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Locoregional Therapy for Hepatocellular Carcinoma with and without Extrahepatic Spread

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Abstract

Objective—This study evaluates the use of locoregional therapy in patients with hepatocellular carcinoma (HCC) with and without extrahepatic disease (EHD).

Methods—Patients who underwent locoregional therapy for HCC were identified from institutional databases. Clinicopathologic and treatment characteristics were compared between patients with and without EHD. Survival and progression were assessed using the Kaplan-Meier method and multivariate analysis was completed.

Results—Of 224 included patients, 39(17%) had radiologic evidence of EHD. Patients without EHD were older than those with EHD (68.8+/-10.1 vs. 65.0+/-11.7 years, $p=0.04$), however, underlying liver disease/function and tumor characteristics were not different. Type of locoregional therapy (HAE vs. DEB TACE, $p=0.12$; RFA+embolization, $p=0.07$) was similar. Progression occurred in 75% (169/224) of patients. Progression free survival did not differ

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between the two groups (13[10.3–15.7] months EHD vs.18 [14.6–21.4] months no EHD, $p=0.13$). Overall survival (OS) was 13(4.1–21.9) months and 25(20.4–29.6) months in the EHD and no EHD groups, respectively ($p=0.02$). On multivariate analysis, systemic therapy following locoregional treatment was the only variable independently associated with PFS (HR 0.70(0.49–1.00), $p=0.04$) while EHD (HR 1.60(1.02–2.50), $p=0.04$) and tumor size (HR 1.77(1.21–2.58), $p=0.003$) were independently associated with worse OS.

Conclusions—Patients with HCC and limited EHD treated with locoregional therapy have worse OS than patients without EHD; however, PFS was not different. Use of systemic therapy following locoregional therapy was independently associated with improved PFS in this cohort and suggests further prospective studies of locoregional, systemic and combination therapies are necessary to improve outcome in this high risk population of patients.

Introduction

Over the past three decades the incidence of HCC in the United States has nearly tripled. This rise is primarily driven by increased rates of chronic Hepatitis C (HCV) infection and nonalcoholic fatty liver disease (NAFLD) [1]. Treatment options and prognosis for HCC are contingent on the complex interplay between the degree of underlying liver disease and tumor stage at diagnosis. Despite recommendations for regular HCC screening in high risk populations by The American Association for the Study of Liver Disease (AASLD) [2] implementation in the United States has been poor with less than 20% of eligible patients undergoing routine surveillance [3]. Consequently, more than two thirds of patients present with advanced disease that is not amenable to curative resection or transplantation and five-year survival remains very poor (<5%) [4].

Patients with BCLC intermediate or advanced HCC are diverse and include those with locally advanced disease as well as those with EHD, decompensated liver disease, and/or poor functional status [5]. The heterogeneity of this cohort, the complicated interaction between tumor burden and liver function, accompanied by the concurrent evolution of locoregional and systemic therapies makes treatment decisions amongst this group complex, and multidisciplinary evaluation is essential prior to institution of any form of therapy [6]. In patients with intermediate disease confined to the liver, locoregional therapies including hepatic arterial embolization (HAE) and transarterial chemoembolization (TACE) are accepted modes of treatment [7]. In 2002 two randomized clinical trials [8, 9] showed a survival benefit of TACE over best supportive care in patients with intermediate HCC. Furthermore, in a meta-analysis of seven randomized clinical trials of patients with unresectable HCC by Llovet et al. [10] embolization was shown to provide a significant survival benefit when compared to observation alone. Although TACE is regarded by some as the superior method of embolization, recently published randomized clinical trial data have demonstrated no significant survival difference between TACE, DEB TACE and bland HAE [11–13]. Consequently, the most recently published National Comprehensive Cancer Network consensus guidelines for the treatment of HCC suggest embolization, either bland HAE or TACE, as the standard of care for patients with intermediate/advanced HCC without extra hepatic spread or main portal vein involvement [14].

In patients with advanced or metastatic disease, embolization therapy is not considered standard of care and with the advent of sorafenib, primary treatment is often systemic [15, 16]. Natural history studies of HCC suggest that tumor burden within the liver contributes significantly to hepatic decompensation and death [17, 18]. One may therefore hypothesize that the use of locoregional therapies to control liver disease may provide a survival benefit, even in patients with EHD. To date no definitive evidence to support or refute the use of locoregional therapy alone or in combination with systemic therapy exists. Given this paucity of evidence the current study seeks to analyze the use of locoregional therapies, including bland HAE and drug eluting bead chemoembolization (DEB TACE), in patients with advanced HCC with and without low volume EHD and to evaluate the impact on disease progression and survival.

Methods

Study Design

This retrospective study was approved via waiver of patient consent obtained from the institutional review board at the study center. All patients who underwent HAE or DEB TACE for the treatment of HCC between January 1, 2008 and August 1, 2013 were identified from prospectively maintained institutional and service specific databases. Only those patients in whom the procedure was their first locoregional treatment were included. Diagnosis of HCC was non-invasive and based on the presence of characteristic radiographic findings [2]. In a small minority of patients in whom radiographic features were inconsistent or equivocal, tissue diagnosis was required. Patients with Child-Pugh Class A or B liver function and intermediate or advanced stage HCC, as defined by the Barcelona Clinic Liver Cancer staging system [5] were reviewed at a multidisciplinary hepatobiliary consensus conference. By definition these patients were not candidates for surgery or transplantation. All patients in whom HCC was limited to the liver were considered for transarterial locoregional therapy. Furthermore, patients with limited EHD, defined as solitary bone/adrenal/soft tissue metastasis, scattered small lung nodules or regional nodal disease, were judged as having 'liver dominant' disease, and were also considered for locoregional therapy.

Overall, 607 patients underwent 1205 locoregional procedures between January 2008 and August 2013. Of the 607 patients, 264 had a primary diagnosis of HCC and the medical records of these patients were reviewed. Forty patients who had undergone locoregional treatment for HCC prior to the study period were excluded, while 224 patients were deemed appropriate and included in final analysis. Overall, 177 (79%) were male and the mean age was 68.1 $\pm$ 10.4 years. At the time of initial presentation 39 (17.4%) patients had evidence of extrahepatic disease (EHD) compared to 185 (82.6%) who did not. Table 1 outlines baseline demographic characteristic for the group as a whole and is further stratified by the presence or absence of EHD. Patients without EHD at presentation were significantly older than those with EHD (68.8 $\pm$ 10.1 vs. 65.0 $\pm$ 11.7 years, $p=0.04$). Previous treatment was defined as any HCC directed surgical or systemic therapy received prior to the initial locoregional treatment. Presence and type of underlying liver disease ($p=0.28$), Child-Pugh

classification ($p=0.59$) and use of previous treatment ($p=0.11$) were not different between groups.

Data Collection and Definitions

Target lesion was defined radiographically as the largest measureable lesion in any dimension on initial imaging. EHD was characterized radiographically and recorded according to anatomical site. As previously reported, lymph node involvement by tumor can be difficult to differentiate radiographically from reactive nodal enlargement in the setting of cirrhosis [15]. In the current study all patients with persistently enlarged nodes on radiologic imaging (≥ 1 cm) reported as concerning for metastasis were included in the EHD group [19]. Locoregional therapy was categorized as either bland hepatic arterial embolization (HAE) or drug eluting bead transarterial chemoembolization (DEB TACE) [20]. Planned repeat embolization or ablation in patients with bi-lobar or large target lesions was documented and was considered part of primary treatment cycle and not post embolization treatment.

Electronic medical records of patients in whom length of stay (LOS) was greater than the median LOS for the entire group were reviewed for evidence of post procedural complications. Procedural complications were graded on a scale of 0 to 5 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03) [21] and 30 day mortality was noted. Total follow up time was defined as time from initial embolization to date of last follow up, patient disease status and survival at this time was censored. Disease progression and treatment response were defined radiologically using mRECIST criteria [22]. Date of progression was taken as the date of imaging study documenting disease advancement. Treatment following locoregional therapy included any surgical or systemic treatment of HCC occurring after completion of locoregional therapy.

Embolization Technique

Following critical review, patients who were not candidates for curative resection or transplant were considered for transarterial locoregional therapy. Patients with poor performance status (ECOG PS >1), advanced cirrhosis, tumor burden involving $>75\%$ of liver parenchyma and contraindications to embolization (i.e. renal dysfunction, inadequate arterial access) were excluded. At the study institution bland embolization with Embosphere® Microspheres (Merit Medical Systems, Inc., South Jordan, UT) is the standard approach. However, from November 2007 to March 2012 (inclusive) a randomized trial of embolization with Bead Block® vs LC Bead™ (Biocompatibles UK Ltd, Farnham, UK) was ongoing [12, 20]. Patients meeting trial inclusion criteria who agreed to participate were randomized to bland embolization with Bead Block® or chemoembolization with doxorubicin loaded LC Bead™. Consequently, transarterial therapy amongst those included in the current study cohort was performed with either bland HAE (Embosphere® Microspheres $n=117$, Bead Block® $n=64$) or DEB TACE ($n=43$).

Patients had intravenous access established and hydration begun with normal saline. Selective visceral angiography was performed to identify all the vessels supplying the tumor. Whenever possible, selective tumor vessel embolization was performed. In all cases,

embolization was performed to stasis. Stasis was defined as the absence of antegrade flow within a vessel such that contrast filling the target vessel and branches persisted without washout for 5 cardiac beats after contrast injection [23].

Bland embolization with Embosphere® Microspheres (Merit Medical Systems, Inc, South Jordan, Utah) was used in 117 patients, beginning with the 40–120µm size and moving to the 100–300µm and then the 300–500µm particles as needed to achieve stasis. HAE with Bead Block was performed in a similar fashion. In patients receiving DEB-TACE (n=43), the LC Bead™ was loaded with 150mg of doxorubicin on 100–300µm particles. The dose to be used was divided proportionately in all target vasculature followed by embolization with unloaded particles until stasis was achieved as outlined above. In the case of multifocal bi-lobar disease, either the right or left liver was treated at the first session. Selective embolization in such cases was performed as necessary to avoid non-target embolization.

Following treatment patients were monitored in a post-anesthesia care unit and then transferred to the inpatient unit. Patients were discharged when tolerating a diet, temperature <38.5 °C and pain was controlled with oral analgesics. All patients were subject to standard post embolization surveillance including CT evaluation at 2–4 weeks post procedure and every three months thereafter. Treatment failures were determined on follow up imaging using mRECIST criteria, where progression of disease was defined as increase in the sum of the viable target lesion diameters of greater than 20% and/or similar increase in the sum of the diameters of non-target lesions, and/or development of new tumor(s) [22].

Data Analysis

Statistical analysis was performed using SPSS software, version 21.0 (Chicago IL, USA). Baseline patient characteristics are presented as frequencies and means $\pm$ SD. Follow up time, length of stay, progression and survival data are expressed as median (range). Data was stratified based on the presence or absence of EHD. Comparison of continuous data between groups was carried out using independent T tests or Mann Whitney-U tests where appropriate. Categorical data were compared using Chi-squared analysis and Fisher's exact test where appropriate. Survival analysis for the entire cohort (n=224) was completed according to the Kaplan Meier method. Univariate analysis of patient and tumor related characteristics were completed using log rank test. Variables found to be significant ($p < 0.05$) or close to significant ($P < 0.1$) on univariate analysis were subsequently included in stepwise regression analysis using Cox proportional hazard model for identification of independent predictors of survival/progression. All statistical tests were two tailed and significance set at $p=0.05$.

Results

Characteristics of Locoregional Therapy

A total of 441 procedures were completed in 224 patients. The median number of embolization procedures was 1 (1–8) and was not different between patients with (1 (1–7)) and without (1 (1–8), $p=0.75$) EHD. Pre-treatment albumin was significantly lower in patients with EHD compared to those without EHD (3.61 ± 0.61 vs. 3.80 ± 0.45 g/dL,

$p=0.006$). Target lesion characteristics, extent of disease, and embolization characteristics are outlined in Table 2. No differences were seen between groups in terms of target lesion size ($p=0.24$), number of lesions ($p=0.43$), portal venous involvement ($p=0.09$), or receipt of systemic therapy following locoregional treatment ($p=0.28$). Furthermore, combination treatment with radiofrequency ablation (RFA) and embolization was not different between patients with and without EHD (28.1% vs. 12.8%, $p=0.07$).

Embolization was considered to be clinically successful in 92.4% (207/224) of cases. Clinical success was defined as any of the following based on mRECIST; complete response (CR), partial response (PR) or stable disease (SD) [22]. There were 17 cases of primary treatment failure amongst the entire cohort, etiology of which is outlined in Table 3. Median length of stay (LOS) was 3 (1–56) days and was not different between groups ($p=0.77$). Overall complication rate was 21% (47/224). The majority of complications were minor (32/47, 71%) and consisted primarily of post-embolization syndrome ($n=13$), pleural effusions ($n=9$) and cardiac arrhythmia ($n=2$). Thirty day mortality was 1.8% (4/224), and was not different between patients with (2/39, 5.1%) and without (2/186, 1.1%) EHD at presentation ($p=0.14$).

Median follow up time for the entire cohort was 13 (0–73) months and was not statistically different between patients with EHD (10 (0–48) months) and without EHD (13 (0–73), months) ($p=0.08$). Of the patients alive at the time of analysis (110/224), follow up time was 15 (0–73) months in those without EHD versus 16.5 (1–48) months in those with EHD and was not different ($p=0.62$). At the time of last follow up 114 (50.9%) patients were dead with/of disease, 81 (36.2%) were alive with disease, and 29 (12.9%) had no evidence of disease. Figure 1 outlines disease status at last follow up stratified by presence or absence of EHD. No differences were observed between patients with and without EHD ($p=0.12$). Amongst the entire cohort 46 (20.5%) patients were treated with systemic therapy following locoregional treatment, this was not different between patients with and without EHD (18.9% vs. 28.2% respectively, $p=0.28$).

Progression/Survival Analysis

Among the 224 patients, 169 (75%), had disease progression (local, locoregional, and/or distant) during the follow up period and this was not different between groups ($p=0.55$). However, patterns of progression differed significantly between groups. Patients without EHD were more likely to have disease progression isolated to the liver when compared to patients with EHD (42.2% vs. 12.8%, $p<0.0001$).

Median PFS of patients with and without EHD was 13 (10.3–15.7) months vs. 18 (14.6–21.4) months, respectively, $p=0.13$ (Figure 2). Of the 39 patients with EHD, 22 had lymph nodes as the primary site of EHD (LN+) while 17 patients had EHD that was not in the lymph nodes (LN–). Median PFS was not significantly different between patients with LN+ EHD 12 (7–17) months and LN– EHD 18 (5–31) months, $p=0.18$. Clinicopathological variables significantly associated with PFS on univariate analysis of the entire cohort ($n=224$) included; target lesion size $> 5\text{cm}$ ($p=0.05$) and use of systemic therapy following locoregional treatment (0.02); however, when subjected to multivariate analysis, only use of

systemic therapy following locoregional treatment (HR 0.70 (0.49–1.00, $p=0.04$) remained significant (Table 4).

There were 110 patients (49.1%) alive at the time of data collection. Median OS in patients with EHD was 13 (4.1–21.9) months, compared to patients without EHD, 25 (20.4–29.6) months, $p=0.02$. Figure 3 illustrates OS curves for patients with and without EHD. Median OS among patients with LN+ EHD was 10 (2–18) months compared to 29 (7–51) months for LN– EHD patients. This was not statistically significant ($p=0.09$). On further univariate analysis OS for the entire cohort ($n=224$) was also associated with the number of tumors ($p=0.08$), size of the target lesion ($p=0.002$), portal vein involvement ($p=0.03$), and type of embolization (HAE vs. DEB-TACE, $p=0.04$). On multivariate analysis of these factors, OS was found to be independently related to tumor size $>5\text{cm}$ (HR 1.77(1.21–2.58), $p=0.003$) and presence of EHD (HR 1.60 (1.02–2.50) $p=0.04$) (Table 5) only.

Discussion

The role of locoregional therapy in patients with EHD remains undefined. In this retrospective analysis, we evaluated the use of locoregional therapy in a cohort of patients and compared outcomes amongst patients without EHD to those with limited EHD at the time of presentation. Short term outcomes in terms of length of stay, complication rate, and thirty day mortality were similar between patients with and without EHD, suggesting locoregional therapy is a safe intervention in select patients with limited EHD.

PFS did not differ between patients with EHD and without EHD (13 months vs. 18 months ($p=0.13$), respectively). However, patterns of progression were different between the groups. Patients without EHD were more likely to have isolated liver progression as oppose to progression at an EHD site or a combination of liver and EHD progression. Notably, 28.2% of the patients with EHD and 18.9% of patients without EHD in this study received systemic therapy following locoregional treatment. In a previous retrospective analysis, the addition of systemic therapy to locoregional therapy in patients with EHD appeared to confer a survival benefit [24]. In the current study, although treatment with systemic therapy following locoregional treatment was independently associated with improved progression free survival (HR 0.70 (0.49–1.00), $p=0.04$), it was not associated with OS ($p=0.15$). Median OS in our cohort of patients with EHD treated with locoregional therapy was 13 months and was significantly shorter when compared to OS observed in patients without EHD (25 months, $p=0.02$). Furthermore, in addition to EHD, target lesion size $>5\text{cm}$ was independently associated with OS.

EHD in patients with HCC has consistently been associated with poor prognosis. Cabibbo et al. [25] recently conducted a meta-analysis of 30 randomized control trials of HCC in which the untreated/placebo control arms were evaluated with regards to estimated survival rates. The results of this analysis revealed a cumulative 1-year survival rate of 34% amongst untreated patients with intermediate and advanced HCC. Furthermore, natural history studies of untreated patients with advanced HCC completed in 1999 [17] and 2012 [18], revealed median survivals of 5.4 months and 6.9 months, respectively. In the current study, patients with limited EHD at presentation treated with locoregional therapy had a median

OS of 13 months; nearly double the most recently reported OS of untreated patients [18]. Despite inherent differences between treated and untreated patients the observed prolonged OS in the current study may suggest a potential benefit of locoregional therapy amongst these patients. However, it should be noted that the untreated populations in these published retrospective studies include patients with Childs A, B, and C cirrhosis, poor functional status, and any degree of metastatic spread whereas our study population was limited to Child A and B with good performance status, and limited EHD. Furthermore, over one quarter of patients were exposed to systemic therapy following locoregional treatment, as such observed differences in survival may be overestimated by this comparison.

Baseline demographics of the group in our study with limited EHD were similar to those of the SHARP trial [15]. Median OS of patients treated with sorafenib in this randomized control trial was 10.7 months, similar to the observed 13 month OS observed in the current study. However, given that the SHARP trial was a randomized control trial and the current analysis is retrospective in nature, direct comparison of survival outcomes is not feasible. Nevertheless it is an interesting observation. Furthermore, since 2007 there has been an evolution of the median OS of patients with metastatic HCC. Along with improvement in referral patterns and the presence of second line therapy studies [26], there is also a better understanding of survival outcomes associated with sorafenib based on underlying HCC etiology. For example patients with hepatitis C who are non Asian --- and who make up one third of the patients evaluated in our study --- have a reported median OS of 17 months [27].

The current study has several limitations. It is retrospective in nature and the number of patients with EHD treated with locoregional therapy was small (39/224). The type of locoregional therapy was heterogeneous amongst the entire cohort (bland embolization with Embospheres n=117, bland embolization with Bead Block n= 64, DEB-TACE n=43, and combination embolization + RFA n=57). However, rates of different locoregional therapies were not statistically different between groups, allowing reasonable comparison of locoregional therapy as a whole. Furthermore, this heterogeneity reflects true clinical practice and how locoregional therapies are employed in this complex group of patients, making observations from this evaluation clinically relevant. A large proportion of patients in the EHD group had nodal metastasis (56.4%) which were defined radiologically and not confirmed by tissue diagnosis, thus nodal enlargement secondary to underlying cirrhosis/hepatitis cannot be ruled out and the number of cases of EHD may be overestimated. At baseline patients with EHD were younger than patients without EHD. This may represent a significant selection bias if liver directed therapy was offered only to more robust patients with limited EHD and not to older and potentially more co-morbid patients. Furthermore, in our study we evaluated PFS in patients with and without EHD; this is a difficult metric to compare as it is a composite variable and is dependent on definition of progression (radiographic vs. symptomatic) and surveillance interval; as such, comparison can only be made between patients in our study population in whom follow up after locoregional therapy was standardized. Finally, patients in both arms went on to receive other treatments after locoregional therapy which may have impacted observed survival. With these limitations in mind, the results of the current study confirm previous findings; the presence of EHD is a factor carrying poor prognosis, perhaps indicative of more invasive tumor biology, and it is associated with reduced OS when compared to patients without EHD.

Conclusion

Despite EHD conferring a worse prognosis, this study suggests that treatment with locoregional therapy in selected patients with good performance status and limited EHD is safe and median survival is reasonable (13 months). This suggests that the presence of limited EHD alone should not necessarily contraindicate transarterial locoregional therapy. Interestingly, amongst this cohort of patients, use of systemic treatment following locoregional therapies was independently associated with improved PFS. As such, future studies evaluating locoregional, systemic, and combined modality treatment (systemic + locoregional) in this high risk population with limited EHD are warranted.

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Figure 1.

Disease status at last follow up of patients with hepatocellular carcinoma (HCC) with and without extrahepatic disease (EHD) treated with locoregional therapy. * *Note: the 2 patients within the EHD group who were disease free at last follow up had EHD that was isolated persistent nodal enlargement that resolved with locoregional treatment.*

	0	6	12	24	36	48	60
Number at Risk							
No EHD	185	139	97	45	19	5	4
EHD	39	22	16	7	4	0	0

Figure 2.
Progression Free Survival in patients with (— EHD) and without extrahepatic disease (- - - no EHD) at time of initial embolization.

Figure 3.
 Overall Survival in patients with (— EHD) and without extrahepatic disease (- - - no EHD) at time of initial embolization.

Table 1

Univariate analysis of patient and disease characteristics as related to presence of extrahepatic disease at presentation. (ETOH= alcohol related liver disease, NAFLD= non-alcoholic fatty liver disease, LRT= local radiotherapy).

	Group	No EHD	EHD	p-value
Number of Patients (n)	224	185 (82.6)	39 (17.4)	
Age (years)	68.1+/-10.4	68.8+/-10.1	65.0+/-11.7	0.041
Sex				
<i>Male</i>	177 (79)	144 (77.8)	33 (84.6)	0.345
<i>Female</i>	47 (21)	41 (22.2)	6 (15.4)	
Presence of Underlying Liver Disease	170 (75.9)	143 (77.3)	27 (69.2)	0.284
Type of Liver Disease				
<i>Hepatitis C</i>	67 (29.9)	56 (30.3)	11 (28.2)	0.639
<i>Hepatitis B</i>	38 (17)	30 (16.2)	8 (20.5)	
<i>ETOH</i>	28 (12.5)	26 (14.1)	2 (5.1)	
<i>NAFLD</i>	14 (6.3)	11 (5.9)	3 (7.7)	
<i>Other</i>	13 (5.8)	12 (6.5)	1 (2.6)	
<i>Combination</i>	10 (4.5)	8 (4.3)	2 (5.1)	
Child-Pugh Classification				
<i>A</i>	165 (73.7)	139 (75.1)	26 (66.7)	0.586
<i>B</i>	5 (2.2)	4 (2.2)	1 (2.6)	
<i>No underlying cirrhosis</i>	54 (24.1)	42 (22.7)	12 (30.8)	
Pre-Embolization Laboratory Tests				
<i>Total Bilirubin (mg/dL)</i>	0.98+/-0.64	0.96+/-0.65	1.07+/-0.59	0.352
<i>Albumin (g/dL)</i>	3.80+/-0.5	3.80+/-0.45	3.61+/-0.61	0.006
<i>INR</i>	1.17+/-0.28	1.17+/-0.30	1.16+/-0.15	0.856
Previous Treatment	38 (17.0)	28 (15.1)	10 (25.6)	0.112
Type of Previous Treatment				
<i>Systemic Therapy</i>	9 (4.0)	7 (3.8)	2 (5.1)	0.955
<i>Surgery</i>	16 (7.1)	11 (5.9)	5 (12.8)	
<i>LRT</i>	5 (2.2)	4 (2.2)	1 (2.6)	
<i>Other</i>	8 (3.6)	6 (3.2)	2 (5.1)	

Table 2

Univariate analysis of tumor and embolization characteristics relative to the presence of extrahepatic disease at embolization.

Variable	Group (n=224)	No EHD (n=185)	EHD (n=39)	p-value
Number of Lesions				
1	82 (36.6)	67 (36.2)	15 (38.5)	0.429
<5	71 (31.7)	62 (33.5)	9 (23.1)	
Multifocal	71 (31.7)	56 (30.3)	15 (38.5)	
Size of Target Lesion				
<5cm	108 (48.2)	92 (49.7)	16 (41.0)	0.240
>5cm	110 (49.1)	87 (47.0)	23 (59.0)	
Portal Vein Involvement	36 (16.1)	26 (14.1)	10 (25.6)	0.092
Location of Extrahepatic Spread				
Nodal	-	-	22 (56.4)	
Lung	-	-	14 (35.9)	
Bone	-	-	2 (5.1)	
Adrenal	-	-	4 (10.3)	
Other	-	-	4 (10.3)	
Type of Embolization				
Bland	181 (80.8)	153 (82.7)	28 (71.8)	0.122
Chemoembolization	43 (19.2)	32 (17.3)	11 (28.2)	
Combination Embolization/Ablation	57 (25.4)	52 (28.1)	5 (12.8)	0.067
Number of Embolizations	1.0 (1–8)	1.0 (1–8)	1.0 (1–7)	0.745
Systemic Therapy following Locoregional Treatment	46 (20.5)	35 (18.9)	11 (28.2)	0.278
Length of Stay (days)	3.0 (1–56)	3.0 (1–56)	3.0 (1–11)	0.774
Complication (any)	47 (21)	37 (20.0)	10 (25.6)	0.516
30d Mortality	4 (1.8)	2 (1.1)	2 (5.1)	0.142
Any Progression of Disease (%)	169 (75.4)	138 (74.6)	31 (79.5)	0.552
Liver only Progression (%)	83 (37.1)	78 (42.2)	5 (12.8)	<0.0001
EH only Progression (%)	7 (3.1)	5 (2.7)	2 (5.1)	0.613
Progression liver & EH (%)	80 (35.7)	56 (30.3)	24 (61.5)	<0.0001
Site of First Progression Liver (%)	128 (57.1)	114 (61.6)	14 (35.9)	<0.0001
Site of First Progression EH (%)	23 (10.3)	14 (7.6)	9 (23.1)	0.016
First Progression both Liver & EH (%)	17 (7.6)	9 (4.9)	8 (20.5)	0.004
Follow up time (months)	13 (0–73)	13 (0–73)	10 (0–48)	0.077

Table 3

Etiology of primary embolization failures.

Etiology of Treatment Failure	Number of Patients
<i>Local Hepatic Progression Only</i>	1
<i>Distant Hepatic Progression Only</i>	0
<i>Local & Distant Hepatic Progression</i>	4
<i>New or Progressive EHD Only</i>	1
<i>Local/Distant Hepatic Progression & New or progressive EHD</i>	8
<i>Other</i>	3
Total	17

Table 4

Univariate and multivariate progression free survival analysis as related to patient, tumor, and embolization variables.

Variable	Status	N	Progression	Univariate Analysis			Multivariate Analysis	
				Median +/-SE	95% CI	p- value	Hazard Ratio	p- value
Sex	Female	47	28	16 (2.2)	11.8–20.2	0.786		
	Male	176	141	16 (1.9)	12.3–19.7			
Underlying Liver Disease	No	53	39	21 (4.2)	12.8–29.2	0.969		
	Yes	170	130	15 (1.6)	11.9–18.1			
Child-Pugh Classification	A	165	127	16 (1.6)	12.9–19.1	0.620		
	B	5	4	13 (17.5)	0–47.3			
Number of Lesions	I	81	53	22 (4.5)	13.1–30.9	0.369		
	<5	71	58	17 (1.7)	13.7–20.3			
Size of Target Lesion	Multifocal	71	58	13 (1.7)	9.7–16.3			
	<5cm	108	78	22 (3.3)	15.5–28.5	0.048	1.0	0.075
Extrahepatic Disease	>/=5cm	109	87	14 (1.0)	12.0–16.0		1.32 (0.97–1.80)	
	No	184	138	18 (1.8)	14.6–21.4	0.134		
Previous Treatment	Yes	39	31	13 (1.3)	10.3–15.7			
	No	185	138	16 (1.5)	13.0–19.0	0.190		
Systemic Therapy following Locoregional Treatment	Yes	38	31	19 (3.4)	12.3–25.7			
	No	178	125	14 (1.1)	11.8–16.2	0.018	1.0	0.038
Type of Embolization	Yes	46	44	25 (3.3)	18.5–31.5		0.70 (0.49–1.00)	
	Bland	181	128	17 (2.1)	12.9–21.1	0.187		
Complication (any)	Chemo	42	41	16 (2.6)	11.0–21.0			
	No	176	136	16 (1.7)	12.6–19.4	0.388		
Portal Vein Involvement	Yes	47	33	19 (2.9)	13.3–24.7			
	No	187	143	18 (1.9)	14.4–21.6	0.138		
	Yes	36	26	12 (3.7)	4.8–19.2			

Table 5

Univariate and multivariate overall survival analysis as related to patient, tumor, and embolization variables.

Variable	Status	N	Dead	Univariate Analysis			Multivariate Analysis	
				Median +/-SE	95% CI	p- value	Hazard Ratio	p- value
Sex	<i>Female</i>	47	24	16 (2.5)	11.1–20.9	0.363		
	<i>Male</i>	177	90	25 (2.6)	19.9–30.1			
Underlying Liver Disease	<i>Yes</i>	170	83	24 (2.7)	18.7–29.3	0.510		
	<i>No</i>	54	31	23 (4.1)	15.0–31.0			
Number of Lesions	<i>I</i>	82	35	25 (1.7)	21.7–28.3	0.080	1.0	0.275
	<i><5</i>	71	34	24 (5.6)	13.0–35.0		0.91 (0.56–1.48)	0.703
Size of Target Lesion	<i>Multifocal</i>	71	45	13 (3.2)	6.7–19.3		1.30 (0.82–2.07)	0.263
	<i><5cm</i>	108	45	29 (3.5)	22.2–35.8	0.002	1.0	0.003
Extrahepatic Disease	<i>>/=5cm</i>	110	68	16 (2.4)	11.2–20.8		1.77 (1.21–2.58)	
	<i>No</i>	185	89	25 (2.4)	20.4–29.6	0.023	1.0	0.039
Previous Treatment	<i>Yes</i>	39	25	13 (4.5)	4.1–21.9		1.60 (1.02–2.50)	
	<i>No</i>	186	95	22 (2.5)	17.1–26.9	0.263		
Systemic Therapy following Locoregional Treatment	<i>Yes</i>	38	19	24 (7.2)	10.0–38.0			
	<i>No</i>	178	85	20 (3.3)	13.6–26.4	0.149		
Type of Embolization	<i>Yes</i>	46	29	29 (3.4)	22.3–35.7			
	<i>Bland</i>	181	82	27 (3.3)	20.6–33.4	0.044	1.0	0.248
Complication (any)	<i>Chemo</i>	43	32	19 (3.0)	13.2–24.8		1.29 (0.84–1.97)	
	<i>No</i>	177	85	24 (2.0)	20.0–28.0	0.300		
Portal Vein Involvement	<i>Yes</i>	47	29	19 (3.4)	12.4–25.6			
	<i>No</i>	188	93	24 (2.2)	19.6–28.4	0.034	1.0	0.677
Disease Progression (any)	<i>Yes</i>	36	21	13 (5.5)	2.2–23.8		1.12 (0.66–1.88)	
	<i>No</i>	54	17	NR	NR	0.811		
	<i>Yes</i>	169	96	24 (2.10)	19.9–28.1			