest cohort of HCC patients with PVT (without metastases) treated with Y90 radioembolization.

METHODS

This retrospective study was compliant with the Health Insurance Portability and Accountability and was approved by the Northwestern University Institutional Review Board. All subject signed informed consent for the treatment. The study is a subset analysis of a 1000-patient cohort of consecutive HCC patients who were treated with Y90 radioembolization at our institution from December 2003 – March 2017. For the purpose of isolating the appropriate cohort, we excluded patients who: 1) did not exhibit PVT at baseline, and 2) demonstrated extrahepatic metastases in efforts to reduce this confounding effect on survival. This resulted in the identification of a 185-patient cohort who demonstrated PVT at baseline imaging. The sample was further subdivided by Child-Pugh scores (CP-A, CP-B7, ≥CP-B8). In a prior analysis, we reported long-term outcomes of a 291-patent cohort that included 96 patients with PVT-only disease. In this study, we shed light on our experience in 185 PVT-only patients treated over a 14-year period (*14*).

Evaluation and Staging

HCC was diagnosed based on radiographic findings according to guidelines or biopsy (*15*). Portal vein tumor thrombus was diagnosed based on enhancement during arterial phase of contrast injection during cross-sectional imaging (*16*). The location of PVT was also assessed (segmental, lobar, main). Six patients with main PVT had extending tumor thrombus to the superior mesenteric vein. These were included in the main PVT group for the purposes of this study. Patients were classified by Child-Pugh, United Network for Organ Sharing, and BCLC criteria.

Patients had prior cross-sectional imaging that elucidated tumor number, size, and location. Patient history, a physical examination, and Eastern Cooperative Oncology Group (ECOG) performance status were assessed during

initial clinic visits. The decision to treat patients with Y90 was made during a weekly multidisciplinary tumor board.

Y90 Treatment

Tumor blood supply and lung shunt fraction were evaluated from planning angiography and technetium-99m macro-aggregated albumin (Tc-99m MAA). Radioembolization was then performed per standard methodology delivering a radiation dose of 80-150 Gy to the hepatic parenchyma using glass microspheres (*17,18*).

AFP Producers

AFP producers within the cohort were defined as patients who had AFP>100 ng/mL at baseline. Their laboratory AFP values were collected until their last day of follow-up. AFP responders were defined as patients who had >50% decrease in their AFP from baseline. Patients were also considered to have a normalized AFP if they achieved an AFP ≤13.

Laboratory Toxicities

Clinical and laboratory assessment was performed at baseline, 1-3 months following radioembolization, and every 3 months thereafter. Laboratory toxicities were graded according to the Common terminology criteria for adverse events (CTCAE) version 4.0 (*19*). If patients already met criteria for CTCAE version 4.0 toxicity at baseline and the grade of toxicity did not progress following Y90, the toxicity was considered not attributable to Y90.

Statistical Analysis

Overall survival was estimated using Kaplan-Meier method. Univariate analysis was conducted using Kaplan-Meier and log-rank test. Multivariate analysis was conducted using Cox proportional hazards regression. All statistical analyses were conducted using IBM® SPSS® Statistics V24.

RESULTS

Baseline Characteristics

(Table 1) demonstrates demographics and baseline characteristics at the date of first Y90 treatment. 74 patients (40%) were CP-A, 51 (28%) were CP-B7 and 60 (32%) were ≥CP-B8. Forty-three (23%) patients had segmental PVT, 77 (42%) displayed main PVT, and 65 (35%) displayed branch PVT.

Laboratory Toxicities (Table 2)

Child Pugh A. At baseline, grade 1/2 toxicities were noted: bilirubin 28% (n=21), albumin 66% (n=49) and alkaline phosphatase 45% (n=61). None exhibited grade 3/4 toxicity. New toxicities following treatment were noted: bilirubin 8% (n=6) grade 1/2 and 10% (n=7) grade 3/4; albumin 0 (n=0) grade 1/2 and 3% (n=2) grade 3/4; alkaline phosphatase 10% (n=7) grade 1/2 and 0 (n=0) grade 3/4.

Child Pugh B7. At baseline, grade 1/2 toxicities were noted: bilirubin 31% (n=16), albumin 49% (n=25) and alkaline phosphatase 55% (n=28). None exhibited grade 3/4 toxicity. New toxicities following treatment were noted: bilirubin 8% (n=4) grade 1/2 and 12% (n=6) grade 3/4; albumin 0 (n=0) grade 1/2 and 14% (n=7) grade 3/4; alkaline phosphatase 24% (n=12) grade 1/2 and 6% (n=3) grade 3/4.

Child Pugh ≥ B8. At baseline, grade 1/2 toxicities were noted: bilirubin 20% (n=12), albumin 57% (n=34) and alkaline phosphatase 73% (n=44). None exhibited grade 3/4 toxicity. New toxicities following treatment were noted: bilirubin 32% (n=19) grade 1/2 and 32% (n=19) grade 3/4; albumin 12% (n=7) grade 1/2 and 23% (n=14) grade 3/4; alkaline phosphatase 12% (n=7) grade 1/2 and 3% (n=2) grade 3/4.

Survival stratified by Child-Pugh (Table 3)

CP-A patients (N=74) had a median overall survival of 13.3 months (95% CI:8.7-15.7). When sub-stratified by location of PVT, survival was 14.3 months (95% CI:12.0-17.8) for segmental, 14.2 months (95% CI:7.3-19.5) for lobar and 7.7 months for main (95% CI:4.6-13.8) (P=0.78). Patients with AFP >100 had a survival of 7.8 months (95% CI:6.9-15), compared to 15.6 months (95% CI:13.2-20.7, P=0.16) for AFP ≤100. Baseline tumor size ≤5 cm had a survival of 14.2 months (95% CI: 11.4-24) and >5 cm had a survival of 11.7 months (95% CI:7.8-17.7, P=0.27) **(Supplementary Figure 1).**

CP-B7 patients (N=51) had a median overall survival of 6.9 months (95% CI:5.3-10.1). When sub-stratified by location of PVT, survival was 6.5 months (95% CI:3.4-38) for segmental, 6.9 months (95% CI:4.6-13.3) for lobar and 7.7 months for main (95% CI:4.8-11.1) (P=0.82). Patients with AFP >100 had a survival of 6.4 months (95% CI:4.6-10.4) compared to 7.9 months (95% CI:6.4-14.4, P=0.94) for AFP ≤100. Baseline tumor size ≤5 cm had a survival of 14.4 months (95% CI:6.9-20.1) compared to 6.4 months (95% CI:4.8-8.1, P=0.04) for >5 cm **(Supplementary Figure 2).**

CP≥B8 patients (N=60) had a median overall survival of 3.9 months (95% CI:2.9-5.0). When sub-stratified by location of PVT, survival was 8.4 months (95% CI:1.2-75.2) for segmental, 4.4 months (95% CI:2.5-9.7) for lobar and 3.4 months for main (95% CI:2.5-4.6) (P=0.015) Patients with AFP >100 had a survival of 3.3 months (95% CI:2.3-4.8) compared to 4.8 months (95% CI:4.1-9.5 P=0.09) for AFP ≤100. Baseline tumor size ≤5 cm had a survival of 12.6 months (95% CI:2.3-21.7), and >5 cm had a survival of 3.6 months (95% CI: 2.3-4.8, P=0.01) **(Supplementary Figure 3).**

Univariate and Multivariate Analyses

Univariate survival analysis using Kaplan-Meier and Log-rank test, showed statistically significant survival benefit in patients with baseline albumin >3.5 g/dL (P=0.002), baseline bilirubin < 2mg/dL (P<0.0001), absence of ascites (P=0.0015), tumor size ≤5 cm (P=0.0007), solitary (P=0.001), unilobar disease (P=0.0015), non-infiltrative tumors (P=0.01), ECOG PS 0 or 1 (P=0.0001), and baseline AFP < 100 ng/dL (P=0.05). Patients who had either segmental or lobar PVT had better survival outcomes than patients with PVT involving main portal vein (P=0.008).

Multivariate analysis using Cox-proportional hazards regression showed bilirubin < 2mg/dL, bilirubin 2-3mg/dL, absence of ascites, tumor size ≤5 cm, solitary lesion, baseline AFP <100 ng/dL, ECOG 0 or 1, to be significant prognosticators of survival **(Table 4).**

AFP Producers. Patients who were AFP producers (N=123) were also analyzed. At 1-month post- Y90, 101 patients had follow-up; AFP nonresponders (N=52) had a median overall survival of 4.8 months (3.7-7.7) versus 8.5 months (95% CI: 6.5-14.3, P=0.018) for AFP responders (N=49). At 3 months post-Y90, 65 patients had laboratory follow-up; AFP non-responders (N=22) had a median survival of 6.9 months (95% CI: 5.3-8.9), while AFP responders (N=43) had a survival of 13.3 months (95% CI: 8.7-17.7, P=0.021). Patients with normalized AFP at any follow up in AFP producers (N=12) had a survival of 23.9 months (20-124), while non-normalized AFP producers (N=89) had a survival of 6.4 months (4.9-7.8, P<0.0001) **(Supplementary Table 1).**

DISCUSSION

HCC patients presenting with PVT have limited treatment options because they are affected by the tumor and underlying liver cirrhosis that is further complicated by the development of PVT. Further, unless they have preserved liver function (CP-A), they are precluded from most clinical trials and systemic agents (*15*). Our results indicate that Y90 radioembolization clinically meaningful overall survival for HCC patients with PVT when compared to published outcomes with systemic agents, predominantly in patients with preserved liver function.

Many treatments have been implicated in palliating or providing a survival benefit for patients with advanced stage HCC. Sorafenib, a small-molecule multikinase inhibitor, remains to be the current systemic treatment of choice for advanced HCC patients. A randomized controlled trial of sorafenib for advanced hepatocellular carcinoma patients found that it increased overall survival and median time to radiologic progression by almost 3 months when compared to the placebo group (*20*). Another phase III trial found that sorafenib demonstrated improved survival in HCC patients with both macrovascular invasion and metastatic disease (*21,22*). Recently, Bruix et al. found that regorafenib, another multikinase inhibitor, provided a survival benefit for HCC patients with PVT who tolerated sorafenib but progressed while on therapy(*9*). The study population included only Child Pugh A patients. The regorafenib group showed an overall survival of 10.6 months in comparison to 7.8 months for the placebo group (*9*). Johnson et al. (2013) found that brivinib, a tyrosine kinase inhibitor, demonstrated similar overall survival and time to progression when compared to sorafenib as a first line of treatment, but sorafenib was better tolerated when compared to brivinib (*23*). Nivolumab, a programed death-1 blocking antibody, has shown promising preliminary results as both a first and second line systemic therapy for advanced stage HCC (*24*).

Y90 has proved to be the locoregional treatment of choice in cases with portal vein invasion (*25*). The small size of Y90 glass microspheres (30 microns) allows for deep infiltration into the tumor without ischemia of the hepatic parenchyma (*7*). Occluding arterial flow to a hepatic region which has no portal venous flow due to malignant portal vein invasion could result in complete loss of blood supply and unfavorable outcomes. Moreover, for most late-stage HCC patients, maintenance of hepatic blood flow is a priority to preserve liver function. Theoretically, this makes a microembolic therapy appealing in such a scenario (*26*).

Until very recently, there were no studies comparing Y90 and sorafenib as a sole treatment for advanced stage HCC. However, a new clinical study comparing Y90 resin microspheres to sorafenib found that the median overall survival for the Y90 arm was not improved over the sorafenib arm. Additionally, there was no significant difference in progression-free survival between the two groups (*27*). There were however, significant differences between the two groups with regards to therapy safety, toxicity profile, and quality-of-life. Patients treated with Y90 had fewer and less severe treatment-related side effects and displayed toxicity and tolerability advantages. Y90 patients also sustained their health status whereas sorafenib patients had a significant decline in quality-of-life (*27,28*). The low toxicity profile makes Y90 a promising therapy for treatment-naïve late stage HCC patients.

For CP-A and CP-B7, there was no significant difference in survival among segmental, branch and main PVT. This is interesting since previous studies have repeatedly found that patients with branch PVT had a significantly longer survival than main PVT (*29*). For CP-A patients, baseline tumor size was not a prognosticator of survival. This could indicate that as long as PVT patients display

preserved liver function, Y90 can be an effective treatment for such patients. For CP-B7 and ≥CP-B8 patients, tumor size was found to be related to survival. Tumors <5 cm had significantly longer survivals compared to larger tumors, indicating that the 5-cm mark is significant in assessing tumor size prior to treatment.

AFP responders (baseline AFP >100) were found to have significantly better survival at the 1-month and 3-month landmarks compared to AFP nonresponders, irrespective of CP score. Patients with high AFP levels who became normalized post-Y90 had a large survival benefit when compared to non-normalized AFP producers. It has been found that AFP response after locoregional therapy can be used as a tool to assess tumor response, survival, and progression (*30*). More specifically, AFP was correlated with EASL imaging response and survival (*31*). Future studies should investigate whether AFP level changes can predict survival in PVT patients.

Previous studies have shown that a significant portion of CP-A PVT patients treated with Y90 eventually progressed to CP-B/C (*29*). This suggests that CP-A patients have a limited time interval after Y90 but prior to disease progression where they are still eligible for systemic agents by CP class. The concept of Y90 followed by adjuvant systemic treatment should be investigated (*32*).

A few comments about the recently reported SARAH and SIRVENIB trials are warranted, given that their focus was on “advanced disease”. First, the definition of “advanced” is clear in guidelines and is meant to incorporate PVT, performance status 1 or 2, or extrahepatic metastases (*6*). These trials loosened the criteria of advanced to include intermediate (and even early) stage patients, potentially diluting any effect Y90 might have over sorafenib. The studies should be interpreted as not meeting their endpoint and with the statistical design, one

can conclude that in those patients, Y90 was no better and no worse than sorafenib. The studies were not powered for non-inferiority and a declaration that they provide the same survival cannot be made. The studies may have also been limited by the lack of modern dosimetry and “boost” techniques, current becoming standards of care in this patient population (*33,34*). While the analyses were appropriately by intention-to-treat, this has the secondary effect of biasing in favor of sorafenib, since many more patients are able to start therapy in pill form than those who pass the lung shunt fraction study. Despite designs that favored sorafenib, the secondary endpoints (response, quality-of-life) all favored Y90, factors that are very relevant to patients when considering treatment options. Also, while these two studies did not meet their endpoint, it does not mean there is no clinical effect of Y90 in this patient population. Demonstrating the benefit of Y90 may require trial designs that are more finely-tuned, with more detailed and homogenous inclusion criteria. It would not be the first time an evolving treatment required several trials and different designs before a positive one was illustrated; several of the early chemoembolization studies were negative before the seminal studies establishing it as standard of care in intermediate HCC. The same approach may be required of Y90 (*35*).

Unique strengths of this analysis include that it is the largest homogenous patient cohort of PVT patients without the confounder of metastases with long-term 10-year follow-up. These data can be used to help design future studies. Limitations include the lack of a control arm and the retrospective nature of the study.

CONCLUSION

Y90 radioembolization for HCC patients with PVT appears to have an acceptable safety profile, with survivals in CP A patients outperforming CP B. This study confirms prior reports of survival in PVT patients treated with Y90, and appears to exceed similar patients treated with systemic therapies. Despite the negative studies recently reported, Y90 is a reasonable treatment option in properly selected PVT patients. Further controlled studies are needed to confirm its role in treating advanced stage HCC patients in comparison to systemic therapies or other locoregional treatments.

REFERENCES

1. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol.* 2009;27:1485-1491.

2. Fitzmaurice C, Dicker D, Pain A, et al. The global burden of cancer 2013. *JAMA Oncol.* 2015;1:505-527.

3. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65:87-108.

4. Geschwind JFH, Salem R, Carr BI, et al. Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. *Gastroenterology.* 2004;127:S194-S205.

5. Demirjian A, Peng P, Geschwind JF, et al. Infiltrating hepatocellular carcinoma: seeing the tree through the forest. *J Gastrointest Surg.* 2011;15:2089-2097.

6. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis.* 1999;19:329-338.

7. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. *Hepatology.* 2008;47:71-81.

8. Rimassa L, Santoro A. Sorafenib therapy in advanced hepatocellular carcinoma: the SHARP trial. *Expert Rev Anticancer Ther.* 2009;9:739-745.

9. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;389:56-66.

10. Zhu AX, Rosmorduc O, Evans TR, et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol.* 2015;33:559-566.

11. Yoshidome H, Takeuchi D, Kimura F, et al. Treatment strategy for hepatocellular carcinoma with major portal vein or inferior vena cava invasion: a single institution experience. *J Am Coll Surg.* 2011;212:796-803.

12. Zhang XB, Wang JH, Yan ZP, Qian S, Liu R. Hepatocellular carcinoma invading the main portal vein: treatment with transcatheter arterial chemoembolization and portal vein stenting. *Cardiovasc Intervent Radiol.* 2009;32:52-61.

13. Lee HS, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY. The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. *Cancer.* 1997;79:2087-2094.

14. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* 2010;138:52-64.

15. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst.* 2008;100:698-711.

16. Piscaglia F, Gianstefani A, Ravaioli M, et al. Criteria for diagnosing benign portal vein thrombosis in the assessment of patients with cirrhosis and hepatocellular carcinoma for liver transplantation. *Liver Transpl.* 2010;16:658-667.

17. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. *J Vasc Interv Radiol.* 2006;17:1251-1278.

18. Salem R, Lewandowski RJ, Gates VL, et al. Research reporting standards for radioembolization of hepatic malignancies. *J Vasc Interv Radiol.* 2011;22:265-278.

19. Health UDo, Services H. Common terminology criteria for adverse events (CTCAE) version 4.0. *National Cancer Institute.* 2009.

20. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med.* 2008;359:378-390.

21. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 2009;10:25-34.

22. Cheng AL, Guan Z, Chen Z, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase III Sorafenib Asia-Pacific trial. *Eur J Cancer.* 2012;48:1452-1465.

23. Johnson PJ, Qin S, Park JW, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol.* 2013;31:3517-3524.

24. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet.* 2017.

25. Salem R, Lewandowski R, Roberts C, et al. Use of Yttrium-90 glass microspheres (TheraSphere) for the treatment of unresectable hepatocellular carcinoma in patients with portal vein thrombosis. *J Vasc Interv Radiol.* 2004;15:335-345.

26. Donahue LA, Kulik L, Baker T, et al. Yttrium-90 radioembolization for the treatment of unresectable hepatocellular carcinoma in patients with transjugular intrahepatic portosystemic shunts. *J Vasc Interv Radiol.* 2013;24:74-80.

27. Vilgrain V, Abdel-Rehim M, Sibert A, et al. Radioembolisation with yttrium–90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial. *Trials.* 2014;15:474.

28. Vilgrain V, Bouattour M, Sibert A, et al. GS-012 - SARAH: a randomised controlled trial comparing efficacy and safety of selective internal radiation therapy (with yttrium-90 microspheres) and sorafenib in patients with locally advanced hepatocellular carcinoma. *Journal of Hepatology.* 2017;66:S85-S86.

29. Memon K, Kulik L, Lewandowski RJ, et al. Radioembolization for hepatocellular carcinoma with portal vein thrombosis: impact of liver function on systemic treatment options at disease progression. *J Hepatol.* 2013;58:73-80.

30. Riaz A, Ryu RK, Kulik LM, et al. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. *J Clin Oncol.* 2009;27:5734-5742.

31. Memon K, Kulik L, Lewandowski RJ, et al. Alpha-fetoprotein response correlates with EASL response and survival in solitary hepatocellular carcinoma treated with transarterial therapies: a subgroup analysis. *J Hepatol.* 2012;56:1112-1120.

32. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Eur J Cancer.* 2012;48:599-641.

33. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival

in hepatocellular carcinoma patients with portal vein thrombosis. *J Nucl Med.* 2015;56:339-346.

34. Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with 90 Y-loaded glass microsphere radioembolization. *Liver Int.* 2017;37:101-110.

35. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet.* 2002;359:1734-1739.

Table 1: Baseline Characteristics

		N=185
Demographics	<65	104 (56.2%)
	≥65	81 (43.8%)
	Male	148 (80%)
	Female	37 (20%)
Largest Tumor Size	<5 cm	50 (27%)
	≥5 cm	135 (73%)
Portal Vein Thrombosis	Segmental	43 (23%)
	Lobar	65 (35%)
	Main	77 (42%)
Distribution	Solitary	53 (28.6%)
	Multifocal	132 (71.4%)
Tumor Infiltration	Non- Infiltrative	80 (43%)
	Infiltrative	105 (57%)
Tumor Location	Unilobar	107 (57.8%)
	Bilobar	78 (42.2%)
Method of Diagnosis	Imaging	121 (65.4%)
	AFP	6 (3.2%)
	Biopsy	58 (31.4%)
ECOG Performance Status	0	77 (41.6%)
	1	93 (50.3%)
	2	15 (8.1%)
Underlying Liver Disease	ETOH	26 (14.1%)
	HCV	94 (50.8%)
	HBV	17 (9.2%)
	NASH	6 (3.2%)
	Unknown	22 (11.9%)
	Cryptogenic	14 (7.6%)
	Other	6 (3.2%)
Imaging Cirrhosis	Present	164 (88.6%)
	Absent	21 (11.4%)
Ascites	Absent	123 (66.5%)
	Moderate	54 (29.2%)
	Severe	8 (4.3%)
Child Pugh Score	A	74 (40%)
	B7	51 (28%)
	≥B8	60 (32%)
Bilirubin (mg/dL)	<2	156 (84.3%)
	2-3	17 (9.2%)
	>3	12 (6.5%)
Prior Liver Directed Therapy	None	170 (92%)
	Resection	4 (2.2%)
	Chemoembolization	8 (4.3%)
	Radio-frequency ablation	3 (1.6%)
AFP (ng/mL)	≤100	62 (33.5%)
	>100	123 (66.5%)
Albumin (mg/dL)	>3.5	20 (10.8%)
	2.8-3.5	93 (50.3%)
	<2.8	72 (38.9%)

(AFP = alpha-fetoprotein; ETOH = Ethanol; HCV = Hepatitis C Virus; HBV = Hepatitis B Virus; ECOG = Eastern Cooperative Oncology Group; NASH = Non-alcoholic steatohepatitis;

Table 2: Toxicities

Child-Pugh Class	Grade	Toxicity	Toxicity Grades at Baseline N (%)*	New Post Y90 Toxicities N (%)*
A	Grade 1/2	**Albumin**	49 (66)	0 (0)
B7			25 (49)	0 (0)
≥B8			34 (57)	7 (12)
A	Grade 3/4		0 (0)	2 (3)
B7			0 (0)	7 (14)
≥B8			0 (0)	14 (23)
A	Grade 1/2	**Bilirubin**	21 (28)	6 (8)
B7			16 (31)	4 (8)
≥B8			12 (20)	19 (32)
A	Grade 3/4		0 (0)	7 (10)
B7			0 (0)	6 (12)
≥B8			0 (0)	19 (32)
A	Grade 1/2	**Alkaline phosphatase**	45 (61)	7 (10)
B7			28 (55)	12 (24)
≥B8			44 (73)	7 (12)
A	Grade 3/4		0 (0)	0 (0)
B7			0 (0)	3 (6)
≥B8			0 (0)	2 (3)

*expressed as percentage of baseline Child-Pugh

Table 3: Overall survival stratified by Child-Pugh

Liver Function	Factor	Variable	n=Number of Patients (%)	Median Survival (95% CI)	P-Value	Overall Survival
Child Pugh A (N=74)	Age	≥65	30 (41)	17.7 (8.7-19.5)	0.32	13.3 (8.7-15.7)
		<65	44 (59)	11.7 (7.3-14.2)		
	Sex	Male	54 (73)	13.7 (8-19.1)	0.35	
		Female	20 (27)	13.2 (7.7-17.7)		
	PVT	Segmental	24 (32)	14.3 (12.0-17.8)	0.78	
		Lobar	27 (37)	14.2 (7.3-19.5)		
		Main	23 (31)	7.7(4.6-13.8)		
	AFP	>100 mg/dL	27 (37)	8.0 (7.0-15.0)	0.16	
		≤100 mg/dL	47 (63)	15.6 (13.2-20.7)		
	Baseline Tumor Size	≤5 cm	25 (34)	14.2 (11.4-24.0)	0.27	
		>5 cm	49 (66)	11.7 (7.8-17.7)		
Child Pugh B7 (N=51)	Age	≥65	24 (47)	6.4 (4.5-8.1)	0.11	6.9 (5.3-10.1)
		<65	27 (53)	7.9 (5.8-13.3)		
	Sex	Male	43 (84)	6.9 (5.0-9.1)	0.60	
		Female	8 (16)	6.5 (3.4-11.0)		
	PVT	Segmental	11 (22)	6.5 (3.4-38)	0.82	
		Lobar	17 (33)	6.9 (4.6-13.3)		
		Main	23 (45)	7.7 (4.8-11.1)		
	AFP	>100 mg/dL	36 (71)	6.4 (4.6-10.4)	0.94	
		≤100 mg/dL	15 (29)	7.9 (6.4-14.4)		
	Baseline Tumor Size	≤5 cm	9 (18)	14.4 (6.9-20.1)	**0.04**	
		>5 cm	42 (82)	6.4 (4.8-8.1)		
≥Child Pugh-B8 (N=60)	Age	≥65	27 (45)	3.5 (2.5-5.0)	0.34	3.9 (2.9-5.0)
		<65	33 (55)	4.1 (2.9-6.7)		
	Sex	Male	51 (85)	3.9 (2.7-5.0)	0.45	
		Female	9 (15)	4.1 (2.7-9.5)		
	PVT	Segmental	8 (13)	8.4 (1.2-75.2)	**0.015**	
		Lobar	21 (35)	4.4 (2.5-9.7)		
		Main	31 (52)	3.4 (2.5-4.6)		
	AFP	>100 mg/dL	41 (68)	3.3 (2.3-4.8)	0.09	
		≤100 mg/dL	19 (32)	4.8 (4.1-9.5)		
	Baseline Tumor Size	≤5 cm	16 (27)	12.6 (2.3-21.7)	**0.01**	
		>5 cm	44 (73)	3.6 (2.3-4.8)		

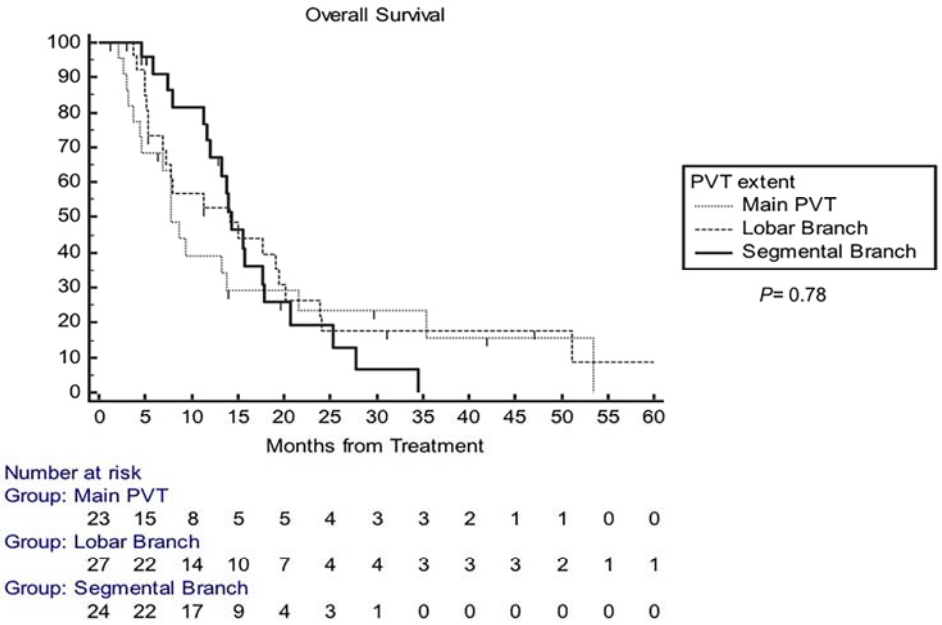
(PVT = Portal Vein Thrombosis; AFP = Alpha-fetoprotein)

Table 4: Uni/Multivariate Analyses

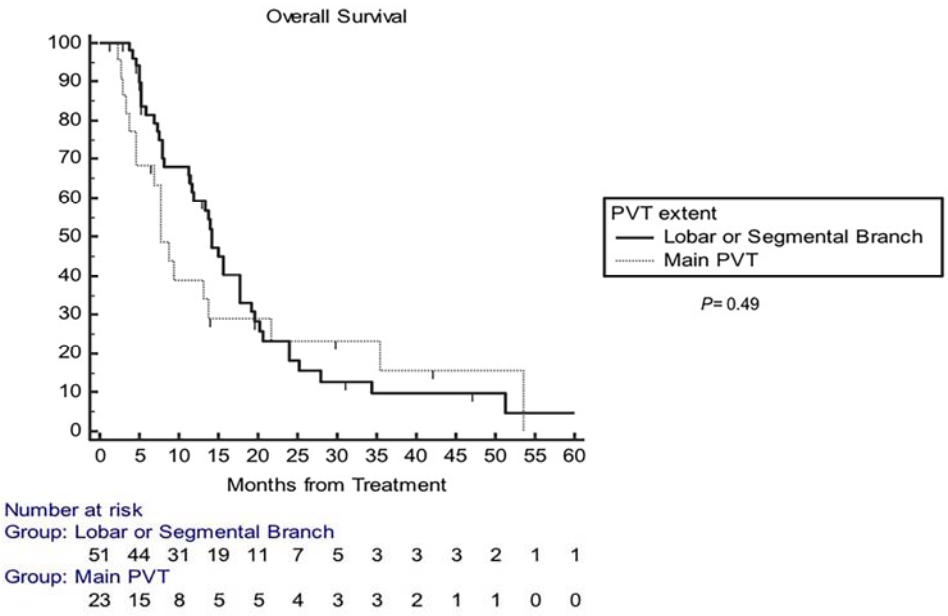
	Univariate analysis				Multivariate analysis	
Predictor	Category	OS (95% CI)	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age	<65	7.8 (5.8-11)	0.9 (0.6-1.2)	0.49	N/A	N/A
	≥65	7.5 (5-9.4)	1		N/A	
Sex	Female	9.5 (5.3-13.7)	0.9 (0.6-1.3)	0.6	N/A	N/A
	Male	7.3 (5.8-8.5)	1		N/A	
Albumin	>3.5 g/dl	11.7-21	0.4 (0.2-0.7)	**0.002**	0.7 (0.4-1.4)	0.3
	2.8-3.5 g/dl	7.8 (6.4-11.4)	0.7 (0.5-0.9)		0.7 (0.5-1)	0.07
	<2.8 g/dl	4.8 (4-7.7)	1		1	
Bilirubin	<2 mg/dL	8 (7.3-11)	0.15 (0.03-0.6)	**<0.0001**	0.16 (0.07-0.3)	**<0.0001**
	2-3 mg/dL	5 (2.2-9.7)	0.24 (0.05-1.2)		0.18 (0.07-0.43)	**0.0001**
	>3 mg/dL	2 (1.2-3)	1		1	
Cirrhosis	Absent	6.8 (6.2-8.9)	0.95 (0.6-1.6)	0.86	N/A	N/A
	Present	7.7 (5-20)	1		N/A	
Ascites	Absent	8.8 (7.7-12)	0.6 (0.4-0.85)	**0.0015**	0.6 (0.4-0.9)	**0.01**
	Present	4.6 (3.5-6.4)	1		1	
Baseline Tumor Size	≤5 cm	13.9 (11-20)	0.5 (0.4-0.75)	**0.0007**	0.64 (0.42-0.97)	**0.037**
	>5 cm	6.4 (5-7.8)	1		1	
Number of lesions	Solitary	12.6 (7.7-19)	0.6 (0.4-0.78)	**0.001**	0.62 (0.4-0.98)	**0.04**
	Multifocal	6.5 (5-7.9)	1		1	
Infiltration	Non-infiltrative	12.6 (7.7-14)	0.67 (0.5-0.9)	**0.01**	1 (0.7-1.5)	0.9
	Infiltrative tumor	6.2 (4.6-7.7)	1		1	
Tumor distribution	Unilobar	9.4 (7.7-13.3)	0.6 (0.4-0.8)	**0.0015**	0.68 (0.46-1)	0.068
	Bilobar	5 (4.5-6.5)	1		1	
AFP	<100	11.4 (7.9-13.9)	0.7 (0.5-0.9)	**0.05**	0.67 (0.5-0.96)	**0.03**
	≥100	6.5 (5-7.7)	1		1	
ECOG	0	8 (6.7-13.8)	0.32 (0.14-0.78)	**0.0001**	0.44 (0.24-0.8)	**0.01**
	1	7.7 (5.2-9.5)	0.35 (0.15-0.8)		0.39 (0.22-0.7)	**0.001**
	2	2.5 (2-4.6)	1		1	
PVT Extent	Segmental	13.8 (8.5-15.7)	0.54 (0.36-0.8)	**0.008**	0.8 (0.5-1.3)	0.4
	Lobar	7.7 (5.3-10.4)	0.7 (0.5-1)		0.8 (0.5-1.2)	0.2
	Main	5 (4-7.7)	1		1	

Supplementary Table 1: Survival analysis based on AFP trends.

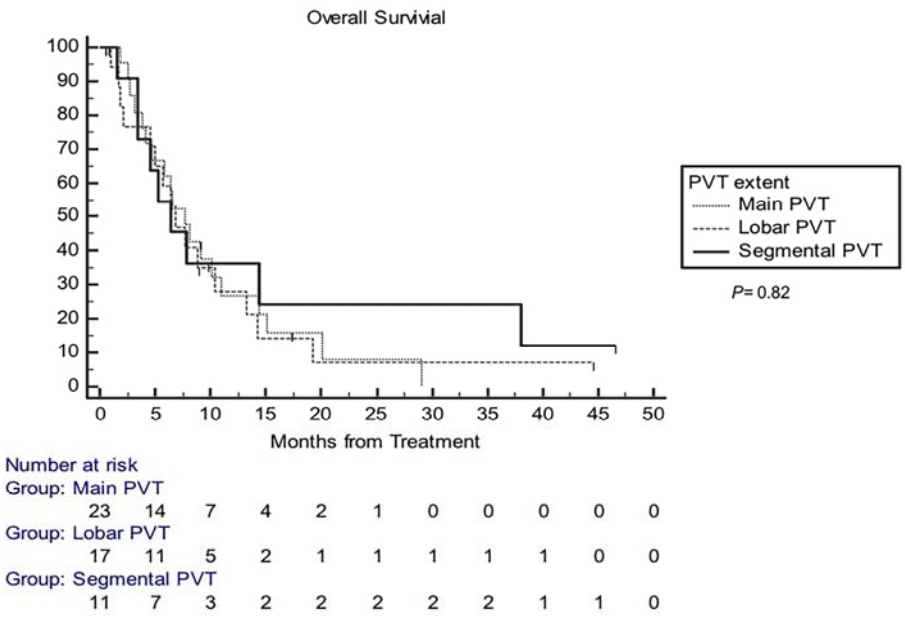
Landmark	Response	N (%)	median OS (95%CI)	P
Baseline (n=185)	<100	123 (66%)	11.4 (7.9-13.9)	0.05
	≥100	62 (34%)	6.5 (5-7.7)	
AFP follow-up at any time point (n=101)	Responders (AFP<13 ng/dL)	12 (12%)	23.9 (20-124)	**<0.0001**
	Non / partial responders	89 (88%)	6.5 (4.8-7.8)	
1-month (n=101)	Responders (≥50% decrease from baseline)	49 (48%)	8.5 (6.5-14.3)	**0.018**
	Non-responders (<50% decrease from baseline)	52 (52%)	4.8 (3.7-7.7)	
3-month (n=65)	Responders (≥50% decrease from baseline)	43 (66%)	13.3 (8.7-17.7)	**0.021**
	Non-responders (<50% decrease from baseline)	22 (34%)	(5.3-8.9)	



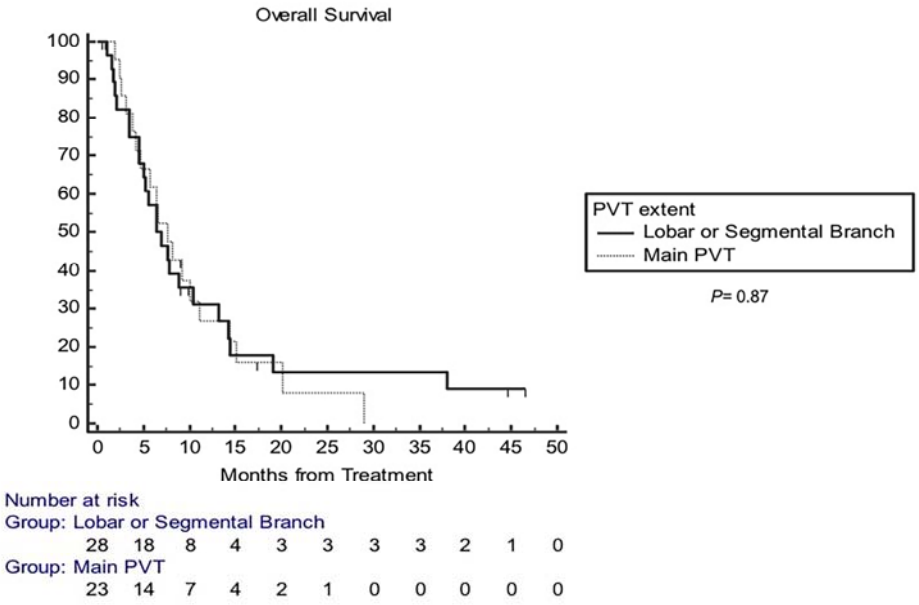
Supplementary Figure 1A: Overall Survival: CP A Main vs. Lobar Vs. Segmental



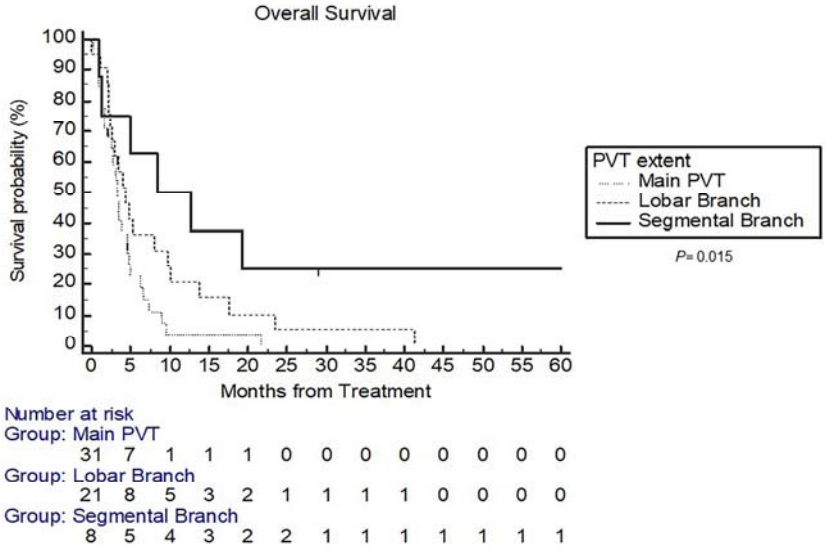
Supplementary Figure 1B: Overall Survival: CP A Main vs. Lobar/Segmental



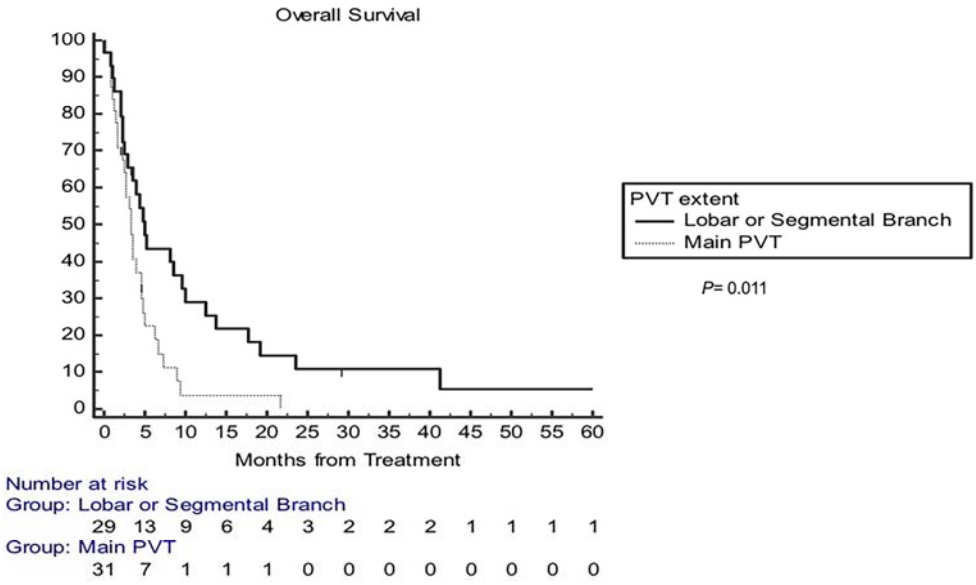
Supplementary Figure 2A: Overall Survival: CP B7 Main vs. Lobar vs. Segmental



Supplementary Figure 2B: Overall Survival: CP B7 Main vs. Lobar/Segmental



Supplementary Figure 3A: Overall Survival: CP ≥B8 Main vs. Lobar vs. Segmental



Supplementary Figure 3B: Overall Survival: CP ≥B8 Main vs. Lobar/Segmental