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Baseline albumin-bilirubin (ALBI) in Western patients with hepatocellular carcinoma treated with stereotactic body radiotherapy

Baseline albumin-bilirubin (ALBI) in Western patients with hepatocellular carcinoma treated with stereotactic body radiotherapy (SBRT)

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Summary

In a prospective series of 102 Western patients with Child Pugh A hepatocellular carcinoma (HCC) managed with stereotactic body radiotherapy (SBRT), the baseline albumin-bilirubin (ALBI) score was evaluated as a predictor of survival and hepatic toxicity. ALBI was an independent significant predictor of toxicity and survival, and was more discriminating than Child Pugh score. Thus, ALBI warrants further investigation and should be included as a factor for stratification in future clinical trials.

Abstract

Purpose: To assess the baseline albumin-bilirubin (ALBI) grade as a predictor of toxicity and survival in a prospective cohort of Western patients with hepatocellular carcinoma (HCC) treated with stereotactic body radiotherapy (SBRT) in two prospective trials.

Methods and materials: 102 patients with Child Pugh A liver disease who received 6-fraction SBRT for HCC were included. Univariate and multivariable logistic regression investigated factors associated with toxicity, defined as an increase in Child Pugh score of ≥2 within 3 months of SBRT. Univariate and multivariable Cox regression investigated factors predictive of overall survival (OS). ALBI was analysed as a continuous and binary variable in separate analyses.

Results:

On multivariable analysis of toxicity, including ALBI as a continuous variable, ALBI (odds ratio (OR) per 0.1 unit increase: 1.51 (95% confidence interval (CI):1.23-1.85, p=0.00074), mean liver dose (OR:1.31 (95%CI:1.02-1.68), p=0.036) and dose received by 800cc of normal liver (D800) (OR:1.10 (95%CI:1.01-1.20, p=0.028), were significant. When including ALBI as a dichotomous variable, ALBI grade remained a significant predictor of toxicity (OR:7.44 (95%CI:2.34-23.70, p=0.00069).

On multivariable analysis of OS, including ALBI as a continuous variable, ALBI (Hazard ratio (HR) per 0.1 increase: 1.09 (95%CI:1.03-1.17, p=0.004), tumour thrombus (HR:1.94 (95%CI:1.23-3.07, p=0.004) and being treated in Trial 1 vs. 2 (HR:1.92 (95%CI:1.23-3.03), p=0.004) were significant. Similarly, when including ALBI as a binary variable, ALBI, tumour thrombus and trial were significant predictors of OS.

When ALBI was considered, Child Pugh score (A6 vs A5) was not significant in multivariable models analysing toxicity or survival. Concordance statistics indicated models containing ALBI were superior to those containing Child Pugh.

Conclusions: Baseline ALBI was more discriminating than Child Pugh score in predicting OS and toxicity in patients with Child Pugh A liver disease. ALBI should be used as a factor for stratification in future HCC SBRT trials.

Introduction

Patients with hepatocellular cancer (HCC) who are unsuitable for resection or radiofrequency ablation (RFA) may be appropriate for stereotactic body radiotherapy (SBRT). The Child Pugh (CP) score is a convenient bedside tool, frequently used to assess cirrhosis severity and predict survival in patients with liver disease, and also often used to guide HCC patient selection for treatment, including SBRT. Most often SBRT is reserved for patients with Child Pugh A (CP-A) disease, while more caution is required in treating those with Child Pugh B (CP-B) disease, where toxicity is more common[1].

Despite its ease of use, there are disadvantages in the CP score[2,3], including the subjective nature of determining the degree of ascites and severity of encephalopathy, and the discretising of the continuous variables within the scoring system (bilirubin, albumin and INR) resulting in information loss[2,4]. In addition, the ceiling levels for each component were chosen empirically, rather than being based on definite changes in outlook between categories[2,4]. There has also been concern regarding the appropriateness of CP for assessing liver dysfunction in HCC, as it was originally designed for assessing surgical outcomes in patients with bleeding oesophageal varices[5]. Furthermore, some factors within the scoring system may be correlated (e.g. albumin and ascites) and other potentially important factors (e.g. creatinine) are not included[2,6,7]. The inclusion of ascites within the CP score further limits its usefulness in HCC where vascular invasion may increase portal pressure leading to ascites, due to tumour rather than liver dysfunction.

More recently, Johnson et al described the albumin-bilirubin (ALBI) score for determining prognosis in HCC patients[4]. ALBI is calculated as a continuous variable using serum bilirubin and albumin and can be categorised into 3 prognostic groups. The ALBI model was developed from a cohort of 1313, predominantly CP-A, Japanese HCC patients, then validated in >5000 patients from elsewhere. It has been suggested that ALBI is more discriminating than CP score[4].

Our group previously evaluated SBRT in a cohort of CP-A HCC patients, treated within two prospective trials[8]. Multivariable analysis identified two significant factors predictive of overall survival (OS): the presence/absence of tumour vascular thrombosis and whether patients were treated in Trial 1 or 2, with patients from the more recent trial (Trial 2) faring better, an observation which was unexplained. The CLIP score, which incorporates CP, HCC burden, alpha-fetoprotein (AFP) and tumour thrombosis, was non-significant on univariate analysis[8]. More recently, predictors of liver toxicity (defined as worsening of CP score by ≥2 points within 3 months post-SBRT) were analysed for the same cohort. Child Pugh score A6 vs. A5 and lower platelet count were predictive of increased toxicity, in addition to dosimetric factors (mean liver dose (MLD) and D800)[9].

This report aimed to evaluate baseline ALBI as a potential predictor of hepatic toxicity and survival in HCC patients treated with SBRT in the above trials. A secondary goal was to investigate if ALBI could account for the survival differences observed between patients in Trial 1 and 2 in the original analysis[8].

Methods and materials:

Patients

This analysis included 102 patients from two prospective trials investigating SBRT for HCC between 2004 and 2010 at Princess Margaret Cancer Centre, Toronto[8]. Preliminary clinical outcomes have been reported previously[8]. This analysis included the same cohort, with updated follow-up. Patients had CP-A baseline liver function and were deemed unsuitable for transplantation, resection, transarterial chemoembolization (TACE) and RFA. For patients who had received previous liver directed therapies, eligibility for SBRT required progression following the last therapy.

Treatment

Treatment techniques have been described in detail previously[8]. In brief, breath hold with active breathing control or abdominal compression was used to minimize respiratory motion when possible. The gross tumour volume (GTV) was visible HCC including any vascular invasion, defined using multiphasic intravenous contrast-enhanced planning CT and MRI. For most patients there was no expansion for clinical target volume (CTV; i.e. GTV=CTV). The planning target volume (PTV) was 5mm for patients treated in breath hold. Patients treated with abdominal compression and free breathing had an internal target volume based PTV. Prescription dose was individualized based on the liver effective volume irradiated (Veff). Treatment was delivered in 6 fractions on alternate days with daily volumetric image-guidance. Patients were reviewed every 3 months with clinical examination, blood work and imaging.

ALBI

ALBI was calculated from baseline blood work according to Johnson et al[4]:

ALBI = ($\log_{10}$ bilirubin x 0.66) + (albumin x -0.085)
(bilirubin measured in μmol/L, albumin in g/L)

The following cut-points can be used to define three prognostic groups:

ALBI grade 1: ≤-2.60
ALBI grade 2: >-2.60 to ≤-1.39
ALBI grade 3: >-1.39

Statistics

Relationship between ALBI and CP score

The relationship between ALBI as a continuous variable and CP score was assessed using the independent samples *t*-test. The Chi-square test was used to investigate the relationship between ALBI as a binary variable (all patients had ALBI grade 1 or 2) and CP score.

Toxicity analysis

Univariate and multivariable logistic regressions were performed to measure the odds of developing toxicity, defined as an increase in CP score of ≥2 within 3 months of SBRT completion in the absence of definite HCC progression, according to RECIST criteria, version 1.1 Patients who developed toxicity prior to disease progression were considered as having experienced a toxicity event. Patients who developed toxicity at the same time as definite progressive disease were excluded from this toxicity analysis, since HCC progression may contribute to decline in CP score in these patients. The following baseline factors were tested in univariate analysis: age, gender, tumour volume, normal liver volume, tumour thrombus (yes/no), CP score (A5/A6), platelet count, underlying liver disease (hepatitis B/C/other), previous liver directed therapy (yes/no), ALBI, prescribed dose, MLD, Veff, physical and biological normal tissue complication probability (NTCP)[10] and dose received by 800cc of liver (D800). Given the widely accepted importance of MLD as a predictor of toxicity in HCC treated with radiotherapy[9,11], it was decided a priori to force MLD into the final multivariable toxicity model. All other variables with *p*-values <0.2 on univariate analysis were also included in the multivariable analysis with the final model selected using backwards selection (but keeping MLD in the model).

ALBI was evaluated as both a continuous and binary variable in two separate analyses, to determine the utility of the ALBI system in both formats.

To exclude multi-collinearity between variables, variance inflation factors (VIF) were calculated for covariates eligible for inclusion within the multivariable analysis. Factors with VIF >10.0 were considered indicative of multi-collinearity. Where such factors existed, these were reviewed and removed as necessary to avoid multi-collinearity (i.e. only VIF <10.0 were included in the multivariable analysis)[12]

Survival analysis

Median time to death was calculated from the date of SBRT start using the Kaplan-Meier method. Univariate and multivariable hazard ratios were calculated using Cox Proportional-Hazards. Baseline age, gender, tumour volume, normal liver volume, tumour thrombus, CP score, platelet count, underlying liver disease, AFP, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), extra-hepatic disease (yes/no), trial, ALBI, prescribed dose and MLD were tested in univariate analysis. Variables with $p<0.2$ on univariate analysis were included in the multivariable analysis, with the final model selected using backwards selection.

As for logistic regression, ALBI was evaluated as both a continuous and dichotomous variable in two separate analyses. As for the toxicity analysis, VIF were calculated to guard against multi-collinearity in the multivariable model.

In both analyses, to compare the predictive ability of ALBI versus CP score, c-statistics (concordance statistics) for the final models were computed.

Analyses were done using R version 3.3.1. All *p*-values were two-sided with $p<0.05$ considered statistically significant.

Results

Median follow-up of the 102 available patients using the censoring distribution was 50.9 months (95% confidence interval (CI):38.9-60.6). Toxicity outcomes and dosimetric data were available for 99 patients, of whom 26 (26.3%) experienced an increase in CP of ≥2 following SBRT. Of the 99 patients included in the toxicity analysis, four were classified as being without toxicity on the basis of CP score increases <2 and controlled HCC at approximately 1 month after SABR completion. All other patients (96%) had evaluation at 3 months. Four patients who developed toxicity also experienced mild tumour progression (not meeting RECIST definition), which was not considered a confounding factor for toxicity. A further three patients included in the toxicity analysis developed progressive disease within 3 months but did not develop toxicity. No patients underwent transplant or any other liver directed therapies, nor re-irradiation, within this 3 month time period. No patients experienced classic radiation-induced liver disease (RILD)[11]. One included patient, with intra-biliary HCC, who had toxicity within 3 months as defined above, also developed biliary toxicity, which began one month after SBRT. Two patients, who were excluded from the toxicity analysis on account of no dosimetric data being available and insufficient follow up, also experienced progressive disease within three months. Characteristics of patients overall and by toxicity outcome are shown in Table 1. Median survival was 16.9 months (95%CI: 10.4-21.3 months), with 1 and 3 year OS of 54.6% and 20.1% respectively. ALBI grade was 1 or 2 for all patients; none were categorised grade 3.

Relationship between ALBI and CP scores

Patients with higher baseline CP scores were more likely to have higher baseline ALBI scores (*t*-test $p<0.001$) and ALBI grades (χ^2 $p<0.001$).

Fifty-two of fifty-six patients (92.8%) in ALBI group 1 had CP-A5 disease and 25/46 patients (54.3%) in ALBI group 2 had CP-A6 disease (Figure 1

Supplementary Material). The average ALBI in patients with CP-A5 disease was -2.74 and -2.2 in those with CP-A6 disease.

Predictors of toxicity

On univariate analysis, baseline CP score and ALBI, both as a continuous and binary variable, were significant predictors of toxicity following SBRT (Table 2). In addition, platelet count, MLD, Veff, the biological NTCP and D800 were significant on univariate analysis. Age, normal liver volume, tumour thrombus, prescribed dose and physical NTCP also reached the threshold for inclusion within the multivariable analysis (i.e $p<0.2$). Veff was strongly correlated with MLD (Pearson's $r=0.87$), thus Veff was not carried into the multivariable analysis. All variables carried into the multivariable model had VIF<10.0, thus there were no concerns over multi-collinearity.

On multivariable analysis, including ALBI as a continuous variable, higher ALBI values, MLD and D800 values were significant predictors of toxicity occurring within three months of SBRT (ALBI odds ratio (OR):1.51, 95%CI:1.23-1.85, $p=0.000074$; MLD OR:1.31, 95%CI:1.02-1.68, p=0.036; D800 OR:1.10, 95%CI:1.01-1.20, p=0.028; Table 3). Child Pugh score A5 vs A6 was eliminated from the multivariable model.

On multivariate analysis, including ALBI as a binary variable, ALBI grade (OR:7.44; 95% CI:2.34-23.70, $p=0.00069$) was the only statistically significant predictor of toxicity (Table 3). Mean liver dose (OR:1.24, 95%CI:0.985-1.56, $p=0.07$) and D800 (OR:1.08, 95%CI:0.995-1.17, $p=0.066$) remained in the final model and although approaching, did not reach, statistical significance.

The final multivariable model using ALBI as a continuous variable had a c-statistic of 0.868, indicating that this model has very good predictive ability (c-statistic=0.5 implies a model does no better at predicting outcome than chance). When ALBI was modelled as categorical, the c-statistic was 0.831. The same model replacing ALBI with CP score had a predictive ability of 0.830.

Survival

On univariate analysis, including all 102 patients, ALBI as both a continuous and categorical variable was a significant predictor of OS (Table 4). Baseline CP score was not a significant predictor of OS on univariate analysis (*p*-value=0.063, but below the threshold for inclusion in the multivariable analysis). Age, normal liver volume, tumour thrombus, PS, Trial 2 vs 1, and MLD were also significant on univariate analysis. In addition, gender, tumour volume and prescribed dose had *p*-values sufficient for inclusion within the multivariable analysis. All included variables had VIF <10.0, thus there were no concerns over multi-collinearity. The development of toxicity (as defined above) was also noted to have a significant impact on OS, with median OS for patients with and without toxicity of 5.1 months and 27.3 months ($p<0.001$), respectively. This factor was not included in the multivariable analysis, however, as it was baseline characteristics that were of interest.

Median survivals for patients in ALBI groups 1 and 2 were 19.8 and 8.5 months respectively (Figure 1a; log-rank $p=0.008$). In contrast, the Kaplan-Meier curves for patients with CP-A5 and CP-A6 disease are seen to overlap (Figure 1b; log-rank $p=0.061$, median survivals: CP-A5: 17.5 months, CP-A6: 10.4 months).

On multivariable analysis with ALBI as a continuous variable, tumour thrombus (Hazard ratio (HR):1.94, 95% CI:1.23-3.07, $p=0.004$), higher ALBI score (HR per 0.1 unit increase:1.09, 95%CI:1.03-1.17, $p=0.004$) and being treated in Trial 1 compared to 2 (HR:1.92, 95%CI:1.23-3.03, $p=0.004$) were significant predictors of inferior survival.

On multivariable analysis with ALBI as a binary variable, tumour thrombus (HR:1.89, 95%CI:1.20-2.98 $p=0.006$), increased ALBI grade (HR: 1.79, 95%CI:1.14-2.80, $p=0.011$) and being in Trial 1 compared to 2 (HR:1.89, 95%CI:1.20-2.94, $p=0.005$) were predictive of inferior OS.

The c-statistics from models using ALBI as continuous and categorical variables were 0.643 and 0.628, respectively. The c-statistic from the model replacing ALBI with CP score was 0.625.

Discussion

This report evaluated the ALBI scoring system as a potential prognostic marker in HCC patients with CP-A liver disease treated with 6-fraction SBRT within two prospective trials. The ALBI scoring system was also evaluated as a predictor of toxicity. In addition, this project aimed to establish if the inclusion of ALBI in survival analyses could account for the previously observed OS differences between patients treated in Trial 1 and 2[8]. On multivariable analysis for survival, baseline ALBI, both as a continuous and binary variable, was an independent prognostic factor. Furthermore, the ALBI system proved more discriminating than CP score (A5 vs A6) in determining OS, with ALBI remaining in multivariable models, while CP score was thrown out, and ALBI-based models having marginally superior c-statistics. The previously observed differences in outcome between patients in Trial 1 or 2 remained significant, despite the addition of ALBI and therefore this difference remains unexplained. This observation, however, is likely multifactorial, perhaps relating to a learning curve and evolution of radiation imaging, planning, delivery and image-guided radiotherapy over the time period of the studies[8]. In addition, as observed in the original analysis[8], tumour thrombus remained an independent detrimental factor for OS.

As in the original ALBI publication, the use of ALBI grade allowed the identification of two distinct prognostic groups within the category of CP-A disease, with those in ALBI group 1 and 2 experiencing median survivals of 26 and 14 months, respectively[4]. In this current report, examining Western patients managed with SBRT, patients in ALBI group 1 and 2 had median survivals of 19.8 and 8.5 months respectively (p=0.008; and CP-A5 and CP-A6 patients had median survivals of 17.5 and 10.4 months respectively, p=0.061). All patients in

this report were deemed unsuitable for transplant, resection, TACE or RFA, with 55% having macrovascular invasion, and as such would be expected to fare less well than those suitable for established treatments[8]. Other groups have also found ALBI grade to be useful in determining outcomes amongst HCC patients undergoing liver resection, TACE, radioembolization and systemic therapies, and frequently ALBI is more discriminating than CP scores[13-17]. Other groups have also investigated the incorporation of ALBI within other recognised staging systems[18,19]. Until recently, however, ALBI as a prognostic indicator has not been specifically investigated in the setting of SBRT. Another report, investigating ALBI in a smaller prospective cohort of 40 HCC patients treated with SBRT[20], found that a worsening of ALBI by 0.5 after SBRT was predictive of inferior survival, while, interestingly, the baseline ALBI grade was not predictive of OS[20]. This is in contrast to the evaluation presented here and could be as a result of the smaller number of patients (40) included in the study by Toesca et al and/or as a result of the loss of information when discretising the ALBI score. In keeping with this current study, however, baseline CP was also not found to be a significant predictor of OS[20]. A recent retrospective analysis of Taiwanese HCC patients treated with SBRT found ALBI grade 2 vs. 1 to be a significant predictor of OS on univariate (but not multivariable) analysis and both ALBI and CP were found effective in predicting radiation-induced liver disease[21]. The retrospective nature, shorter median follow-up and smaller proportion (38%) of patients with macrovascular invasion in the above analysis make this a different population to the prospective series presented here.

In addition to being predictive of OS, baseline ALBI was predictive of toxicity following SBRT and also outperformed CP classification for this purpose, with ALBI remaining in multivariate models and displaying marginally superior c-statistics. Thus, it appears likely that ALBI grade, with less subjectivity and fewer components than CP, may be a marker of prognosis and toxicity useful for treatment selection and stratification within trials. Although calculated as a continuous variable, and accepting that some information is lost in the discretising process, the use of ALBI grade facilitates practical clinical application, without loss of significance as a prognostic or toxicity-predictive

value. One limitation of ALBI is the need for a calculation algorithm, relative to CP score, which can be manually computed.

Consistent with our previous toxicity analysis[9], mean liver dose and D800 remained significant predictors of toxicity when analysing ALBI as a continuous variable. Mean liver dose and the low dose region of the liver DVH curve (e.g. D800) have also been shown in other series to be related to liver toxicity[11,22,23]. Although, mean liver dose and D800 were not statistically significant when including ALBI as a dichotomous variable in the toxicity analysis, likely the result of statistical variability and a loss of statistical power when dichotomising the variable, these factors did approach significance, again reflecting their importance in liver toxicity risk. In addition to ALBI, the presence of tumour thrombus was identified as an independent predictor of inferior survival in this series. The importance of this factor as a negative prognostic feature is well established and not surprising[24,25].

This work has limitations: a greater number of patients is required to further evaluate ALBI, especially in patients with more advanced liver dysfunction: the value of ALBI in patients with CP-B and CP-C HCC is unknown. That said, this report is consistent with other literature examining ALBI in HCC, predominantly treated with other therapies, and this is the largest investigating ALBI in the setting of SBRT in a prospective Western population. Another limitation is a lack of information regarding the details of previous liver directed therapies on the risk of toxicity following SBRT. The use of previous liver directed therapies, however, was not found to be significant in this series, but could be considered in future investigations. ALBI could also be investigated with regard to other outcome measures (e.g. progression free survival) and the impact of changes in ALBI on outcome.

In conclusion, in patients with Child Pugh A liver disease, baseline ALBI was identified as an independent prognostic factor in Western HCC patients treated with SBRT. ALBI was also predictive of toxicity following SBRT. For both survival and toxicity, ALBI proved more discriminating than CP score. ALBI grades may

prove useful in patient selection for SBRT as a potential prognostic marker and as a marker for toxicity, and therefore should be included as a patient stratification factor in future clinical trials.

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Figure and table legends

Figure 1. a) Survival in ALBI groups 1 and 2 and b) Survival in CP class A5 and A6

Table 1. Baseline characteristics

Table 2. Univariate logistic regression for toxicity

Table 3. Multivariate logistic regression for toxicity

Table 4. Univariate Cox regression for overall survival

Table 5. Mulitvariate Cox regression for overall survival

Table 1. Baseline characteristics

Patient and disease factors						
	Overall (n=102)		Toxicity analysis (n=99)			
			Patients with toxicity (n=26)		Patients without toxicity (n=73)	
	n	%	n	%	n	%
Age (years)						
Median	69.4		67.31		71.76	
Range	40.4-90.3		40.4-83.8		45.8-90.3	
Gender						
Male	80	78%	21	81%	58	80%
Female	22	22%	5	19%	15	21%
Tumour volume (cc)						
Median	123.1		136.2		106.9	
Range	1.3-1913.14		2-1735		1-1913	
Normal liver volume* (cc)						
Median	1270.7		1637		1230	
Range	766.5- 3966.8		870-2278		767-3967	
Macrovascular HCC invasion						
Yes	56	55%	18	69%	35	48%
No	46	45%	8	31%	38	52%
Baseline Child Pugh class						
A5	73	72%	13	50	58	80%
A6	29	28%	13	50	15	21%
Baseline ALBI grade						
Median	-2.63		-2.35		-2.71	
Range	-3.40- -1.64		-2.8- -1.6		-3.4- -1.9	
Group 1	56	55%	6	23%	49	67%
Group 2	46	45%	20	77%	24	33%
Baseline platelet count						
Median	141		108		151	
Range	55-834		55-328		62-834	
Underlying liver disease						
Hepatitis B	39**	38%	8	31%	29	40%
Hepatitis C	31	30.%	9	35%	22	30%
Other	32	31%	9	35%	22	30%
Baseline AFP						
Median	163		503		125	
Range	<6-714500		<6-167850		<6-714500	
ECOG performance status						
0	50	49%	14	54%	36	49%
1	40	39%	9	35%	31	42%
2	12	12%	3	12%	6	8%
Extra-hepatic disease						
Absent	90	88%	21	81%	67	92%
Present	12	12%	5	19%	6	8%
Previous liver directed therapy†						

Surgery	9	9%	6	23%	3	4%
TACE	22	22%	6	23%	16	22%
RFA	35	34%	8	31%	27	37%
PEI	16	16%	3	12%	12	16%
Any	51	50%	12	46%	38	52%
None	51	50%	14	54%	35	48%
Trial						
1	50	49%	13	50%	34	47%
2	52	51%	13	50%	39	53%
Dosimetric factors (6 fractions)						
Prescribed dose (Gy)	36		34.5		36.6	
Median	24-54		25.8-54		24-54	
Range						
Mean liver dose (Gy)††	16.0		16.96		15.26	
Median	4.3-21.4		9.6-20.71		4.3-21.1	
Range						
Veff						
Median	0.43		0.508		0.4088	
Range	0.09-0.80		0.2-0.8		0.09-0.7	
Physical NTCP (%)						
Median	12.8		15.6		10.7	
Range	0-92.4		0-92.4		0-61.5	
Biological NTCP (%)						
Median	0.8		2.8		0.6	
Range	0-18.9		0-18.3		0-18.9	
D800 (Gy)						
Median	7.45		14.25		5.95	
Range	0-28.9		1.8-28.9		0-27.9	

*Normal liver volume was the total liver volume minus GTV

**8 had coexistent Hepatitis C

† More than one therapy may apply

†† Mean liver dose was based on dose received by liver minus GTV

TACE: trans-arterial chemo-embolization, RFA: radiofrequency ablation, PEI: percutaneous ethanol injection

Note. 3 patients excluded from toxicity analysis as no dosimetric data available

Table 2. Univariate logistic regression for liver toxicity

		Univariate analysis	
Patient details		Odds radio (95% confidence interval)	*p* value (*p*<0.2 carried into multivariate analysis*)
	Age	0.97 (0.94-1.01)	**0.18***
	Gender (Female vs Male)		0.89
	Total tumour volume (per 100cc increase)		0.42
	Normal liver volume (per 1000cc increase)	1.92 (0.75-4.90)	**0.17***
	Thrombus (Yes vs No)	2.44 (0.94- 6.32)	**0.066***
	Baseline Child Pugh (A6 vs A5)	3.87 (1.49- 10.10)	**0.0055***
	Baseline platelet count	0.991 (0.98- 0.998)	**0.018***
	Underlying liver disease (Hepatits C vs hepatitis B) (Other vs hepatitis B)		0.721
	Previous liver directed therapy Any vs none	0.79 (0.32-1.94)	0.61
	Baseline ALBI (0.1 unit increase; *continuous variable*)	1.37 (1.17-1.60)	**<0.0001***
	Baseline ALBI Grade 2 vs 1 (*ordinal variable*)	6.81 (2.42- 19.20)	**0.00028***
SBRT treatment details			
	Prescribed dose	0.95 (0.89-1.02)	**0.160***
	Mean liver dose†	1.31 (1.08-1.59)	**0.0052***
	Veff (0.1 unit increase)	1.66 (1.16-2.38)	**0.0054****
	Physical NTCP	1.02 (0.996-1.04)	**0.11**
	Biological NTCP	1.11 (1.02-1.20)	**0.016***
	D800	1.12 (1.05-1.20)	**0.00052***

* Included in multivariate analysis, odds ratios and confidence intervals only shown for variables with *p*<0.2.
**Not included in multivariate analysis to avoid multicollinearity as strongly correlated with mean liver dose.
† Mean liver dose was based on dose received by liver minus GTV
NTCP: normal complication probability

Table 3. Multivariate logistic regression for toxicity

		Odds ratio (95% confidence interval)	*p* value
Model using ALBI as continuous variable			
	Baseline ALBI (0.1 unit increase; *continuous variable*)	1.51 (1.23-1.85)	0.000074
	Mean liver dose*	1.31 (1.02-1.68)	0.036
	D800	1.10 (1.01-1.20)	0.028
Model using ALBI as ordinal variable			
	Baseline ALBI Grade 2 vs 1 (*ordinal variable*)	7.44 (2.34- 23.70)	0.00069
	Mean liver dose*	1.24 (0.985-1.56)	0.07
	D800	1.08 (0.995-1.17)	0.066

Note. Mean liver dose was forced into the final model given the general acceptance of its importance in predicting toxicity
* Mean liver dose was based on dose received by liver minus GTV

Table 4. Univariate Cox regression for overall survival

Patient details		Hazard ratio (95% confidence interval)	*p* value (*p*<0.2 carried into multivariate analysis*)
	Age	0.980 (0.96-0.999)	**0.036***
	Gender (Male vs Female)	1.56 (0.88-2.80)	**0.130***
	Tumor volume (per 100cc increase)	1.05 (0.999-1.100)	**0.055***
	Normal liver volume (per 1000cc increase)	1.55 (1.06-2.28))	**0.024***
	Thrombus (Yes vs No)	1.77 (1.13-2.78)	**0.012***
	Baseline Child Pugh (6 vs 5)	1.58 (0.98- 2.54)	**0.063***
	Baseline platelet count		0.23
	Underlying liver disease (Hepatits C vs hepatitis B) (Other vs hepatitis B)		0.648
	Baseline AFP (per 10,000 unit increase)		0.51
	Baseline ECOG Performance status 1 vs 0 2 vs 0	 2.00 (1.24-3.23) 2.22 (1.05-4.70)	 **0.004*** **0.036***
	Extra-hepatic disease (yes vs No)		0.20
	Trial (2 vs 1)	0.57 (0.37-0.89)	**0.013***
	Baseline ALBI (0.1 unit increase; *continuous variable)*	1.090 (1.026-1.158)	**0.005***
	Baseline ALBI Grade 2 vs 1 *(ordinal variable)*	1.809 (1.157-2.827)	**0.009***
SBRT treatment details			
	Prescribed dose	0.98 (0.95-1.01)	**0.10***
	Mean liver dose**	1.11(1.02-1.20)	**0.012***

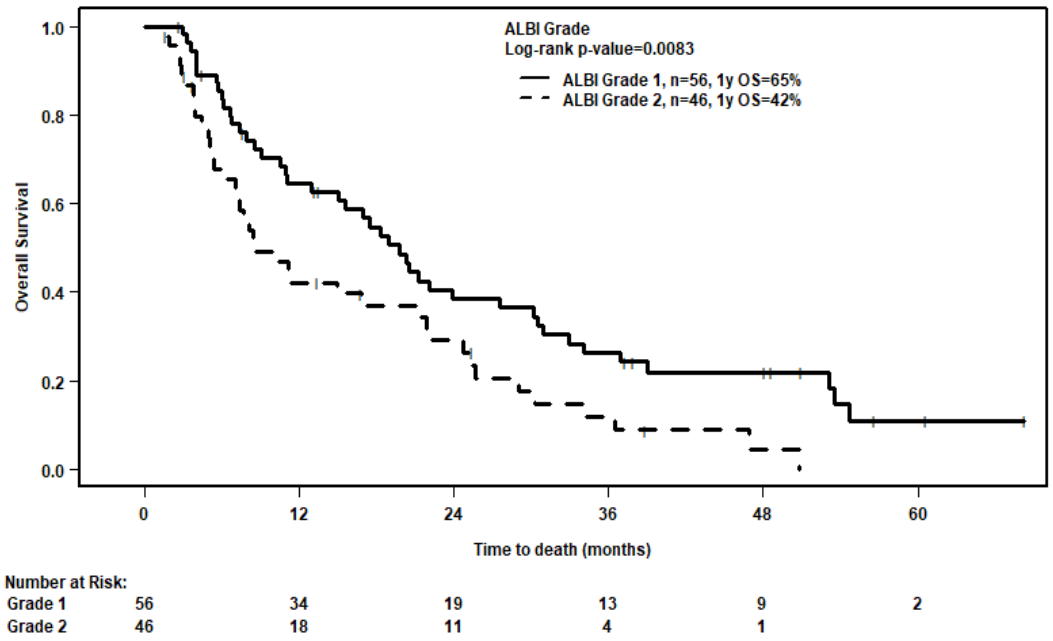
*Variables with *p*<0.2 (shown in bold text) included in multivariate analysis, hazard ratios and confidence intervals only shown for variables with *p*<0.2
** Mean liver dose was based on dose received by liver minus GTV

Table 5. Mulitvariate Cox regression for overall survival

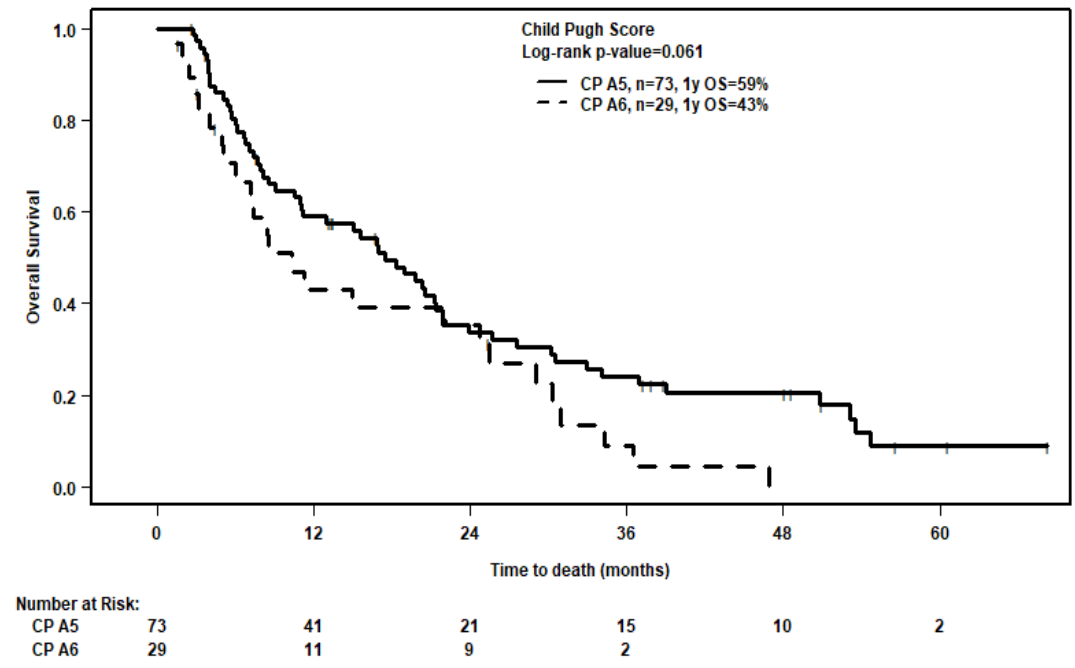
Factor		Hazard ratio	*p* value
Model using ALBI as continuous variable			
	Thrombus (Yes vs No)	1.94 (1.23-3.07)	0.004
	Baseline ALBI (0.1 unit increase; *continuous variable)*	1.09 (1.03- 1.17)	0.004
	Trial (2 vs 1)	0.52 (0.33-0.81)	0.004
Model using ALBI as ordinal variable			
	Thrombus (Yes vs No)	1.89 (1.20-2.98)	0.006
	Baseline ALBI Grade 2 vs 1 *(ordinal variable)*	1.79 (1.14-2.80)	0.011
	Trial (2 vs 1)	0.53 (0.34-0.83)	0.005

Figure 1. a) Survival in ALBI grades 1 and 2 and b) Survival in CP class A5 and A6

a)



b)



Supplementary Material

Figure 1. Relationship between ALBI as a continuous variable and Child Pugh score (independent samples *t*-test $p<0.01$; data jittered to illustrate spread of results, red solid circles represent those with toxicity and blue open circles represent those without toxicity)