

available at www.sciencedirect.com

The ENRY analysis: a 325-patient European multicentre analysis

Bruno Sangro*

Liver Unit, Clinica Universidad de Navarra, and Centro de Investigacion Biomedica en Red de Enfermedades Hepaticas y Digestivas (CIBEREH), Pamplona, Spain

ARTICLE INFO

Keywords:

Radioembolisation
Selective Internal Radiation Therapy
 ^{90}Y
Yttrium-90
Liver-directed therapy
Advanced hepatocellular carcinoma
HCC
BCLC stage

1. Introduction

Between September 2003 and December 2009, the ENRY (European Network on Radioembolisation with Yttrium-90 resin microspheres) group collated data on 325 consecutive patients with a confirmed diagnosis of hepatocellular carcinoma (HCC) who received selective internal radiation therapy (SIRT), also known as radioembolisation, with yttrium-90 (^{90}Y) resin microspheres (SIR-Spheres®) at eight European centres.¹ Multiple analyses were conducted according to disease stage, prior treatment and key prognostic markers such as liver function (as measured by individual variables such as bilirubin levels or by composite variables such as the Child–Pugh score) and tumour burden (as measured by nodularity, portal vein thrombosis [PVT], extrahepatic disease [EHD] or performance status). These analyses have helped provide some important insights into questions of the safety and efficacy of this procedure

*Correspondence: Bruno Sangro, MD, Liver Unit, Clínica Universitaria de Navarra, Avda. Pio XII 36, 31008 Pamplona, Spain. Tel: +34 948 296 637; fax: +34 948 296 500.
E-mail address: bsangro@unav.es (B. Sangro).

and enabled more meaningful comparison with other treatments in patients with the same stage of disease.¹

The ENRY study population had primarily good liver function (Child–Pugh class A; 82.5%), underlying cirrhosis (78.5%) and Eastern Cooperative Oncology Group (ECOG) performance status (ECOG ≥ 1 ; 45.7%). Many had multinodular disease (75.9%), invading both lobes (53.1%) including some with high alpha-fetoprotein (>400 ng/mL; 34.9%), PVT (23.3%) and EHD (9.2%). Most patients (93.2%) received SIRT as a single procedure (median activity administered 1.6 GBq) and were followed-up for a median of 10.0 months.

2. Safety and tolerability

ENRY provides a comprehensive analysis of the safety and tolerability of SIRT in a cohort with a high incidence of cirrhosis.¹ Patients were assessed for procedure-related adverse events up to 7 days post-SIRT and thereafter, for radiation-related adverse events up to 3 months. Overall, there was a low incidence of mainly

Table 1 – Main procedure-related clinical adverse events by severity in HCC patients treated with ⁹⁰Y resin microspheres

Adverse event	CTCAE v3: No. (%)				
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Nausea and/or vomiting	104 (32.0%)	89 (27.4%)	14 (4.3%)	1 (0.3%)	0
Abdominal pain	88 (27.0%)	70 (21.5%)	13 (4.0%)	5 (1.5%)	0
Fever	40 (12.3%)	36 (11.1%)	4 (1.2%)	0	0
Fatigue	112 (34.5%)	100 (30.8%)	10 (3.1%)	2 (0.6%)	0

Procedure-related events (fatigue, nausea and vomiting, abdominal pain and fever) were evaluated from day 1 to day 7.
CTCAE v3: Common Terminology Criteria for Adverse Events version 3.0.

Table 2 – Main radiation-related laboratory adverse events by severity in HCC patients treated with ⁹⁰Y resin microspheres

Organ	Variable	All Grades		Grade ≥3	
		Pre-treatment	Month 3	Pre-treatment	Month 3
Liver	Bilirubin	22.6%	48.6%*	0.0%	5.8%*
	Albumin	38.0%	39.7%	0.0%	0.8%
	INR	22.4%	31.4%	0.0%	1.8%
	ALT	59.6%	57.4%	1.8%	3.3%
	Creatinine	8.3%	11.6%	0.4%	1.4%
GI tract	Platelets	44.4%	52.6%	2.2%	3.4%
	GI ulcers	0	3.7%	0	1.8%
Lungs	Pneumonitis	0	0	0	0

Radiation-related events were evaluated from day 8 to month 3.
CTCAE v3: Common Terminology Criteria for Adverse Events version 3.0
*p-value <0.001 by exact McNemar test comparing Grade 3–4 CTCAE at month 3 versus Grade 3–4 pre-SIRT.

mild, transient post-procedural adverse events (Table 1).¹ The incidence of radiation-related events was generally unremarkable except for an increase in the proportion of patients with raised bilirubin levels compared with the pretreatment assessment (Table 2).¹

3. Survival

Median survival was 13.1 months (95% confidence interval [CI] 10.9–15.8) and varied significantly by Barcelona Clinic Liver Cancer (BCLC) stage (Fig. 1).

3.1. Is age a limitation for SIRT?

In patients stratified by age (<70 yrs or ≥70 yrs), median survival (95% CI) was similar regardless of age: 12.8 months (10.8–17.9) vs 14.5 months (10.6–16.8), respectively in each group (p=0.942).¹ SIRT was equally well tolerated in both populations.

3.2. Is SIRT suitable for Child–Pugh B patients?

Reduced functional reserve and impaired regenerative ability of the cirrhotic liver increase the risk of liver failure, especially for patients who have had prior extensive resection, or liver insult from toxins, acute viral hepatitis or external irradiation. In the ENRY

analyses, patients receiving SIRT with Child–Pugh B had a shorter median survival (95% CI) than patients with Child–Pugh A: 10.0 months (6.1–13.8) vs. 14.9 months (11.9–17.1); p=0.006. Key factors, such as the presence of ascites, were thought to contribute to the lower survival with SIRT: median survival (95% CI) with and without ascites: 6.1 months (4.4–8.6) vs. 14.1 months (11.8–17.9); p<0.001.

3.3. How does SIRT compare with transarterial chemoembolisation (TACE) in intermediate-stage HCC?

Typical candidates for SIRT have either advanced- or intermediate-stage HCC and are generally considered poor candidates for TACE. By contrast, the main randomised studies supporting the efficacy and safety of TACE are primarily in intermediate- and early-stage disease including patients who cannot be treated with radical therapies because of either age, tumour size and location, cirrhosis or comorbidities. There are, however, several series with TACE that include patients with intermediate- and even advanced-stage disease. In a recent case series evaluation analyzed by BCLC stage, TACE (n=172)² was found to be broadly equivalent to SIRT (n=325)¹ with median overall survivals of 17.4 months (95% CI 13.9–18.8) and 16.9 months (95% CI 12.8–22.8), respectively, in intermediate- (BCLC) stage 'B'. These findings are supported by a third large case series

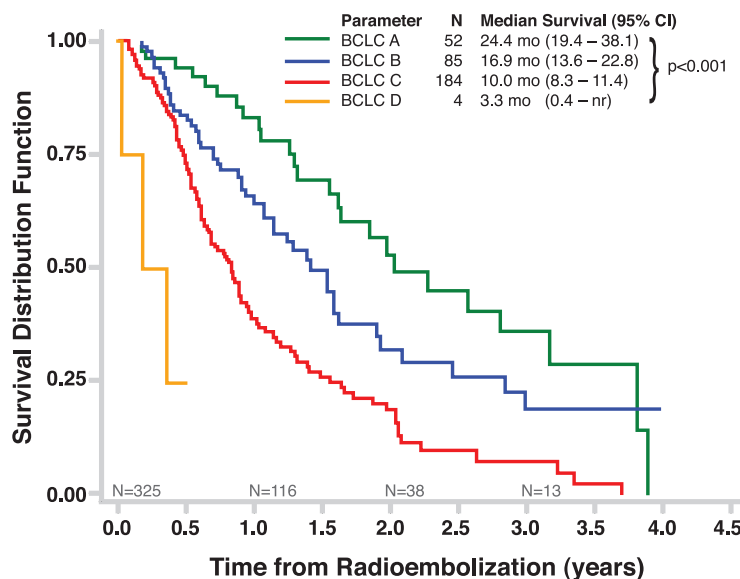


Fig. 1 – Survival of HCC patients treated with ^{90}Y resin microspheres stratified by BCLC stage. Reproduced with permission from Sangro B, Carpanese L, Cianni R et al.,¹ on behalf of European Network on Radioembolization with yttrium-90 resin microspheres (ENRY). Survival after ^{90}Y resin microsphere radioembolization of hepatocellular carcinoma across BCLC stages: A European evaluation. *Hepatology* 2011;54:868–78.

from the USA in BCLC stage ‘B’ HCC, which found that patients receiving SIRT with ^{90}Y -glass microspheres ($n=291$) had a median overall survival of 17.2 months (95% CI 13.5–29.6 months).³

Importantly, data from ENRY show that survival following SIRT appears particularly promising for the subset of patients with intermediate-stage HCC who are considered poor candidates for TACE (i.e. those with bilobar and/or multiple [>5] tumors; median survival: 15.4–16.6 months) as well as for those who had failed prior TACE or transarterial embolisation (TAE) (median survival: 15.4 months).¹

3.4. How does SIRT compare to sorafenib in the advanced-stage population?

More than half the candidates (56.3%) for SIRT from the ENRY study had advanced- (BCLC) stage C HCC due to the presence of either vascular invasion, EHD or altered cancer-related performance status.

Median survival in this subset was 10.0 months (95% CI 7.7–10.9) and treatment was well-tolerated, although fatigue (mostly mild grade 1 events) was more common in patients with deteriorating ECOG performance status.⁴ Investigators found that SIRT was as effective and equally well tolerated in patients with and without PVT without any significant reduction in overall survival or increased risk of laboratory parameter adverse events.⁴

It is notable that comparisons of the populations from the ENRY and sorafenib studies include a very similar population of patients with mixed intermediate- and advanced-stage HCC,⁵ although the studies of sorafenib tended to include a higher percentage of patients with

EHD, particularly in the Asia-Pacific trial⁶. Even so, 58% (189 of 325) of patients from the ENRY cohort matched the inclusion criteria for the SHARP trial. Analyses of these cohorts found a significant overlap in terms of overall survival between the two treatment modalities,⁷ with a median overall survival with SIRT of 10.8 months (95% CI: 8.8–12.8) in SHARP-equivalents and 10.2 months (95% CI: 8.3–11.8) in a subset of these patients with PVT or EHD. Studies are ongoing to evaluate the relative safety and efficacy of these two treatments either in combination or as monotherapies.

4. Conclusion

SIRT appears to be a particularly promising treatment in cohorts who may not otherwise be considered for locoregional therapy, i.e. patients with intermediate-stage HCC who are poor candidates for TACE (bilobar and/or multiple tumours) and/or have failed prior TACE/TAE, or patients with advanced-stage HCC, particularly those with PVT. Further prospective evaluations of the clinical benefit for SIRT in these patient populations are warranted.

Conflict of interest statement

The author has received lecture and consulting fees from Sirtex Medical and Bayer Schering Pharma.

REFERENCES

1. Sangro B, Carpanese L, Cianni R, et al. for the European Network on Radioembolization with Yttrium-90 Resin Microspheres (ENRY). Survival after yttrium-90 microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**:868–78.
2. Lewandowski RJ, Mulcahy MF, Kulik LM, et al. Chemoembolization for hepatocellular carcinoma: comprehensive imaging and survival analysis in a 172-patient cohort. *Radiology* 2010; **255**:955–65.
3. 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.
4. Sangro B, Ettorre G, Cianni R, et al. Survival and tolerability following ⁹⁰Y-resin microsphere radioembolisation in patients with unresectable BCLC stage C hepatocellular carcinoma (HCC). European Association for the Study of the Liver (EASL) Congress, *Journal of Hepatology* 2011; **54**(Suppl 1):S36; Abstract 650.
5. Llovet J, Ricci S, Mazzaferro V, et al. for the SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**:378–90.
6. 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.
7. Sangro B, Carpanese L, Salvatori R, et al. Safety and efficacy of radioembolization amongst patients who met the inclusion criteria for the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial. 5th International Liver Cancer Association (ILCA) Meeting, September 2011; Abstract P-141.