Yttrium-90 radioembolization for hepatocellular carcinoma in hepatitis B: commentary on a 103-patient Asian cohort

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Y90 radioembolization [also known as selective internal radiation therapy (SIRT)] is recognized as a safe and effective therapy for hepatocellular carcinoma (HCC), with a particular role for Y90 in patients with large tumors and/or portal vein thrombosis (PVT). Studies from Europe and the United States, comprised of 776 patients in aggregate, have demonstrated comparable results when taking into account cohort differences in terms of baseline Child–Pugh classification and tumor stage defined by the Barcelona Clinic Liver Cancer system (BCLC) [1–4]. These Western studies included patients predominately with hepatitis C and/or alcohol as the underlying cause of liver disease with limited numbers of patients with hepatitis B virus (HBV) (9–30 %).

HBV is the leading cause of HCC worldwide, with over 50 % of all causes of HCC attributable to HBV. While there is convincing data from the REVEAL study that the risk of HCC is impacted by the height of the HBV viral load (VL), there has not been conclusive data that achieving an undetectable HBV VL negates the risk of eventual HCC development. This is hypothesized to be related to the integration of cccDNA into the host DNA with a carcinogenetic capacity via genetic instability. Clinical-pathologic differences have been reported between HBV versus Hepatitis C virus (HCV), the former being more commonly associated with larger tumors,

younger age and lower cirrhosis rates [5]. Other single center retrospective reports have sought to determine if a difference exists in outcomes with various therapeutic options. Viral etiology was not found to have an impact on outcome among patients treated with transarterial chemoembolization (TACE) [6]. However, the etiology of disease has been apparent in orthotopic liver transplant (OLT), with a significant decrease in overall survival (OS) in HCV due to recurrent HCV post-transplant [7]. Systemic therapy with sorafenib was associated with shorter median OS among Asian patients relative to a Western cohort; however, there was a similar degree of survival benefit associated with sorafenib relative to placebo (hazard ratios 0.69 and 0.68, respectively) [8, 9].

The experienced team from Singapore has reported a retrospective analysis of 103 Asian patients with nearly half (47.6 %) of the patients with HBV-induced HCC treated with Y90 [10]. The tumor characteristics were comparable to the Western cohorts (Table 1). Safety and tolerability were also similar to other cohorts. While the authors demonstrated a comparable median OS of 14.4 months, the time-to-progression (TTP) of 5.3 months was shorter. Progression (using RECIST 1.1 at 3 months after therapy) was available in only half of the entire cohort (potentially affecting the results and lower response rate). Nonetheless, it is of interest that progression was not seen in the treated lesion(s) and the analysis was limited to the first Y90 administration, demonstrating excellent local tumor control; such a pattern of metastases and the high local control rates have been reported previously [11, 12]. However, 38 % of disease control was due to stable disease which, among TACE cohorts, has been found to predict worse outcomes compared to those with complete/partial response [13]. The use of RECIST 1.1, without taking into account presence of necrosis, makes it impossible to

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Table 1 Clinical experience with radioembolization in HCC

	NW (<i>n</i> = 291) Single center glass ^a	Essen (<i>n</i> = 108) Single center glass ^b	European (<i>n</i> = 325) Multicenter resin ^c	Milan (<i>n</i> = 52) Single center glass ^d	Asian (<i>n</i> = 103) Single center resin ^e
Patient characteristics					
CP A/B/C (%)	45/52/3	77/22(≤7)/0	82/18/0	83/17(≤7)/0	59/38/3
BCLC A/B/C/D (%)	17/28/52/3	2/47/51/0	16/27/56/1	0/33/67/0	1/27/69/3
Mean tumor size (cm)	7.0	–	–	5.6	8.8
Multifocal (%)	73	–	76	69	81
PVT (%)	43	31	23	67	
Extrahepatic mets (%)	16	30	9	–	12
Outcomes					
Overall survival (months)	CP A: 17.2	CP A: 17.2	CP A: –	CP A: –	CP A: 21.7
	CP B: 7.7	CP B: 6.0	CP B: –	CP B: –	CP B: 7.1
	BCLC A: 26.9	BCLC A: –	BCLC A: 24.4	BCLC A: –	BCLC A: –
	BCLC B: 17.2	BCLC B: 16.4	BCLC B: 16.9	BCLC B: 18	BCLC B: 23.8
	BCLC C: 7.3	BCLC C: not reached	BCLC C: 10.0	BCLC C: 13	BCLC C: 11.8
TTP (months)	7.9	10.0	–	11	5.3
	CP A 10.8				CP A 5.7
	CP B 8.4				CP B 4.6
Adverse events					
Abdominal pain (%)	23 (grades 1–2)	56 (grades 1–2)	27 (all grades)	6 (grades 3–4)	12
GI ulcers (%)	0	0	3.7	0	1.9

^a Salem et al. [1]^b Hilgard et al. [2]^c Sangro et al. [4]^d Mazzaferro et al. [3]^e Yu et al. [10]

speculate if less favorable outcomes would be anticipated in the radioembolization cohort with stable disease. Additionally, nearly 20 % of patients had TACE prior to Y90. It is conjecture that such patients may have derived less of a robust response if the timing of sequential Y90 was too short to permit vascular recanalization post-TACE.

The authors admit that their data preclude the ability to correlate the impact of viral etiology on the outcomes in patients treated with radioembolization. In the multivariate analysis, HCV was associated with improved OS (hazard ratio = 0.13), and furthermore there was a noted trend of HBV leading to a lower OS compared to non-HBV patients (12.4 vs. 18.1 months, $p = 0.76$). The authors did not report if there were a greater proportion of HCV patients that eventually underwent OLT. While TTP was censored after receipt of 1 Y90 session, and was likely impacted by the short imaging follow-up time, OS was not, potentially resulting in a confounding effect of post-progression treatment.

Liver parameters (bilirubin, albumin) were independent predictors of OS, both of which can be impacted by the degree of underlying liver disease, HCC progression, and treatment decision in terms of radiation dose and degree of treated liver. It is not stated if there was a difference in

these laboratory values in HBV versus HCV; HCV can be associated with an overall greater degree of liver impairment due to HBV generally being able to be suppressed with potent anti-viral agents. Due to the retrospective nature of this study, the authors were also not able to ascertain if active viral replication, specifically HBV, impacted OS. The REVEAL study clearly showed a biological gradient of HBV viral load and ALT levels in the risk of developing cirrhosis and HCC. Whether this “gradient” exists once a patient develops HCC is less clear. Another clinical consideration that is becoming more apparent among patients with HBV is the co-existence of hepatitis D (HDV) associated with a more aggressive hepatitis and increased HCC risk [14]. Other factors that could have an impact in HBV-induced hepatocarcinogenesis include genotype, mutations and antiviral therapy. In future analyses, examining outcomes in HCC with various therapeutic modalities, stratification based on the presence of active HBV replication, including HBsAg titers and HDV status, may help decipher the heterogeneity in outcomes observed in many studies.

Mortality was predominately related to tumor progression (84.6 %); however, the majority of disease progression

was related to development of new lesions consistent with intrahepatic metastasis despite disease control of 100 % in the targeted lesion(s). Inarrairaegui et al. [15] reported that OS was significantly affected by the development of new lesions within the treatment area at 3 months in advanced HCC treated with Y90 (19 vs. 7 months, $p = 0.002$), leading the authors to conclude that survival was dependent on biological aggressiveness of the tumor. The authors in this study did not provide details as to whether the new lesions were within the treated field. This leads to the question of whether combining a systemic agent with local regional therapy would lead to augmentation of tumor control. Unfortunately, this approach has led to conflicting results in the pre-OLT setting (Y90 + sorafenib) and in BCLC B (TACE/drug-eluting beads + sorafenib), with the most encouraging results among a HCV alone cohort [16–20]. However, it is apparent that, with tumor progression, many patients develop hepatic decompensation, limiting the ability to initiate sorafenib [21, 22]. These clinical realities and the interaction between treatment/progression/liver function potentially suggest the earlier use of systemic agents *prior to* the development of tumor progression when synthetic function is maintained [21]. Side-effects and cost would need to be factored into such decisions. Ongoing controlled trials will eventually answer this very important clinical question.

These data contribute to the growing body of clinical evidence supporting Y90 in HCC with OS rates comparable to Western series. The question of whether HBV has worse outcomes relative to HCV in general and with specific therapies such as radioembolization remains speculative. Certainly, with the advent of direct acting anti-viral for HCV and response rates exceeding 90 %, it is hypothesized that outcomes in HCV-induced HCC will improve, especially post-OLT. This may highlight potential differences in hepatocarcinogenesis (and hence prognosis) from HBV or HCV and make them more apparent.

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