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Radioembolization Super Survivors: Extended Survival in Non-Operative Hepatocellular Carcinoma

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Abstract

Purpose—To identify baseline characteristics and long-term prognostic factors in non-transplant patients with unresectable hepatocellular carcinoma (HCC) who had prolonged survival after treatment with yttrium-90 radioembolization (Y90).

Materials and Methods—67 "Super Survivors" (defined as ≥3 years survival after Y90) were identified within our 1,000-patient Y90 database (2003–2017). Baseline imaging and follow-up occurred at 1 months and every 3 months thereafter. Overall survival (OS) was calculated with Kaplan-Meier estimates with log-rank test in sub-groups: Child-Pugh (CP) score, distribution of disease, portal vein thrombus (PVT), and technique (segmental vs lobar Y90).

Results—Median age 69.5 years (range: 45–94 years); 69% male; 60% solitary HCC; 79% unilobar disease; 12% PVT; 10% ascites; Barcelona Clinic Liver Cancer Stage A-54%/B-28%/ C-16%/D-2%; CP A-70%/B-28%/C-2%. Longest baseline tumor diameter was 5.4 ± 4.0cm (mean ± SD). All patients had an imaging response (either partial or complete response). Median OS was 67.5 months (95% confidence interval; 55.2–82.5). CP score and main PVT stratified median OS (p=0.0007 and p=0.0187, respectively). Beyond 3 years, segmental vs lobar Y90 was associated

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Ethical Approval Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Statement: Informed consent was obtained from all individual participants included in the study.

with improved OS with a median OS of 80.2 vs 46.7 months, respectively (p=0.0024). Dosing >200Gy was not a significant predictor of improved OS.

Conclusions—Super survivors spanning the BCLC Staging System maintained durable OS after radioembolization that was stratified by the extent of underlying liver disease. The common variable among all patients was an imaging response. Segmental vs lobar Y90 may have a long-term associated OS benefit.

Keywords

radioembolization; hepatocellular carcinoma; yttrium-90; survival

INTRODUCTION

Yttrium-90 radioembolization (Y90) is a minimally invasive outpatient procedure offered for unresectable hepatocellular carcinoma (HCC). While once reserved only for the salvage setting in patients with multifocal disease and/or portal vein tumor thrombus, radioembolization is now applied across the spectrum of early to advanced HCC Barcelona Clinic Liver Cancer Stages [1–4]. Most patients with HCC are never eligible for curative surgery like hepatic resection or transplantation owing to the extent of disease at presentation, presence of portal hypertension, and the limited availability of transplant organs. In BCLC Stage A patients, chemoembolization and radioembolization have demonstrated similar median survivals of 54.2 months and 53.4 months, respectively [5,6]. In this retrospective study, we aimed to identify factors associated with prolonged survival after Y90 in the absence of surgical resection or transplantation. Among 1,000 patients treated with Y90, a subgroup of non-surgical HCC patients who had atypically long survival of three or more years after intra-arterial therapy with Y90 were defined as “Super Survivors” [4]. Our hypothesis based on the existing Y90 evidence in Barcelona Clinic Liver Cancer (BCLC) Stage A patients was that Super Survivors would be young, with excellent Eastern Cooperative Oncology Group (ECOG) performance status (0–1) and have primarily preserved liver function at baseline (Child-Pugh Class A), solitary, non-invasive disease, and the majority would often go on to eventually receive ablation per the American Association for the Study of Liver Diseases (AASLD) guidelines for BCLC Stage A disease [7].

METHODS

The study was a retrospective observational cohort study under our open-label protocol. We queried the Interventional Oncology Registry for all patients who underwent radioembolization (NCT00532740) and complied with the Health Insurance Portability and Accountability Act. Of 1000 HCC patients treated with Y90 between December 1, 2003 and March 31, 2017, 67 patients met the inclusion criteria as Super Survivors. Each patient was reviewed and discussed by a multidisciplinary tumor board including hepatology, oncology, interventional radiology, and transplant surgery.

Study eligibility

Inclusion criteria included (i) image- or biopsy-proven HCC according to AASLD guidelines [7]; (ii) treatment with Y90, as allocated by a multidisciplinary team; (iii) survival

of 3 or more years. Exclusion criterion was (i) surgery including resection or transplantation at any time during 3-year follow up.

Evaluation and Staging

Patient demographics, risk factors, etiology of liver disease, ECOG performance status, BCLC staging, albumin-bilirubin score and Child-Pugh class were recorded.

Y90 Treatments

Visceral angiography and technetium-99m scintigraphy were used to estimate lung shunting, identify extrahepatic perfusion and perform coil embolization if necessary. Included data and the definition for technical success follow previously published reporting standards for radioembolization [8]. Glass microspheres (TheraSphere®, BTG International) were used in each case with treatment on an outpatient basis. Infusions were completed at the segmental or lobar level with adjustments as previously described for radiation segmentectomy and extended-shelf-life (ESL) protocols [9–12].

Outcome Variables

- **Baseline Characteristics.** Baseline characteristics included patient demographics, underlying etiology and extent of liver disease, presence of vascular invasion, liver function, performance status, tumor size and distribution, and cancer staging per BCLC.
- **Treatment.** The treatment characteristics included type of treatment (segmental or lobar), dose, vial size (GBq), embolic load defined as vial size on calibration (40k–70k microspheres per GBq) per treatment mass (GBq/kg), lung shunt fraction, and lung dose.
- **Laboratory toxicity.** Patients received 1 month follow-up in clinic with measurements of serum albumin, bilirubin, alkaline phosphatase, alanine and aspartate transaminase to assess for biochemical toxicities. Lymphopenia and elevated creatinine after treatment were also recorded.
- **Response rate.** Contrast-enhanced MRI or triphasic CT was used to determine World Health Organization (WHO) and European Association for the Study of the Liver (EASL) assessments [13–15]. Reported outcomes include time to response (either partial response or complete response), response at 6–9 months and response at 12 months applying the primary index lesion methodology.
- **Time-to-Progression.** Time-to-progression (TTP) from the date of treatment was calculated using the Kaplan-Meier (KM) method with progression defined as increased size by WHO, increased enhancement by EASL, new lesions meeting HCC criteria adjudicated to the date of first detection, or extrahepatic metastases.
- **Overall Survival.** Survival was identified by the Social Security Death Index with analyses were calculated from the day of first radioembolization to death (in months) by the KM method.

- **Interval Treatment.** The median time to subsequent treatment, the number of treatments, and the conversion to other liver-directed therapies (denoted by "Y90->X" for Y90 followed by X) were recorded for each patient. The maximum and minimum treatment-free-interval was also calculated for each patient and defined as the longest and shortest period between any two treatments, respectively.

Statistics

Medians are reported with 95% confidence intervals (CI) and means ± standard deviation. Overall survival and TTP outcomes were estimated using the KM method and sub-groups were compared with the log-rank test. The hazard ratio and 95% CI was estimated using Cox proportional hazards regression. All analyses were performed using STATA v14.0 (StataCorp, College Station, Tx); $p<0.05$ was considered significant.

RESULTS

Baseline Characteristics

The baseline characteristics for the cohort are shown in Table 1. Solitary lesions were present in 59.7% of patients. Previous liver-directed therapy was received in 13.4% (n=9) of patients. Thirteen patients (19.4%) were referred for treatment from outside hospitals.

Treatment and Dosimetry

All 67 patients were treated successfully. Segmental Y90 was performed in 45/67 (67%) patients; 22 (33%) were lobar treatments. The average number of Y90 treatments was 2.52±1.69 over the course of follow up. The mean dose was 116Gy for lobar and 206Gy for segmental radioembolization (Supplemental Table 1 online only). The extended-shelf life protocol was applied in 28/50 (56%) patients. The median embolic load (GBq/kg liver) was significantly lower at 10.2 (95% CI, 7.9–12.4) in non-extended shelf-life infusions versus 32.3 (95% CI, 25.3–39.2) for extended-shelf-life infusions.

Laboratory Toxicities

Supplemental Table 2 (online only) summarizes laboratory toxicities. Grade 3+ toxicities were elevated AST 2/67 (3%), hypoalbuminemia 1/67 (1%), and elevated bilirubin 4/67 (6%).

Imaging Outcomes

Supplemental Table 3 (online only) presents imaging response. Follow-up imaging was available in 100% of patients (67/67) with 61 of 67 patients (91%) at 6–9 months and 59 of 67 patients (88%) at 12 months. The number of patients achieving WHO response over follow up was 65/67 (97%) and median time to response was 6.1 months (95% CI, 4.7–8.7 months). EASL response was observed in 67/67 patients (100%). Compared to WHO criteria, the median time to PR/CR was significantly earlier for EASL criteria at 2.6 months (95% CI, 1.2–3.4). Dosing of 200Gy or more did not significantly shorten EASL response

(1.2 vs 3.0 months, p=0.1903) or WHO response (5.9 months vs 6.2 months, p=0.9081). Representative cases are showing in Supplemental Figures S1 and S2 (online only).

Time-to-progression

Figure 1 shows TTP. The rate of progression was 36/67 patients (53.7%) over the course of follow up and the median TTP was 33.7 months (95% CI, 22.0–36.9). Primary index lesion progression occurred in 14/67 (20.9%) and 13/67 (19.4%) by WHO and EASL criteria, respectively. Nine patients (13.4%) developed new lesions.

Overall Survival

Figures 2a and b present KM OS curves. Median OS was 67.5 months (95% CI, 55.2–82.5). CP score stratified median OS at 88.1, 69.6, 69.6, 38.1, and 38.6 months for CP scores of 5, 6, 7, 8, and 9, respectively (p=0.0007). Unilobar vs bilobar disease and solitary vs multifocal disease did not stratify OS (p=0.1608, p=0.0917, respectively). The presence of main vs branch vs no PVT was a significant predictor of OS (p=0.0187). Segmental vs lobar radioembolization showed improved OS with median of 80.2 vs 46.7 months, respectively (p=0.0024). Table 2 demonstrates univariate and multivariate analyses. In patients with solitary HCC and no PVT (n=33) dosing of 200Gy or more resulted in a median OS of 82.5 months versus 64.7 months for <200Gy (p=0.0891).

Interval Treatment

During follow up, 56.7% (n=38) of Super Survivors were treated with Y90 and no other modality (isolated Y90), 19.4% (n=13) later underwent RFA, and 14.9% (n=10) later received systemic therapy with sorafenib, 4.5% (n=3) later received TACE, 3% (n=2) later received bland embolization, and one patient received sorafenib in combination with Y90. The average number of Y90 treatments was 2.11±1.37 for isolated Y90 (no alternate therapy), 3.69±2.14 for Y90 followed by RFA, 2.8±1.75 for Y90 followed by sorafenib, 2.67±2.08 for Y90 followed by TACE, and 1.5±0.71 for Y90 followed by bland embolization. The maximum and minimum treatment-free-intervals for each group of patients are shown in Table 3. The longest minimum treatment free interval was observed in patients treated with isolated Y90 with a median 35.6 months (95% CI, 23.8–39.4). For patients crossing over to other treatments including RFA, TACE, bland embolization, and sorafenib, median minimum treatment free intervals were 6.3 (95% CI, 3.2–15.9), 3.4 (95% CI, −4.1–11.4), 19.8 (95% CI, −97.1–136.7), and 2.1 months (95% CI, 0.7–6.4), respectively.

DISCUSSION

Radioembolization is now tailored to the HCC patient’s unique disease state allowing treatment from early to advanced BCLC Stages and has tolerable safety in the setting of hepatic dysfunction [4,16]. These features are reflected in the present study as Super Survivors included the full BCLC A through D and 12% had PVT. While we expected strong survival outcomes in patients with small solitary HCC [6], 40% of Super Survivors had multifocal disease. Comparisons to historical controls are shown in Table 4 with Super

Survivors having more favorable baseline characteristics, higher imaging response rates, and decreased toxicity overall.

The appropriate clinical endpoint for Y90 in the treatment of HCC for improved OS is an imaging response rather than freedom from progression [17]. This is further emphasized in the present study as **ALL** Super Survivors had an imaging response (either WHO or EASL) in primary index lesions over the course of follow up. The average number of Y90 treatments was 2.5 corresponding to <0.5 treatments per year of post-treatment survival. While multiple treatments may be required to achieve response, half of patients do not receive more than one Y90 treatment and multiple factors likely contribute: therapeutic response, toxicity, preference for alternative treatment, systemic disease progression, and survival [4].

The overall median TTP following Y90 was 33.7 months yet the median OS for the cohort was 67.5 months. By exclusion criteria, these patients did not receive surgical intervention. Therefore, we theorize this extended survival following progression is due to the successful application of subsequent liver-directed therapies. This is further supported by the minimum treatment-free-interval of 35.6 months for isolated Y90 that mirrors the median TTP of 33.7 months. The application of segmental treatments significantly improved long-term OS in our cohort supporting the concept of radiation segmentectomy for improved preservation of liver parenchyma, especially in the absence of transplantation [11]. Dosing >200Gy was not associated with improved OS or earlier response consistent with the concept of threshold dose [11,18,19]. Y90 dosing has not been significantly linked to imaging response, survival, or toxicity [16,20,21]. Interestingly, Ahmed et al. have suggested use of imaging surrogates based on the targeted hepatic parenchyma within the treated angiosome which may be an area of future interest for monitoring radiation segmentectomy [22].

At baseline, 34/67 (50.7%) patients in our study were outside Milan criteria. Tumors were >5cm on average and 33% of patients had a previous history of cancer other than HCC. In a prospective randomized controlled trial, patients listed for transplantation who were randomized to radioembolization received liver transplantation at a rate of 87% and radioembolization offers comparable post-transplantation outcomes compared to chemoembolization [23,24]. However, an increasing number of patients are receiving radioembolization as destination therapy and, while many centers offer curative surgery, there is an increasing role of radioembolization in the context of reduced access to surgery (i.e., resource-limited environments that cannot offer transplantation), reduced imminent need for surgery (i.e. curative hepatitis C treatments), longer transplant wait times for HCC patients (6 months before MELD 28 with some recommendations this be extended to 9 months) [25–27].

Limitations

Our definition of Super Survivors introduces guaranteed time bias. Given the limited survival of HCC patients, such patients are rare in the absence of curative surgery so an adequate sample of untreated patients for comparison was not available. Since crossover to alternate therapies is a possible confounder, we describe these therapies in detail, including their interval timing. The TTP data was in-line with our previous experience but it should

not serve as an estimate for TTP following Y90 in all-comers since patients whose progression resulted in death prior to 3-years were excluded in our cohort by definition. Finally, our study was retrospective in nature with the usual associated limitations.

Conclusions

Long-term survival after intra-arterial therapy with radioembolization is possible in select patients. Super survivors who lived 3-years after radioembolization spanned the BCLC Staging System and had advanced age at the time of treatment yet maintained durable OS after radioembolization that was stratified by the extent of underlying liver disease at baseline. All patients achieved an imaging response. Segmental technique was associated with significantly prolonged survival suggesting a long-term benefit to this liver-sparing approach in patients who do not have surgical intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ALBI	Albumin-bilirubin
ALT	ALanine Transaminase
AST	ASpartate Transaminase
BCLC	Barcelona Clinic Liver Cancer
CI	Confidence Intervals
CR	Complete Response
ECOG	Eastern Cooperative Oncology Group
EASL	European Association for the Study of the Liver
ESL	Extended-Shelf-Life
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
KM	Kaplan-Meier

NASH	Non-Alcoholic SteatoHepatitis
OS	Overall Survival
PD	Progressive Disease
PVT	Portal Vein Thrombosis
PR	Partial Response
RFA	RadioFrequency Ablation
SD	Stable Disease
TACE	TransArterial ChemoEmbolization
TTP	Time-To-Progression
WHO	World Health Organizing
Y90	Yttrium-90 radioembolization

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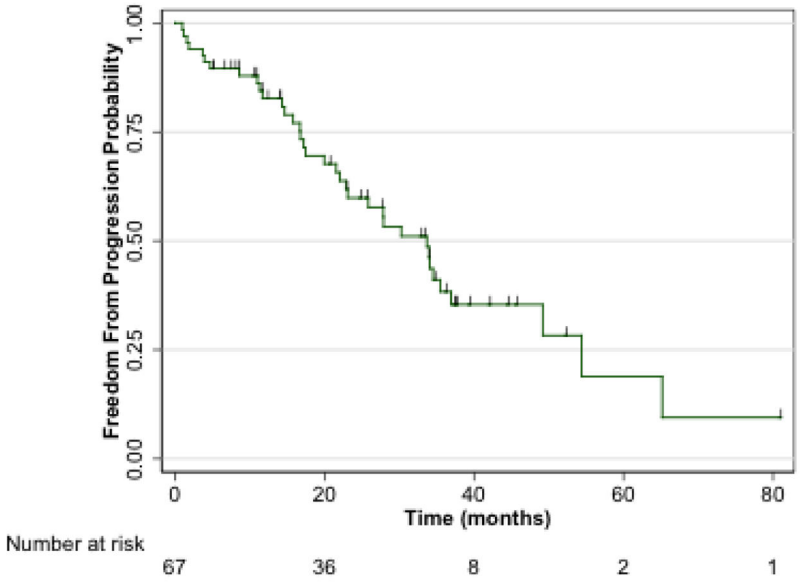
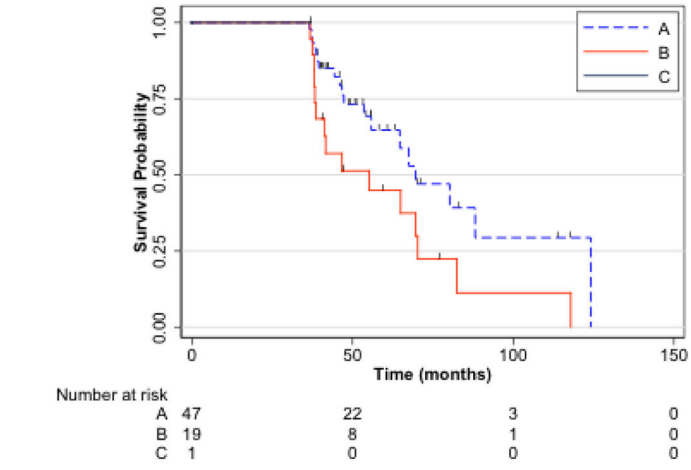
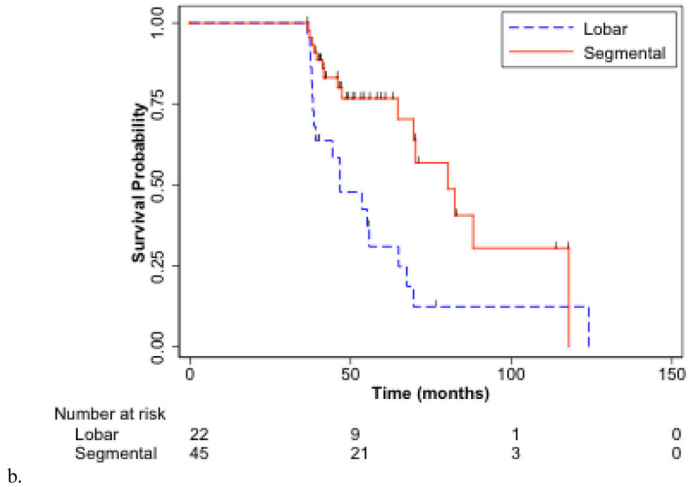


Fig 1.
The median TTP was 33.7 months (95% CI, 22.0–36.9).



a.



b.

Fig 2.

Overall survival from Y90 (a) by Child-Pugh Score and (b) by lobar or segmental Y90.

Table 1

Baseline Characteristics

Characteristic	No. Patients	%
Demographics		
Age (years) *	**48**	**(65, 71)**
< 65 y	**19**	**28.4**
≥ 65 y	**48**	**71.6**
Gender		
Male	**46**	**68.7**
Female	**21**	**31.3**
Ethnicity		
Caucasian	**48**	**71.6**
African American	**6**	**9.0**
Hispanic	**5**	**7.5**
Asian	**7**	**10.4**
Declined	**1**	**1.5**
Risk Factors		
Etiology		
Alcohol	**14**	**20.9**
HCV	**21**	**31.3**
HCV + Alcohol	**3**	**4.5**
Hemachromatosis	**1**	**1.5**
Hemachromatosis + Alcohol	**1**	**1.5**
HBV	**5**	**7.5**
NASH	**7**	**10.4**
NASH + Alcohol	**1**	**1.5**
Autoimmune Hepatitis	**1**	**1.5**
Acute Intermittent Porphyria	**1**	**1.5**
Acetaminophen	**1**	**1.5**
Cryptogenic	**5**	**7.5**
Unknown	**6**	**9.0**
Cirrhosis		
Present	**52**	**77.6**
Absent	**15**	**22.4**
Distribution		
Unilobar	**53**	**79.1**
Bilobar	**14**	**20.9**
No. of lesions		
Solitary	**40**	**59.7**
Multifocal	**27**	**40.3**
Largest Tumor Size (cm)		
Median (IQR)	**4.0**	**4.9**

Characteristic	No. Patients	%
Mean (95% CI)	**5.4**	**(4.4, 6.4)**
AFP (ng/mL)		
<200	**55**	**82.1**
≥ 200	**12**	**17.9**
Previous Therapies		
None	**58**	**86.6**
Resection	**5**	**7.5**
RF ablation	**1**	**1.5**
Percutaneous Ethanol Injection and TACE	**1**	**1.5**
TACE	**1**	**1.5**
Drug-eluting Beads	**1**	**1.5**
Previous Cancer History		
None	**45**	**67.2**
One	**20**	**29.9**
Two or more	**2**	**3.0**
ECOG Performance Status		
0	**46**	**68.7**
1	**20**	**29.9**
2	**1**	**1.5**
Liver Function		
Bilirubin, total serum (mg/dL) *	**0.9**	**(1.0, 1.4)**
Albumin (g/dL) *	**3.3**	**(3.1, 3.4)**
Ascites		
Present	**7**	**10.4**
Absent	**60**	**89.6**
Portal Vein Thrombosis		
Main	**3**	**4.5**
Branch	**5**	**7.5**
Absent	**59**	**88.1**
Staging		
BCLC		
A	**36**	**53.7**
B	**19**	**28.4**
C	**11**	**16.4**
D	**1**	**1.5**
Child-Pugh		
A	**47**	**70.1**
B7	**11**	**16.4**
B8	**5**	**7.5**
B9	**3**	**4.5**
C	**1**	**1.5**
Method of Diagnosis		

Characteristic	No. Patients	%
Biopsy	**37**	**55.2**
Imaging	**30**	**44.8**

Note. –

*Values expressed as median and 95% confidence intervals.

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

Table 2

Characteristic	Univariate	Multivariate
Segmental vs Lobar	0.357 (95% CI, 0.178–0.714; p=0.004)	0.365 (95% CI, 0.170–0.787; p=0.010)
Increased Age	0.977 (95% CI, 0.939–1.017; p=0.258)	0.977 (95% CI, 0.933–1.023; p=0.313)
Multifocal vs Solitary	1.818 (95% CI, 0.898–3.680; p=0.097)	1.561 (95% CI, 0.673–3.619; p=0.300)
Bilobar vs Unilobar	1.785 (95% CI, 0.785–4.061; p-0.167)	0.833 (95% CI, 0.292–2.381; p=0.734)

Note. – Values expressed as Hazard Ratios and 95% Confidence Interval.

Table 3

Treatment-free-intervals.

Characteristic		Minimum Treatment-Free Interval			Maximum Treatment-Free Interval		
	No Patients	Median	Mean	95% CI	Median	Mean	95% CI
Isolated Y90	38	35.63	31.60	23.8–39.4	36.82	37.92	31.3–44.6
Y90−> RFA	13	6.27	9.55	3.2–15.9	20.00	24.69	17.4–32.0
Y90−> Sorafenib	10	2.05	3.54	0.7–6.4	13.60	15.91	6.7–25.1
Y90−> TACE	3	3.40	3.68	−4.1–11.4	7.73	7.97	−3.7–19.6
Y90−> bland embo	2	19.80		−97.1–136.7	23.55		−45.7–92.8
Y90+Sorafenib	1	2.97			2.97		

Note. – Values expressed as months. CI, confidence interval.

Table 4

Comparison to Historical Controls

Table 4.

	Super Survivors		Control Data	
Variable	**Value (%)**	***Comparison***	**Value (%)**	***Reference***
Age ≥ 65 y	72% (48/67)	↑	50% (504/1000)	[4]
Cirrhosis	78% (52/67)	↓	82% (816/1000)	[4]
HCV	31% (21/67)	↓	46% (461/1000)	[4]
Alcohol	21% (14/67)	↑	14% (138/1000)	[4]
NASH	10% (7/67)	↑	6% (60/1000)	[4]
Unilobar	79% (53/67)	↑	64% (639/1000)	[4]
Solitary	60% (40/67)	↑	43% (427/1000)	[4]
PVT	12% (8/67)	↓	27% (270/1000)	[4]
Ascites	10% (7/67)	↓	24% (242/1000)	[4]
ALBI				
1	9% (6/67)	↑	7% (71/1000)	[4]
2	75% (50/67)	↑	64% (637/1000)	[4]
3	16% (11/67)	↓	29% (292/1000)	[4]
Child-Pugh				
A	70% (47/67)	↑	51% (506/1000)	[4]
B	28% (19/67)	↓	45% (450/1000)	[4]
C	2% (1/67)	↓	4% (44/1000)	[4]
Lab Toxicity Grade 3/4				
↓Albumin	1% (1/67)	↓	5% (49/966)	[4]
↑Serum Bilirubin	6% (4/67)	↓	11% (110/966)	[4]
Imaging Response				
WHO				
6–9 months	69% (42/61)	↑	41% (48/116)	[17]
12 months	74% (44/59)	↑	53% (43/81)	[17]
EASL				
6–9 months	83% (51/61)	↑	74% (86/116)	[17]
12 months	78% (46/59)	↑	67% (54/81)	[17]

Note. – Values expressed as percent.

BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; PVT, portal vein thrombosis; WHO, World Health Organization.