Institutional Decision to Adopt Y90 as Primary Treatment for HCC Informed by a 1,000-patient 15-year Experience

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Abbreviations: Y90: Yttrium-90 radioembolization; TARE: transarterial radioembolization; LRT: locoregional therapy; TACE: conventional transarterial chemoembolization; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; CP: Child-Pugh; ITT: intention to treat; LT: orthotopic liver transplantation; QoL: Quality-of-life; OS: Overall survival; PVT: Portal venous thrombosis; RCT: randomized controlled trial; TTP: time-to-progression; UNOS: United Network for Organ Sharing; CTCAE: Common Terminology Criteria for Adverse Events; DEB-TACE: drug-eluting bead chemoembolization; ECOG: Eastern Cooperative Oncology Group; IQR: Interquartile range; CI: 95% Confidence Interval; HR: Hazard Ratio.

ABSTRACT

Y90 transarterial radioembolization (TARE) is a transarterial locoregional therapy (LRT) for hepatocellular carcinoma (HCC). In this study, we present overall survival outcomes (OS) in a 1000-patient cohort acquired over a 15-year period. Between December 1, 2003 and March 31, 2017, 1000 patients with HCC were treated with TARE as part of a prospective cohort study. A comprehensive review of toxicity and survival outcomes was performed. Outcomes were stratified by baseline Child-Pugh (CP) class, United Network for Organ Sharing (UNOS) and Barcelona Clinic Liver Cancer (BCLC) staging systems. Albumin and bilirubin laboratory toxicities were compared to baseline. OS outcomes were reported using censoring and intention-to-treat methodologies. All treatments were outpatient, with a median 1 treatment per patient. 506 (51%) were CP A, 450 (45%) CP B, and 44 (4%) CP C. 263 (26%) patients were BCLC A, 152 (15%) B, 541 (54%) C, and 44 (4%) D. 368 (37%) were UNOS T1/T2, 169 (17%) T3, 147 (15%) T4a, 223 (22%) T4b, and 93 (9%) N/M. In CP A patients, censored OS for BCLC A was 47.3 (CI: 39.5-80.3) months, BCLC B 25.0 (CI: 17.3-30.5) months, and BCLC C 15.0 (CI: 13.8-17.7) months. In CP B patients, censored OS for BCLC A was 27 (CI: 21-30.2) months, BCLC B 15.0 (CI: 12.3-19.0) months, and BCLC C 8.0 (CI: 6.8-9.5) months. 49 (5%) and 110 (11%) patients developed grade 3/4 albumin and bilirubin toxicities, respectively. **Conclusion:** Based on our experience with 1,000 patients over 15 years, we have made a decision to adopt TARE as the first-line transarterial LRT for patients with HCC. Our decision was informed by prospective data and incrementally reported demonstrating outcomes stratified by BCLC, applied as either neoadjuvant or definitive treatment.

Keywords: Hepatocellular carcinoma; Radioembolization; Yttrium-90; liver cancer

INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary liver cancers, represents the 2nd most common cause of cancer mortality worldwide.(1) For patients beyond curative resection or outside transplant criteria, locoregional therapies (LRT) remain excellent treatment options.(2) These include direct lesion ablation and transarterial approaches, such as chemoembolization (TACE) and radioembolization (TARE).(3)

TARE using Yttrium-90 (Y90) has gained increasing acceptance as an alternative to TACE over the past decade. In comparison with the arterial occlusive macroembolic effects of TACE, the microembolic approach and beta radiation associated with Y90 provides a more versatile application of transarterial treatment leading to acceptable outcomes for all stages of Barcelona Clinic Liver Cancer (BCLC) disease.(4) For early stage A, Y90 has been used to successfully downstage tumors to liver transplantation (LT), hypertrophy the future liver remnant for potential resection, treat recurrences following resection, significantly prolong time-to-progression (TTP) compared with TACE, and represent an alternative to ablation for unablatable lesions.(5-8) For stage B, Y90, which is performed in the outpatient setting, has demonstrated comparable survival yet superior quality-of life (QoL) compared to TACE.(9, 10) For stage C, Y90 is applicable in patients with portal vein thrombosis (PVT), minimizing the risk of ischemic hepatitis given lack of arterial occlusion.(11) Y90 is currently approved by the Food and Drug Administration (FDA) for the management of HCC in patients with portal vein thrombosis and as neoadjuvant therapy prior to resection or transplantation.

We now report on how data derived from our 15-year, 1000-patient experience led to an institutional decision to adopt Y90 as the primary transarterial locoregional treatment for HCC.

METHODS

Patient Cohort

Between December 1, 2003 and March 31, 2017, 1000 patients with HCC were treated with Y90 as part of a prospective cohort study. The study was Health Insurance Portability and Accountability Act compliant, approved by the Northwestern University institutional review board, and registered (NCT00532740). A comprehensive review of toxicity and survival outcomes was performed. All authors had access to the data and approved the final manuscript.

Evaluation and Staging

Pretreatment evaluation included history, physical examination, laboratory/imaging studies, and diagnosis of HCC by biopsy or imaging.(12) Patients were classified by Child–Pugh (CP), United Network for Organ Sharing (UNOS) TNM and Barcelona Clinic Liver Cancer (BCLC) stages.

Treatment Decisions

In 2003, a weekly multidisciplinary tumor board, consisting of diagnostic and interventional radiologists, hepatologists, oncologists, and surgeons was created at Northwestern Memorial Hospital, designed to standardize our institutional approach to patients with HCC. Treatment algorithms were created as guidelines for discussion about ablation vs. trans-arterial therapies vs. resection vs. LT in HCC patients. The algorithm also included treatment objectives (definitive vs. bridging therapies) to either resection or LT. Decisions regarding the use of Y90 were made by consensus, with final decision made by the patient following informed consent. During the study period, a randomized controlled trial (RCT) was completed and recently published.(8)

Treatment (TARE with Y90)

Pretreatment mesenteric angiography and technetium-99m macroaggregated albumin scanning were performed to assess lung shunting. Patients received treatment with glass-based microspheres (TheraSphere, BTG International, UK). Technical and dosimetry

considerations for Y90 have been described; target dose was 120 Gy for lobar infusions. Later in our experience with the application of radiation segmentectomy and lobectomy, target doses were modified to >190 and 150 Gy, respectively.(5, 13)

Imaging Follow-up

Per our institutional protocol, 4-6 week scans were obtained following each treatment and subsequently at 2-3 month intervals. Response and TTP data have been previously published and replicated by many centers. It will not be a focus of this analysis.

Clinical and Laboratory Toxicities

Patients were followed for adverse events by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, recorded at 4-6 weeks after every treatment. Since new toxicities depend on a) baseline laboratory abnormality (ex: grade 1 bilirubin toxicity in CP B) and b) baseline tumor burden, we chose to provide significant granularity on this topic, and stratified toxicity by baseline TNM (tumor burden) and liver function (Child-Pugh) and followed each stratum longitudinally. For patients without toxicities at baseline, the development of any grade was considered new. For patients with baseline grades 1-2 toxicities, only those who progressed to grades 3-4 were considered new. For patients with baseline grades 3-4, no new toxicities could be reported. This approach is conservative, since no attempt is made to provide attribution of causality. Of the 1000 patients, data were available for 966 patients (see **RESULTS**).

Statistical Analyses

Overall survival analysis (OS) was performed using Kaplan-Meier method and log-rank. In order to capture OS without the confounding effect of curative treatment, censored OS was calculated from first Y90 until death, last follow-up or curative therapy. In order to capture individualization of patient care and management of patients outside strict guidelines (e.g. LT for good biology T4a disease), intention to treat (ITT) survival was also reported from first Y90 until date of death or last follow-up, irrespective of subsequent treatments. Uni and multivariate analyses were performed. A $P<0.05$ was considered significant.

RESULTS

Baseline Characteristics

Table 1 lists the baseline characteristics of the 1000 patient cohort. Median age was 65 years [Interquartile Range (IQR): 58-72]. Approximately half (n=506, 50.6%) were CP A, and 816 (82%) showed classical imaging signs of cirrhosis. 54% patients were UNOS stages T1-T3, while 427 (43%) had solitary tumors. 889 (89%) were treatment-naïve.

Y90 Treatments

A total of 1577 Y90 treatments were performed with median of 1 (range: 1-8) per patient. Median dose per treatment was 119 Gy (IQR:91-156). For more limited disease (T1-T3) and segmental injections, median dosage infused was 1.1 GBq (IQR:0.7-1.7); for multifocal/advanced disease (≥T4a) and lobar injections, median dosage infused was 2.1 (IQR:1.4-2.8) (P<0.0001). Median lung-shunt fraction was 5.4% (IQR:3.2-9), with a median lung dose of 3 Gy (IQR:1.5-6.6).

Laboratory Toxicities and Early Mortalities

Tables 2 and 3 provide detailed description of bilirubin and albumin toxicities.

a-T1/T2: New G3-4 bilirubin toxicities were noted in 3% (6/190), 19% (29/149) and 19% (4/21) of CP A, B and C patients.

b-T3: New G3-4 bilirubin toxicities were noted in 3% (3/97), 8% (5/60) and 25% (1/4) of CP A, B and C patients.

c-T4a: New G3-4 bilirubin toxicities were noted in 11% (8/71), 21% (13/62) and 14% (1/7) of CP A, B and C patients.

d-T4b: New G3-4 bilirubin toxicities were noted in 9% (8/89), 16% (19/116), and 11% (1/9) of CP A, B and C.

e-N/M: New G3-4 bilirubin toxicities were noted in 9% (4/43), 15% (7/46) and 0% of CP A, B and C patients.

A similar pattern in albumin toxicities were noted (**Table 3**).

Overall, 49 (5%) patients developed new grade 3/4 albumin toxicities, 110 (11%) showed grade 3/4 bilirubin toxicities for all CP classes.

34 patients did not have laboratory follow-up within 4-6 weeks after Y90: 8 patients died within 8 weeks at outside centers with no laboratory follow-up available (3 x T4b, 4 x T4a, 1 x T1 [baseline Child-Pugh B8]); 26 were lost to clinical follow-up.

Early Mortality: 16 patients died within 30 days (1.6% overall cohort mortality). 13 had PVT +/- extrahepatic metastases, translating into 13/316=4% 30-day mortality in this high-risk group (UNOS ≥T4b). 3 patients (2 x UNOS T4a, 1 x UNOS T2 [solitary lesion]) died within 30 days in the lower risk group (UNOS T1-T4a), translating into 3/684=0.4% 30-day mortality. No patient developed radiation pneumonitis or gastritis.

Overall Survival Analyses by BCLC (Table 4)

BCLC A: 263 patients were BCLC A. Of the 158 (60%) CP A patients, 16 (10%) were resected and 49 (31%) underwent LT. Of the 105 (40%) CP B patients, 1 (1%) was resected and 46 (44%) underwent LT. Median censored survival was 47.3 months [95% Confidence Interval (CI):39.5-80.3)] for CP A and 27 months (CI:21-30.2) for CP B (p<0.0001). ITT survivals were 102 (CI:80-120) and 38 months (CI:29-118) for CP A and CP B, respectively (p=0.005). See **Figures 1a, 1b**.

BCLC B: 152 patients were BCLC B. Of the 91 CP A patients, 5 (5%) were resected and 9 (10%) underwent LT. Of the 61 CP B patients, none were resected and 8 (13%) underwent LT. Median censored survival was 25 months (CI:17.3-30.5) for CP A and 15 months (CI:12.3-19) for CP B (p=0.037). ITT survivals were 30 months (CI:21.4-33) and 16 months (CI:12.6-24.5) for CP A and CP B, respectively (p=0.2). **See Figures 2a, 2b**.

BCLC C: 541 patients were BCLC C. Of the 257 CP A patients, 12 (5%) were resected and 28 (11%) underwent LT. Of the 284 CP B patients, 1 (0.5%) was resected and 32 (11%) underwent LT. Median censored survival was 15 months (CI:13.8-17.7) for CP A and 8 months (CI:6.8-9.5) for CP B (p<0.0001). ITT survivals were 16.6 (CI:14.5-20.6) and 8.4 months (CI:6.8-10) for CP A and CP B, respectively (p<0.0001). See **Figures 3a, 3b**.

BCLC D: 44 patients were BCLC D. All were CP C and 14 (31%) underwent LT. Median survival in the 30 non-transplanted patients was 4.6 months (CI:2.5-6); for the 14 patients that underwent LT, 92% were alive at year 5.

Uni/Multivariate Analyses (Table 5)

Expected variables were significant on univariate analyses (bilirubin, albumin, vascular invasion, others). Multivariate models confirmed baseline bilirubin, albumin, ascites, vascular invasion, metastases, distribution, performance status, AFP <100 and index tumor <5 cm to be significant predictors of survival. Survival was not affected by HCV status (**Supplemental Table 1**).

DISCUSSION

The last 25 years have seen significant advancements in the treatment of HCC. For early BCLC A, selection criteria for surgical resection, LT and ablation have been refined, with demonstrated long-term benefits. For intermediate BCLC stage B, TACE has been shown to improve survival when compared to placebo. For advanced BCLC stage C, both sorafenib and regorafenib have also been shown to improve survival.(2, 14, 15) Parallel to these developments, Y90 was FDA approved in 1999 and made available for clinical use in early 2000. Since then, this microembolic radiation therapy has gained increasing acceptance as an alternative to TACE. Our institutional HCC tumor board was set up when ablation and TACE were evolving as neoadjuvant therapy to LT. In 2003, we began to use Y90 exclusively for patients with portal vein thrombosis. We subsequently became incrementally more inclusive as our observations demonstrated that Y90 was associated with significant efficacy to the point where TACE and TARE became alternative options for transarterial LRT. Having performed comparative studies using historical controls, we compared the two modalities using an RCT, the results of which demonstrated TTP superiority of TARE over TACE. The purpose of this report is to summarize our cumulative 15-year, 1000-patient experience with HCC patients in an attempt to highlight the application of Y90 to various BCLC stages that has resulted in an institutional decision to adopt Y90 as the primary LRT for patients with HCC limited to the liver.

We have previously reported on toxicities following Y90.(16) We now present detailed outcomes stratified by baseline tumor burden and CP score, including bilirubin and albumin levels. Using this expanded dataset, we confirm that toxicities are low for limited disease (T1-T3) irrespective of liver function, when segmentectomy technique can be applied. This observation is particularly relevant for patients awaiting LT when segmental infusion of Y90 can be used for treatment of new nodules in CP B or C patients. For more diffuse T4a disease or more, toxicity is related to baseline status, and tolerability may be limited if baseline liver function is compromised. In such cases, more toxicities should be anticipated, either as result of Y90 or natural progression of liver disease.

We have also previously reported survival outcomes related to various clinical scenarios and tumor stage. This current report confirms that survival for BCLC stages A-C patients treated with Y90 (47, 25 and 15 months, respectively) compare favorably with survival expectations of BCLC A (36-50 months), BCLC B (18-26 months) and BCLC C (11 months) cited by EASL-EORTC guidelines.(2) The finding of 47 months in BCLC A in patients treated with Y90 is comparable those reported in highly selected patients treated with drug-eluting bead chemoembolization (DEB-TACE).(17) Similarly, patients with CP A BCLC B who received Y90 also demonstrated a prolonged survival of 25 months, which is currently considered the new standard, consistent with the BRISK-TACE trial report.(18) Finally, survival in BCLC C patients was also favorable, reflecting the antitumoral effect of Y90 on tumor thrombus, although Eastern Cooperative Oncology Group performance status (ECOG) 1 may have over-estimated the stage of disease given its subjectivity.(19, 20) Our analyses have also captured the survival outcome attributable to the Y90 itself (censored), as well as real-life individualization of patient care (ITT), and post-progression treatments, where the long-term outcomes of alternate treatments post Y90 are also captured. While LT may not be explicitly recommended for disease outside BCLC A, individualization of decision making is suggested in guidelines.(21)

BCLC D patients deserve special mention. Patients with CP C had a median survival of 4.6 months, longer than the expected 3 months by guidelines. While palliative care has traditionally been recommended, it has been recently acknowledged that select BCLC D patients should be considered for LT. Despite risk of hepatic decompensation in CP C patients, we were able to perform segmental TARE in all cases, limit progression and bridge to LT in 14 cases. Among the 14 that received LT, 93% (13/14) were T2 at time of Y90. The risks of Y90 taking into account tumor burden and chance for a timely LT need to be balanced to maximize patient outcomes. While our data cannot advocate for universal use of Y90 in CP C patients, it does demonstrate that a select group may be bridged to LT. The 5-year survival post LT was excellent at 92%. We believe that properly selected BCLC D patients may benefit from selective Y90 followed by LT.

While clinical outcomes weighed heavily into our decision to adopt Y90 as our primary LRT option, a number of significant practical differences between Y90 compared to its alternatives also informed our decision. First, the ability to deliver a potentially curative ablative dose (>190 Gy) to lesions not anatomically accessible to ablation, as well as treat patients with macrovascular invasion, were significant observations.(5, 11) Second, converting HCC patients and small future liver remnants into resection candidates using neoadjuvant radiation lobectomy offered an improvement over portal vein embolization, incorporating a biologic test-of-time and antitumoral effect during the hypertrophy time period.(13, 22) Third, we felt that the seminal finding of our prospective randomized trial showing longer TTP in BCLC A/B was important in patients bridged to LT given requisite waiting times; it is now our bridging treatment of choice. Fourth, we considered our observed 58% downstaging rate from T3 to T2, a significant improvement over TACE (31%), thereby allowing the potential of LT; it is now our downstaging treatment of choice.(6) Other considerations took into account analyses of cost-efficiency of TARE vs TACE previously published.(23) The major difference relates to TACE traditionally requiring an inpatient admission, whereas Y90 has been an outpatient treatment since its inception, thereby decreasing lifetime resource utilization and potentially overall costs. More recently, Y90 has been delivered in one session versus two (same-day treatment), further reducing time to treatment and cost.(10) While there has been a recent effort to provide TACE on an outpatient basis, this is concept is still investigational. Finally, prospective studies have shown that Y90 is associated with better QoL compared to TACE.(9)

Taken together, our tumor board strongly felt that Y90 should become our institutional standard of care for patients with HCC, whether as neoadjuvant (including bridging) or as definitive LRT, unless other considerations cause us to use other modalities. In fact, one of the limitations of enrolling into our RCT comparing TACE vs TARE was that following informed consent, patients chose TARE versus enrolling in the trial for fear of being assigned to the TACE arm. This caused us to stop enrollment significantly short of our target at the request of the cancer center, yet we were able to achieve a statistically significant difference in TTP.(8) Rather than adapting clinical presentations to fit rigid treatment paradigms, TARE

is felt to represent a customizable therapy that matches disease burden and liver function applicable across various disease stages (e.g. boost dosing in PVT, ablative dosing in segmentectomy). This simplifies complex treatment algorithms and decision making, and provides significant clarity in determining prognosis. Y90 glass also represents the only arterial therapy where the intended activity (and hence dose) can always be infused, thereby permitting true treatment standardization and center reproducibility.

Evolving applications of Y90 in the treatment of HCC continue to be explored. Our observed lack of significant lung shunting in patients with limited disease (T1-T3) may permit the consideration of Y90 without mandated lung shunt study, further reducing time to treatment and cost. While two recent trials have reported on Y90 compared to sorafenib, neither study is publicly available for comprehensive peer-review, and the inability of these trials to reach their endpoint in advanced disease should not be conflated with the clear antitumoral effect and clinical applicability of Y90 in non-advanced T1-T4a disease (24, 25). While speculative, the lack of personalized dosimetry may have contributed to the negative trials. The role of response in prognosticating survival is of interest, as recently confirmed for brivanib and Y90 (26, 27). Y90 is also being combined with immunotherapy.

There are strengths and limitations. Limitations include the single center nature of the analysis without a comparator. Also, survival data in advanced HCC attributed by ECOG 1 may have been overestimated.(28) Strengths include that this represents the largest single center prospective cohort of Y90, with sample size and follow-up permitting meaningful analyses that compensate for heterogeneity of lesion size and liver function. Thus, we are able to generate data stratified by UNOS TNM, providing significant granularity of toxicity and survival outcomes by liver function and tumor burden. No toxicity adjustment for tumor progression was made and hence, all toxicities are potentially attributable to treatment; this is deemed to be the most conservative reporting. Child-Pugh and UNOS stage were not included in the multivariate model to limit collinearity artifact. The data are consistent with our initial report of 291 patients as well as other series, with no new safety observations and no attempt to attribute toxicity related to treatment or natural history of cirrhosis.(29-32)

CONCLUSION

Based on an institutional experience with 1,000 patients over 15 years, the largest single-center cohort of patients with HCC treated with Y90, we have made a decision to adopt TARE as the first line of transarterial LRT for HCC limited to the liver. Our decision was informed by data prospectively collected and incrementally reported demonstrating outcomes as expected by the BCLC algorithm for stages A-D, applied as either neoadjuvant or definitive treatment. Compared with TACE, our data confirm that outpatient TARE allows for fewer treatments, better QoL, longer TTP, and versatile application as neoadjuvant LRT combined with either resection or LT.

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Table 1: Baseline Characteristics

		N (%)
Age	<65	496 (50)
	≥65	504 (50)
Gender	Male	752 (75)
	Female	248 (25)
Etiology	Hepatitis C	461 (46)
	Alcohol	138 (14)
	Cryptogenic	64 (6)
	Hepatitis B	89 (9)
	Non-alcoholic steatohepatitis	60 (6)
	Autoimmune hepatitis	15 (2)
	Hemochromatosis	11 (1)
	Primary Biliary Cirrhosis	12 (1)
	Unknown	143 (14)
	Other	7 (0.7)
Performance Status	0	557 (56)
	1	401 (40)
	2	42 (4)
Prior Liver therapy	None	889 (89)
	Resection	48 (5)
	Radiofrequency Ablation	15 (2)
	TACE	40 (4)
	Liver Transplant	6 (0.5)
	Bland Embolization	2 (0.2)
Method of Diagnosis	Liver Biopsy	319 (32)
	Imaging	681 (68)
Cirrhosis on Imaging	Present	816 (82)
	Absent	184 (18)
Ascites	Absent	758 (76)
	Mild-Moderate	214 (21)
	Severe	28 (3)
Tumor Focality	Solitary	427 (43)
	Multifocal	573 (57)
Tumor Distribution	Unilobar	639 (64)
	Bilobar	361 (36)
Vascular Invasion	None	730 (73)
	PVT	
	segmental	43 (4)
	Lobar	93 (9)
	Main	101 (10)

	Hepatic Vein	5 (0.5)
	PVT (Main) + Hepatic Vein	28 (3)
Extrahepatic Metastases	None	907 (91)
	Lymph Nodes	46 (5)
	Other Organs	47 (5)
Index Lesions Size (cm)	<5	548 (55)
	5-10	314 (31)
	>10	138 (14)
Alpha Fetoprotein	>100	409 (41)
	<100	591 (59)
Total Bilirubin (mg/dl)	<2	824 (82)
	2-3	124 (12)
	>3	52 (5)
Albumin (mg/dl)	>3.5	188 (19)
	2.8-3.5	490 (49)
	<2.8	322 (32)
Child-Pugh Class	A	506 (51)
	B	450 (45)
	C	44 (4)
Albumin-Bilirubin grade	1	71 (7)
	2	637 (64)
	3	292 (29)
Barcelona Clinic Liver Cancer	A	263 (26)
	B	152 (15)
	C	541 (54)
	D	44 (4)
United Network for Organ Sharing	T1 (1 lesion < 2 cm)	39 (4)
	T2 (1 lesion < 5 cm, 3 lesions < 3 cm)	329 (33)
	T3 (1 lesion > 5 cm, 2 or 3 lesions [1 > 3 cm])	169 (17)
	T4a (4 or more lesions)	147 (15)
	T4b (vascular invasion)	223 (22)
	N (lymph nodes)	46 (5)
	M (metastases)	47 (5)

Table 2: Bilirubin Toxicities at 4-6 weeks

UNOS Tumor Stage	Baseline Child-Pugh	Baseline Toxicity		Toxicity at 1-month			Net New Toxicity	
				None	Grade 1-2	Grade 3-4	Stable	Progressed
T1/T2	A (N=190)	None	126	93	31	2	93	33
		Grade 1-2	64	8	50	6	58	6
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=149)	None	32	21	10	1	21	11
		Grade 1-2	108	4	76	28	80	28
		Grade 3-4	9	0	3	6	9	0
	C (N=21)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	9	2	3	4	5	4
		Grade 3-4	12	0	0	12	12	0
T3	A (N=97)	None	66	55	11	0	55	11
		Grade 1-2	31	6	22	3	28	3
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=60)	None	18	15	3	0	15	3
		Grade 1-2	40	1	34	5	35	5
		Grade 3-4	2	0	1	1	2	0
	C (N=4)	None	2	1	1	0	1	1
		Grade 1-2	0	N/A	N/A	N/A	N/A	N/A
		Grade 3-4	2	0	0	2	2	0
T4a	A (N=71)	None	48	34	11	3	34	14
		Grade 1-2	23	1	17	5	18	5
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=62)	None	23	12	10	1	12	11
		Grade 1-2	37	5	20	12	25	12
		Grade 3-4	2	0	0	2	2	0
	C (N=7)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	3	0	2	1	2	1
		Grade 3-4	4	0	1	3	4	0
T4b	A (N=89)	None	59	39	16	4	39	20
		Grade 1-2	30	5	21	4	26	4
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=116)	None	45	21	19	5	21	24
		Grade 1-2	67	3	50	14	53	14
		Grade 3-4	4	0	1	3	4	0
	C (N=9)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	1	0	0	1	0	1
		Grade 3-4	8	0	1	7	8	0
N/M	A (N=43)	None	27	20	7	0	20	7
		Grade 1-2	16	3	9	4	12	4
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=46)	None	16	9	5	2	14	29
		Grade 1-2	28	4	19	5	23	5
		Grade 3-4	2	0	0	2	2	0
	C (N=2)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	0	N/A	N/A	N/A	N/A	N/A
		Grade 3-4	2	0	1	1	2	0

Table 3: Albumin Toxicities at 4-6 weeks

UNOS Tumor Stage	Baseline Child-Pugh	Baseline Toxicity		Toxicity at 1-month			Net New Toxicity	
				None	Grade 1-2	Grade 3-4	Stable	Progressed
T1/T2	A (N=190)	None	97	92	4	1	92	5
		Grade 1-2	93	32	60	1	92	1
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=149)	None	11	8	3	0	8	3
		Grade 1-2	132	20	108	4	128	4
		Grade 3-4	6	0	1	5	6	0
	C (N=21)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	18	0	18	0	18	0
		Grade 3-4	3	0	2	1	3	0
T3	A (N=97)	None	46	37	9	0	37	9
		Grade 1-2	51	10	40	1	50	1
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=60)	None	3	3	0	0	3	0
		Grade 1-2	53	7	44	2	51	2
		Grade 3-4	4	0	1	3	4	0
	C (N=4)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	4	0	3	1	3	1
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
T4a	A (N=71)	None	28	20	8	0	20	8
		Grade 1-2	43	3	36	4	39	4
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=62)	None	2	2	0	0	2	0
		Grade 1-2	55	2	48	5	50	5
		Grade 3-4	5	0	2	3	5	0
	C (N=7)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	5	0	4	1	4	1
		Grade 3-4	2	0	1	1	2	0
T4b	A (N=89)	None	28	19	9	0	19	9
		Grade 1-2	61	8	50	3	58	3
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=116)	None	3	1	1	1	1	2
		Grade 1-2	102	10	79	13	89	13
		Grade 3-4	11	0	1	10	11	0
	C (N=9)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	8	1	6	1	7	1
		Grade 3-4	1	0	0	1	1	0
N/M	A (N=43)	None	14	11	3	0	11	3
		Grade 1-2	29	2	24	3	26	3
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A
	B (N=46)	None	1	1	0	0	1	0
		Grade 1-2	42	2	33	7	35	7
		Grade 3-4	3	0	0	3	3	0
	C (N=2)	None	0	N/A	N/A	N/A	N/A	N/A
		Grade 1-2	2	0	2	0	2	0
		Grade 3-4	0	N/A	N/A	N/A	N/A	N/A

Table 4: Survival

Child Pugh	UNOS	N	Overall Survival (Censored*) Median (months)	95% CI	P	Overall survival (Intention to treat) Median (months)	95% CI	P	Transplanted N (%)	Resected N (%)
A	T1/T2	194	61	(37-80)	**<0.0001**	120	(80-120)	**<0.0001**	67 (35)	15 (8)
	T3	102	35.7	(25-44)		39	(30-56)		10 (10)	15 (14.5)
	T4a	75	17	(11-22)		17	(13-24)		4 (5)	1 (1)
	T4b	92	11.3	(8-14)		12	(8.7-14.3)		5 (5)	1 (1)
	M/N	43	9	(7.8-13)		9	(7.8-13)		0 (0)	1 (2)
B	T1/T2	152	27	(20.3-30)	**<0.0001**	64	(32.8-118)	**<0.0001**	69 (45)	1 (0.5)
	T3	63	20	(14.7-35)		24.3	(15-46.7)		11 (17)	0 (0)
	T4a	65	11.5	(6.4-13.5)		11.8	(8.8-15)		4 (6)	0 (0)
	T4b	122	6.2	(4.8-7.6)		6.2	(4.8-7.6)		2 (2)	1 (1)
	M/N	48	4.3	(2.7-6.4)		4.3	(2.7-6.4)		0 (0)	0 (0)
C	T1/T2	22	NR	-	**<0.0001**	NR	-	**<0.0001**	12 (50)	0 (0)
	T3	4	14.8	-		14.8	-		1 (25)	0 (0)
	T4a	7	3.6	(1.6-4.6)		3.6	(1.6-16)		1 (14)	0 (0)
	T4b	9	2.5	(2.3-4.8)		2.5	(2.3-4.8)		0 (0)	0 (0)
	M/N	2	1.7	(1.7-2.3)		1.7	(1.7-2.3)		0 (0)	0 (0)
BCLC	Child Pugh									
A	A	158	47.3	(39.5-80.3)	**<0.0001**	102	(80-120)	**0.005**	49 (31)	16 (10)
	B	105	27	(21-30.2)		38	(29-118)		46 (44)	1 (1)
B	A	91	25	(17.3-30.5)	**0.037**	30	(21.4-33)	0.2	9 (10)	5 (5)
	B	61	15	(12.3-19)		16	(12.6-24.5)		8 (13)	0 (0)
C	A	257	15	(13.8-17.7)	**<0.0001**	16.6	(14.5-20.6)	**<0.0001**	28 (11)	12 (5)
	B	284	8	(6.8-9.5)		8.4	(6.8-10)		32 (11)	1 (0.5)
D	C**	30	4.6	(2.5-6)		-	-		-	0 (0)
	C***	14	-	-		92% alive at 5 years	-		14 (31)	0 (0)

*censored to resection/LT, **non transplanted, ***transplanted, NR: not reached

Table 5: Univariate/Multivariate analyses

Variable	Category	HR (95% CI)	P value	HR (95% CI)	P value
Age (y)	< 65	1.2 (1-1.42)	**0.0319**	0.98 (0.82-1.17)	0.81
	≥ 65	1		1	
Sex	Male	1.54 (0.95-1.39)	0.1570	0.92 (0.75-1.1)	0.43
	Female	1		1	
Bilirubin (mg/dL)	<2	0.42 (0.24-0.71)	**<0.0001**	0.45 (0.31-0.66)	**<0.0001**
	2–3	0.46 (0.25-8.2)		0.38 (0.24-0.59)	**<0.0001**
	>3	1		1	
Albumin (mg/dL)	>3.5	0.22 (0.16-0.27)	**<0.0001**	0.36 (0.25-0.50)	**0.001**
	2.8–3.5	0.53 (0.43-0.65)		0.72 (0.58-0.87)	**<0.0001**
	<2.8	1		1	
Cirrhosis	Absent	0.31 (0.24-0.38)	**<0.0001**	0.84 (0.65-1.1)	0.19
	Present	1		1	
Vascular Invasion	Absent	0.3 (0.25-0.38)	**<0.0001**	0.47 (0.39-0.58)	**<0.0001**
	Present	1		1	
Metastases	Absent	0.35 (0.23-0.51)	**<0.0001**	0.58 (0.44-0.76)	**0.0001**
	Present	1		1	
Focality	Solitary	0.45 (0.38-0.54)	**<0.0001**	0.59 (0.47-0.75)	**<0.0001**
	Multifocal	1		1	
Distribution	Unilobar	0.52 (0.43-0.62)	**<0.0001**	0.78 (0.63-0.96)	**0.019**
	Bilobar	1		1	
ECOG	0	0.24 (0.13-0.44)	**<0.0001**	0.53 (0.36-0.80)	**0.002**
	1	0.35 (0.19-0.65)		0.60 (0.41-0.88)	**0.010**
	2	1		1	
UNOS stage	T1/T2	0.19 (0.15-0.25)	**<0.0001**	N/A	N/A
	T3	0.3 (0.23-0.4)			
	T4a	0.65 (0.48-0.88)			
	T4b	1			
	N/M	1.2 (0.8-1.9)			
Child–Pugh class	A	0.32 (0.17-0.6)	**<0.0001**	N/A	N/A
	B	0.64 (0.33-1.22)			
	C	1			
Ascites	Absent	0.5 (0.4-0.6)	**<0.0001**	0.63 (0.51-0.78)	**<0.0001**
	Present	1		1	
AFP (ng/mL)	<100	0.46 (0.38-0.55)	**<0.0001**	0.66 (0.55-0.80)	**<0.0001**
	>100	1		1	
Index lesion size (cm)	<5	0.37 (0.28-0.49)	**<0.0001**	0.75 (0.56-0.99)	0.044
	5-10	0.88 (0.65-1.2)		1.1 (0.85-1.41)	0.48
	>10	1		1	

*UNOS and Child-Pugh were excluded from multivariate model to limit co-linearity

FIGURE LEGEND

Figure 1: a) OS of T1/T2 patients comparing CP A and B (censored). b) OS of T1/T2 patients comparing CP A and B (ITT).

Figure 2: a) OS of BCLC B patients comparing CP A and B (censored). b) OS of BCLC B patients comparing CP A and B (ITT).

Figure 3: a) OS of BCLC C patients comparing CP A and B (censored). b) OS of BCLC C patients comparing CP A and B (ITT).

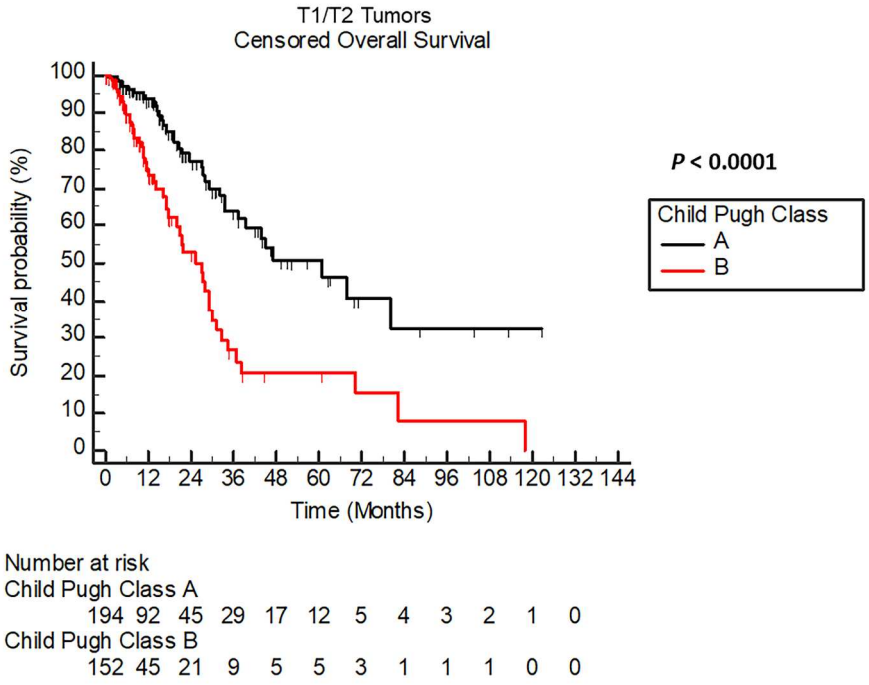

Figure 1a: OS of T1/T2 patients comparing CP A and B (censored).

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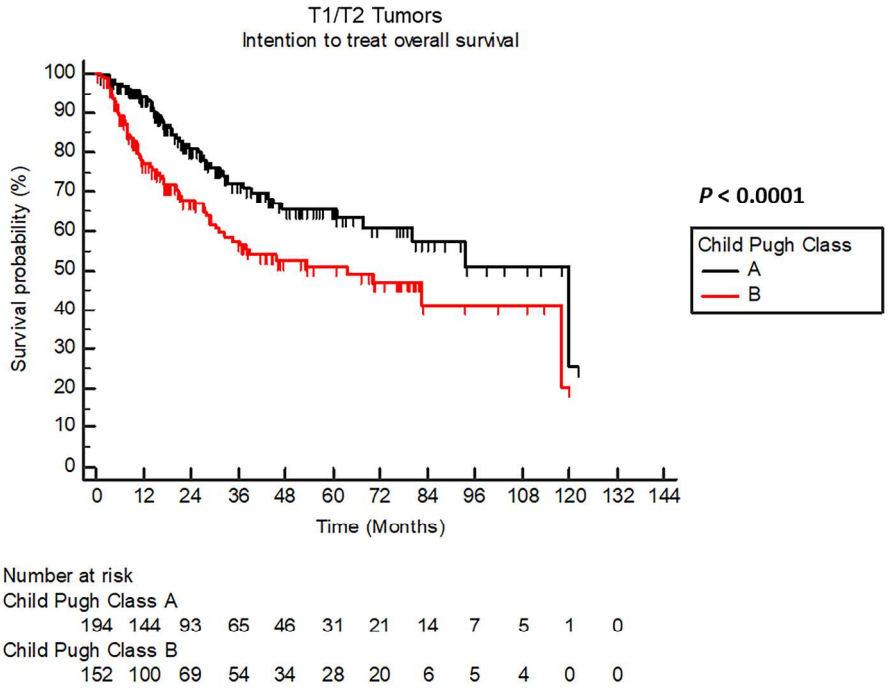

Figure 1b: OS of T1/T2 patients comparing CP A and B (ITT).

254x190mm (300 x 300 DPI)

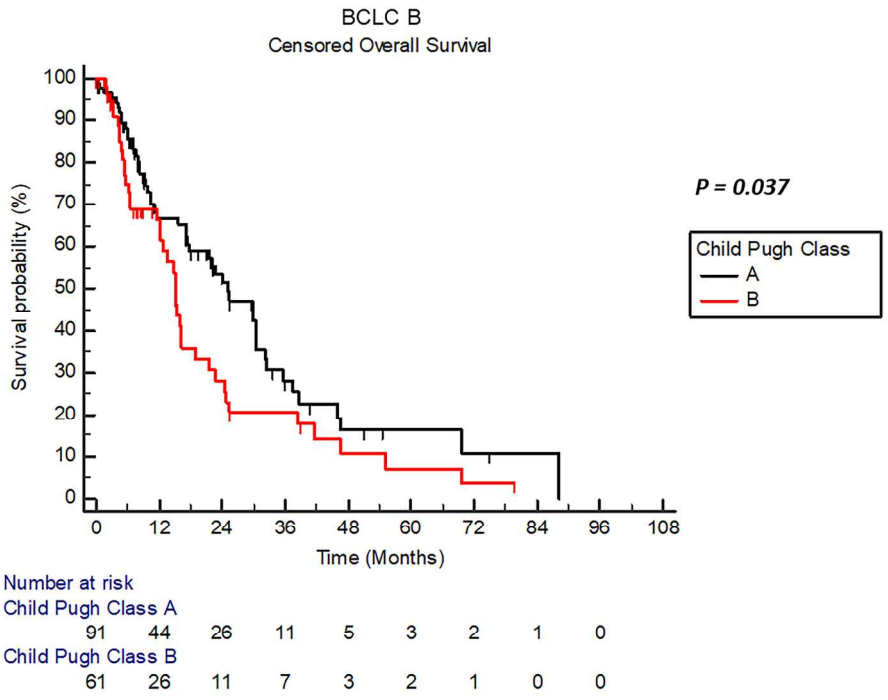

Figure 2a: OS of BCLC B patients comparing CP A and B (censored).

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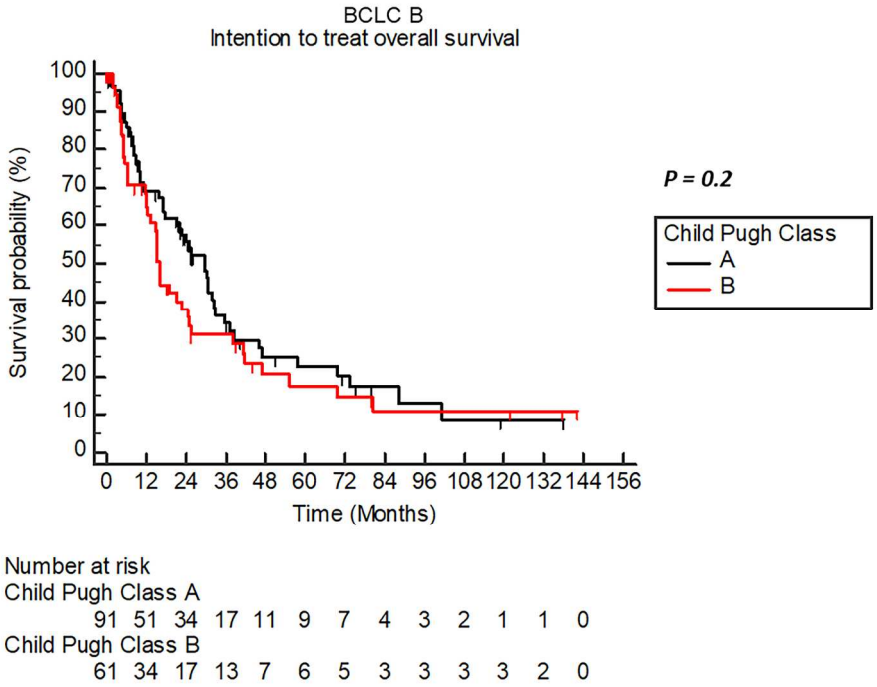

Figure 2b: OS of BCLC B patients comparing CP A and B (ITT).

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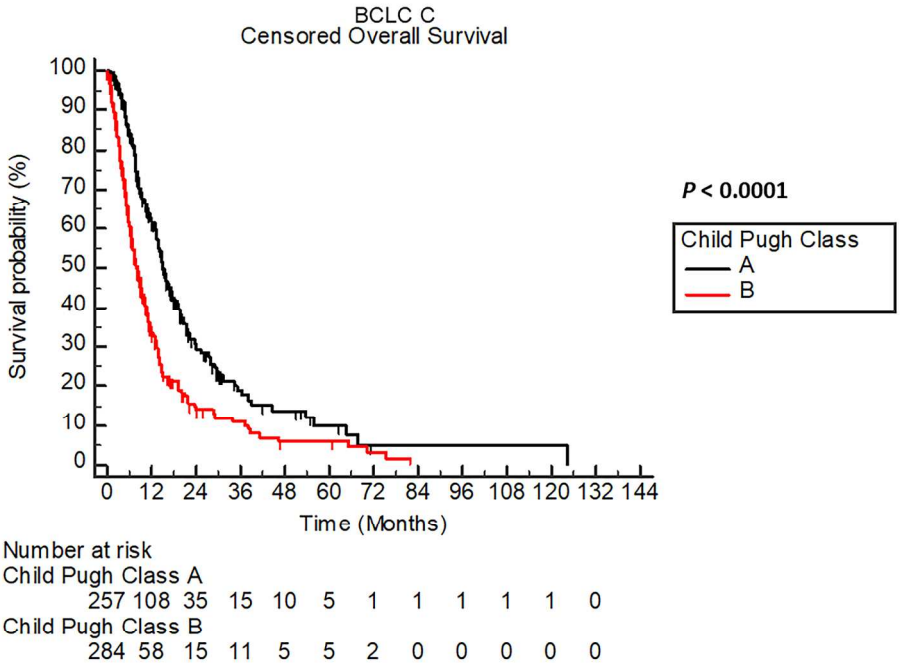

Figure 3a: OS of BCLC C patients comparing CP A and B (censored).

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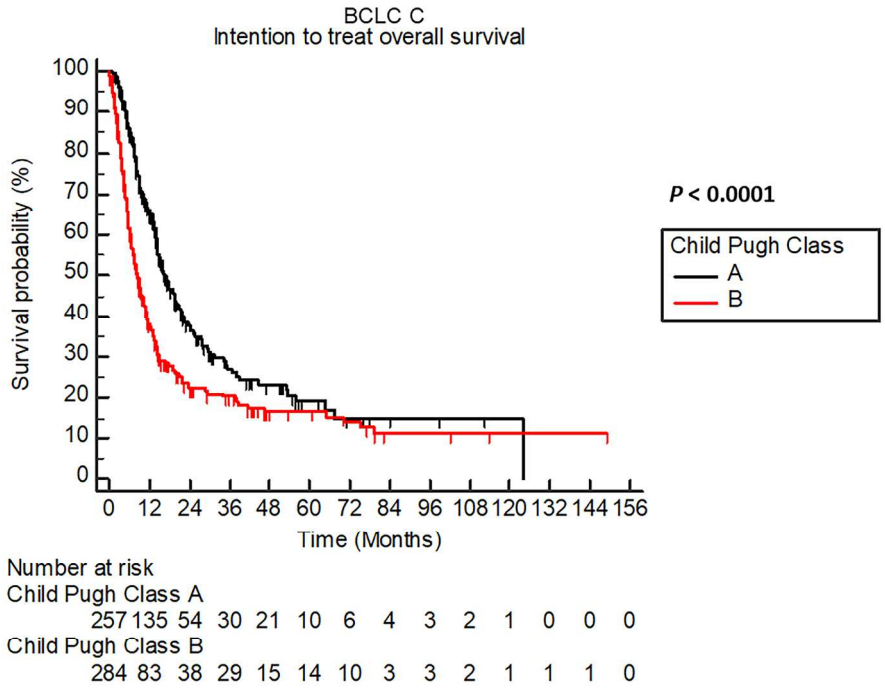

Figure 3b: OS of BCLC C patients comparing CP A and B (ITT).

254x190mm (300 x 300 DPI)