Prognostic Factors for Effectiveness Outcomes After Transarterial Radioembolization in Metastatic Colorectal Cancer: Results From the Multicentre Observational Study CIRT

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Abstract

This study explored factors that can predict effectiveness outcomes after transarterial radioembolization in colorectal liver metastases in the liver. In a cohort of 237 patients, among other factors, we found that an Aspartate transaminase to Platelet Ratio Index (APRI) value of >0.40 was a particularly strong independent predictor of worse overall survival, progression-free survival and hepatic progression-free survival outcomes. **Background:** Transarterial radioembolisation (TARE) with Yttrium-90 resin microspheres is a treatment option for patients with metastatic colorectal cancer in the liver (mCRC). A better understanding of the prognostic factors and treatment application can improve survival outcomes. **Methods:** We analysed the safety and effectiveness of 237 mCRC patients included in the prospective observational study CIRSE Registry for SIR-Spheres Therapy (CIRT) for independent prognostic factors for overall survival (OS), progression-free survival (PFS) and hepatic progression-free survival (hPFS) using the Cox proportional-hazard model. **Results:** The median OS was 9.8 months, median PFS was 3.4 months and median hPFS was 4.2 months. Independent prognostic factors for an improved overall survival were the absence of extra-hepatic disease (*P*= .0391), prior locoregional procedures (*P*= .0037), an Aspartate transaminase to Platelet Ratio Index (APRI) value of ≤0.40 (*P*< .0001) and International Normalized Ratio (INR) ≤1 (*P*= .0078). Partition model dosimetry resulted in improved OS outcomes compared to the body surface area model (*P* = .0120).

Independent predictors for PFS were APRI >0.40 (*P* = .0416) and prior ablation (*P* = .0323), and for hPFS these were 2 to 5 tumor nodules (*P* = .0148), Albumin-bilirubin (ALBI) grade 3 (*P* = .0075) and APRI >0.40 (*P* = .0207). During the study, 95 of 237 (40.1%) patients experienced 197 adverse events, with 28 of 237 (11.8%) patients having a grade 3 or higher adverse events. **Conclusion:** Including easy-to-acquire laboratory markers INR, APRI, ALBI and using partition model dosimetry can identify mCRC patients that may benefit from TARE.

Introduction

Colorectal cancer is the third most common form of cancer worldwide and the second in mortality.[1] The most frequent site of colorectal cancer-associated metastasis is the liver: while about 25% present liver metastases at initial diagnosis, 30% develop liver metastases later during the course of the disease.[2] Potential treatments with curative intent for liver-only metastatic colorectal cancer (mCRC) are complete resection, with a 5-year survival of up to 70% in small, solitary tumors[3] and thermal ablation for tumors of less than three centimetres and clear tumor margins.[4]

Beyond resection or thermal ablation, a plethora of treatment options have been introduced for mCRC. Chemotherapy, usually a combination of irinotecan and/or oxaliplatin with 5-FU/LV used together with biologicals such as cetuximab or panitumumab, and bevacizumab or aflibercept in more advanced disease is well established in earlier therapy lines.[4,5] Liver-directed approaches such as transcatheter arterial chemoembolization (TACE), hepatic artery infusion of chemotherapy, stereotactic radiation, or ablative therapies such as radiofrequency ablation, microwave ablation or cryoablation are treatment options for this patient population.[4-6] However, a comparison of outcomes among techniques remains a challenge and hence, no standardized approach to palliative treatment of liver dominant mCRC has been developed.[6]

In recent years, the body of evidence on the application of transarterial radioembolization (TARE, also known as Selective Internal Radiation Therapy [SIRT]) with Yttrium-90 (Y90) has grown.[7] In brief, TARE is an interventional therapeutic procedure with targeted delivery of high doses of radiation to liver tumors via the hepatic artery by means of glass or resin microspheres.[8] Most of the data supporting the use of TARE has been published for hepatocellular carcinoma (HCC) patients and the procedure has been included in the standard "tool-box" of unresectable HCC.[9-11] In mCRC, the current clinical landscape in systemic treatments, locoregional approaches and surgery remains complex and further evidence on how to implement TARE is warranted.[12]

An early randomized phase 2 trial of TARE in mCRC comparing TARE with Y90 resin microspheres with hepatic arterial chemotherapy showed improved local tumor control in the TARE arm (44% vs. 17%).[13] Further trials and case series, evaluating patients undergoing salvage treatment with TARE in combination with 5-FU/LV were confirming TAREs ability for local disease control with a good toxicity profile.[14-17] Despite these promising early results, large randomized controlled trials comparing systemic treatments in a first line setting (FOLFOX6m ± bevacizumab) with or without the addition Y90 resin microspheres were unable to show benefits to overall survival and progression-free survival in the Y90 arm.[18,19] In the second line setting, the randomized, multicentre open-label EPOCH trial showed that the addition of TARE with Y90 glass microspheres to FOLFOX or FOLFIRI resulted in a prolonged progression free survival with equal safety compared to second-line chemotherapy alone, the trial's primary end point, but no improvement in overall survival (OS).[20] Even though TARE has consistently shown promising results in local tumor control, identifying the patient group that benefits the most of TARE might be the way to improve OS.

The objective of the current subgroup analysis was to report on safety and to investigate effectiveness in terms of potential prognostic factors for OS, progression-free survival (PFS) and hepatic-progression-free survival (hPFS) in patients with liver-dominant mCRC treated with TARE with Y90 resin microspheres, using the data from the European-wide prospective, multicentre observational study CIRSE Registry for SIR-Spheres Therapy (CIRT, NCT 02305459). This study, conducted by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), investigated the clinical application and outcomes of TARE with Y90 resin microspheres (SIR-Spheres Y-90 resin microspheres, Sirtex Medical Pty Limited; St. Leonards, NSW, Australia).[21] This study prospectively included patients with a clinical indication for TARE with Y90 resin microspheres and was open for all cancer types.

Material and Methods

Study Design

The mCRC cohort (n = 237) collected in the CIRT study was used in this analysis. CIRT is a prospective, single device, multi-centre observational study of patients with primary and metastatic hepatic malignancies treated with TARE with Y90 resin microspheres as the standard of care. The CIRT methodology was published by Helmberger et al.[21] Sites were invited to participate if they had reported to have at least 40 TARE cases overall and ten cases in the twelve months prior to invitation. The 27 participating sites were identified and enrolled from April 2014 until April 2017, of which 24 sites enrolled mCRC patients.[22]

Data was collected using a customized electronic data capturing system and electronic case report form that was developed by ConexSys Inc (Lincoln, RI) and hosted on a local secure server in Vienna, Austria maintained by ITEA (Vienna, Austria). Statis-

tical analyses were performed in SAS (Cary, NC) and RStudio (R Foundation, Vienna, Austria).

Patient Selection

Patients eligible for analysis were adults diagnosed with mCRC and scheduled to receive TARE with Y90 resin microspheres. There were no specific exclusion criteria. All included patients signed an informed consent form. This research project was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient recruitment took place between 1 January 2015 and 31 December 2017. Follow-up data was collected until 31 December 2019. Sites were requested to follow-up with the patient every 3 months for 24 months after the first TARE treatment. In addition, sites were encouraged to obtain follow-up information from referring physicians if follow-up evaluations were not performed at the site of the TARE treatment.

Assessments

Detailed information concerning the timing of assessments can be found in Helmberger et al, 2020 [21].

At the time of first treatment, baseline data, demographics and treatment-related data were collected. The number of tumors were considered for the whole liver, whereby the category "uncountable" was included in cases where the number of tumors exceeded reliable counting of lesions. Tumor burden was presented as percentage of tumor volume (mL) per liver volume (mL). Treatment intention was defined before the procedure, whereby "ablation" was defined as an attempt to create an ablative effect with the Y90 resin microspheres, and "palliative" as any intention not part of a curative approach. Information concerning post-TARE treatments, safety data and time to event data were collected at every follow-up. Sites were requested to include available imaging data, but the observational nature of the study prevent any mandates on the type of imaging (CT, MRI, PET). Imaging data was evaluated by the local investigator or physician performing the follow-up imaging. Time-to-event was defined from the date of the first TARE treatment until the date of the event. Safety outcomes are described as occurrences of any adverse events according to the Common Terminology Criteria for Adverse Events, version 4.03. *A priori* expected serious adverse events (SAEs, grade 3 and 4) were abdominal pain, fatigue, fever, nausea, vomiting, gastrointestinal ulceration, gastritis, radiation cholecystitis, radiation pancreatitis, and radioembolization-induced liver disease (REILD) and were included as answer options in the electronic case report form. An open text field allowed for collecting details on other serious adverse events. Clinical parameters were tumor burden, prior procedures, dose methodology, prescribed radiation activity as well as relevant blood markers including albumin, bilirubin, liver transaminases, International Normalised Ratio (INR) and the resulting indicators of liver function: Aspartate Aminotransferase to Platelet Ratio Index (APRI), Albumin-Bilirubin (ALBI) Grade (see Supplement 1 for APRI and ALBI formulas) and the Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) ratio.[23,24] Based on

published literature, we categorized APRI as ≤0.40 or >0.40; and grade ALBI as 1, 2 or 3.[25,26]

Statistical Analysis

Data is presented as mean ± standard deviation or median (interquartile range [IQR]) for continuous variables and number (%) for categorical variables. Percentages are based on the whole cohort (n = 237) unless otherwise indicated. Patients who died during the study are defined to have progression for the purpose of PFS and hPFS. Patients that were alive and progression-free were censored on the day of the last follow-up. The simultaneous occurrence of hepatic progression and extra-hepatic progression was considered as hepatic progression. The median OS, PFS, and hPFS times were calculated with the associated 95% confidence interval (CI).

Multivariable survival analysis for OS, PFS, and hPFS was performed using a Cox proportional-hazards model, whereby the selection of variables was determined following a univariable analysis and a subsequent stepwise variable selection procedure with a significance level of 0.2 when deciding to enter a predictor into the stepwise model. The model with the lowest Akaike information criterion value was considered as the final model. Data was presented using hazard ratio (HR) and 95% confidence interval (CI). All available data are used, and no imputations of missing data are made. Where data was missing, it was indicated in the tables.

An additional propensity score analysis was performed to further analyse the role of the two main methods to calculate the prescribed Y90 activity, [modified] Body Surface Area ([m]BSA) and partition model, in the survival outcomes of TARE treatments (see Supplement 1 for the propensity score analysis methods).

Results

Patient Demographics

The mCRC cohort is represented by 237 patients (23.1% of the total CIRT cohort, 237/1027) from 24 European centres. The median follow-up time was 7.8 months; 42 of 237 (17.7%) of the patients were lost to follow-up at any point during data collection. The median age is 63 years (IQR 55-71) and 62.0% (147/237) are male patients (Table 1). Median time from diagnosis of liver metastases until TARE treatment was 14.4 months (IQR 7.6-25.8). At baseline, most patients had Eastern Cooperative Oncology Group (ECOG) status 0 (143/237, 60.3%) or 1 (72/237, 30.4%) and no extra-hepatic disease prior to treatment (140/237, 59.1%). Nine patients (9/237, 3.8%) presented with radiological evidence of ascites.

Treatment Context and Application

One hundred fifty-two (152/237, 64.1%) patients had bilobar disease. Unilobar disease was mostly right sided (61/237, 25.7%) compared to left sided (23/237, 9.7%). In terms of number of liver tumors, the largest groups had an "uncountable" number (81/237, 34.2%) or five or more liver tumors (79/237, 33.3%), 50/237 (21.1%) had 2 to 5 liver tumors, while 27 of 237 (11.4%) had only one liver tumor. Median total liver tumor burden was 8.9% (IQR 3.8% – 18.3%, Table 2). Body Surface Area (BSA, 123/237, 51.9%) or modified BSA (mBSA, 71/237, 30.0%) were the preferred

Table 1	Baseline Patient Characteristics	
Category	**Subcategory**	**mCRC (n = 237)**
Gender	n	233 (98.3%)
	Male	147 (62.0%)
	Female	86 (36.3%)
Age (years)	n	237 (100%)
	Median, IQR	63.0, 55.0-71.0
Time since primary diagnosis (months)	n	233 (98.3%)
	Median, IQR	19.5, 11.0-34.1
Time since metastatic diagnosis (months)	n	198 (83.5%)
	Median, IQR	14.4, 7.6-25.8
ECOG performance status	n	233 (98.3%)
	0	143 (60.3%)
	1	72 (30.4%)
	2 or higher	18 (7.6%)
Ascites	n	237 (100%)
	Yes	9 (3.8%)
	No	228 (96.2%)
Cirrhosis	n	237 (100%)
	Yes	2 (0.8%)
	No	235 (99.2%)
Number of tumor nodules	n	237 (100%)
	1	27 (11.4%)
	2-5	50 (21.1%)
	>5	79 (33.3%)
	Uncountable	81 (34.2%)
Location of tumor	n	236 (99.6%)
	Bilobar	152 (64.1%)
	Left only	23 (9.7%)
	Right only	61 (25.7%)
Extrahepatic metastases	n	237 (100%)
	Yes	97 (40.9%)
	No	140 (59.1%)
Bilirubin (µmol/L)	n	236 (99.6%)
	Mean ± SD	10.8 ± 8.7
Albumin (g/dL)	n	181 (76.4%)
	Mean ± SD	3.9 ± 0.6
ALBI grade	n	180 (75.9%)
	A1	102 (43.0%)
	A2	75 (31.6%)
	A3	3 (1.3%)
APRI	n	204 (86.1%)
	Mean ± SD	0.5 ± 0.4
	≤0.40	99 (41.8%)
	>0.40	105 (44.3%)
AST/ALT	n	204 (86.1%)
	Mean ± SD	1.4 ± 0.7
	≤0.96	44 (18.6%)
	>0.96	160 (67.5%)
INR	n	176 (74.3%)
	Mean ± SD	1.1 ± 0.1
	≤1	78 (32.9%)
	>1	98 (41.4%)

ALBI = Albumin-Bilirubin; ALT = Alanine Aminotransferase; APRI = Aspartate Aminotransferase to Platelet Ratio Index; AST = Aspartate Aminotransferase; BCLC = Barcelona Clinic Liver Cancer; ECOG = Eastern Cooperative Oncology Group; INR = International Normalized Ratio; IQR = Interquartile Range; mCRC = metastatic colorectal cancer; SD = Standard Deviation.

Table 2	Treatment-Associated Parameters	
Category	**Subcategory**	**mCRC (n = 237)**
Activity prescribed (GBq)	n	
	Whole liver (median; IQR)	1.50 (1.20;1.80)
	Right lobe (median; IQR)	1.20 (0.90;1.40)
	Left lobe (median; IQR)	0.50 (0.0;0.80)
Target treatment	n	237 (100%)
	Whole liver	114 (48.1%)
	Right lobe	90 (38.0%)
	Left lobe	26 (11.0%)
	Segmental	7 (3.0%)
Were all liver tumors targeted	n	198 (83.5%)
	Yes	137 (57.8%)
	No	45 (19.0%)
	Unknown	16 (6.8%)
Technical success: delivered activity within 90% of the prescribed activity	n	237 (100%)
	Yes	222 (93.7%)
	No	15 (6.3%)
Target tumor volume (mL)	n	199 (84.0%)
	median; IQR	131 (55-287)
Target liver volume (mL)	n	199 (84.0%)
	median; IQR	1480 (1287-1791)
Total tumor burden (%)	n	199 (84.0%)
	median; IQR	8.9% (3.8%-18.3%)
Right-lobe tumor burden (%)	n	80 (33.8%)
	median; IQR	10.3% (5.0%-21.3%)
Left-lobe tumor burden (%)	n	61 (25.7%)
	median; IQR	10.4% (3.3%-19.7%)
Number of treatments	n	237 (100%)
	1	210 (88.6%)
	2	27 (11.4%)
Method to calculate the dose	n	236 (99.6%)
	BSA	123 (51.9%)
	Modified BSA	71 (30.0%)
	Partition model	42 (17.7%)

BSA = Body Surface Area; GBQ = Giga-becquerel; IQR = Interquartile Range; mCRC = metastatic colorectal cancer.

methods for determining the dose. Partition model was used in 42/237 (17.7%) patients. Whole liver treatment was prescribed in 114 of 237 (48.1%) patients, compared to right (90/237, 38.0%) and left (26/237, 11.0%) separately. Median prescribed activity was 1.50 GBq for whole-liver treatments (IQR 1.20-1.80), 1.20 GBq for right lobe treatments (IQR 0.90-1.40) and 0.50 (IQR 0.00-0.80) for left lobe treatments. Technical success, defined as delivered activity within 90% of the prescribed activity, was achieved in 222 of 237 (93.7%) patients.

At patient enrolment, 226 of 237 (95.4%) patients had received prior systemic therapy (previously: 1 line, 68/237 (30.1%); 2 to 3 lines 78 of 237 (32.9%); >3 lines 77 of 237 (32.5%), primarily FOLFOX (129/237, 54.4%) and FOLFIRI (90/237, 38.0%) regimens (Table 3 and Supplemental 2) and 86 of 237 (36.3%) had received prior locoregional treatments, of which 66 of 86 (76.7%) were surgical and 27 of 86 (31.4%) ablative procedures (Table 3). The investigator-assessed treatment intent was predomi-nantly palliative (176/237, 74.3%) or tumor downsizing (41/237, 17.3%). Following TARE, 87 of 237 (36.7%) of the patients received further systemic treatment and 35 of 237 (14.8%) received locoregional treatments, the majority of which were provided >4 weeks after TARE in patients without progression (29/35, 82.9% for locoregional treatments, and 54/87, 62.1% for systemic treat-ments, see Supplemental 3).

Effectiveness

The median OS was 9.8 months (95% CI 8.3-12.9). Univari-able analysis (Supplement 4) showed favourable OS for ECOG 0, absence of extra-hepatic disease, low tumor burden, right-sided tumors, partition model and APRI ≤0.40 (Figure 1). Multivari-able analysis (Table 4) identified independent prognostic factors for a worse overall survival as the presence of extra-hepatic disease (HR 1.48, 95% CI 1.02-2.14, $P=$ .0412), an APRI value of >0.40 (HR 2.25, 95% CI 1.54-3.30, $P<$ .0001) and INR <1

Table 3	treatment context of TARE	
Category	**Subcategory**	**mCRC (n=237)**
Intention of TARE	n	237 (100%)
	Ablation	18 (7.6%)
	Bridge to surgery or transplant	2 (0.8%)
	Down-sizing/down-staging	41 (17.3%)
	Palliative	176 (74.3%)
Before TARE		
Locoregional procedures	n[a]	86 (36.3%)
	Surgery	66 (27.8%)
	Ablation	27 (11.4%)
	TACE	3 (1.3%)
	Abdominal radiotherapy	6 (2.5%)
	Other embolotherapies	3 (1.3%)
Systemic therapies	n	237 (100%)
	Yes	226 (95.4%)
	No	11 (4.6%)
Number of systemic therapy lines	n	223 (94.1%)
	1	68 (30.1%)
	2-3	78 (32.9%)
	>3	77 (32.5%)
	Missing	3 (1.3%)
After TARE		
Locoregional procedures	n[a]	35 (14.8%)
	Surgery	10 (4.2%)
	Ablation	11 (4.6%)
	TACE	6 (2.5%)
	Abdominal radiotherapy	10 (4.2%)
	Other embolotherapies	2 (0.8%)
Systemic therapies	n	193 (81.4%)
	Yes	87 (36.7%)
	No	106 (44.7%)
Number of systemic therapy lines	n	87 (36.7%)
	1	25 (10.5%)
	2-3	25 (10.5%)
	>3	34 (14.3%)

[a] Patients can have multiple locoregional procedures before or after TARE. mCRC = metastatic colorectal cancer; TACE = Transcatheter Arterial Chemoembolization; TARE = Trans-arterial Radioembolization.

(HR 1.66, 95% CI 1.13-2.43, $P=$ .0091). Prior locoregional procedures predicted an improved OS (HR 0.34, 95% CI 0.17-0.71, $P=$ .0038). Furthermore, patients whose prescribed dose was determined with partition model had an increased chance of surviving longer compared to patients treated with the BSA or mBSA model (HR 0.45, 95% CI 0.24-0.84, $P=$ .0120, Figure 2). To further challenge this result, a propensity score analysis considering the population used for the multivariable model was performed. The matching showed a large degree of variability among cases and patient matching could only be performed in a smaller group. Considering 159 patients for the propensity score analysis using Inverse Probability Treatment Weighting, we obtained for OS a HR 0.59 (0.32-1.06; $P=$ .0792, data not shown).

Median PFS was 3.4 months (95% CI 3.1-4.1) and median hPFS was 4.2 months (95% CI 3.4-4.7). Univariable analysis found a significantly worse PFS (Supplement 5) for ECOG >0, presence of extra-hepatic disease, >5 tumor nodules and uncountable tumor nodules, ALBI grade A3, AST/ALT >0.96, and APRI >0.40. Intention to downsize the tumor predicted a better PFS. ECOG 1, uncountable tumor nodules, ALBI grade A3, AST/ALT >0.96, and APRI >0.40 predicted worse hPFS (Supplement 6). In multivariable analysis (Table 4), independent predictors for PFS were APRI >0.40 (HR 1.42, 95% CI 1.01- 1.98, $P =$ .0416) and prior ablation (HR 0.59, 95% CI 0.36-0.96, $P=$ .0323), and for hPFS these were 2 to 5 tumor nodules (HR 0.42 (0.21-0.85, $P=$ .0148), ALBI grade 3 (HR 5.29, 95% CI 1.56-17.97, $P=$ .0075) and APRI >0.40 (HR 1.50, 95% CI 1.06-2.11, $P=$ .0207). Dose method-

Figure 1 | Kaplan-Meier graph comparing Aspartate aminotransferase to Platelets Ratio Index (APRI) <0.40 with >0.40 in terms of overall survival (A), progression-free survival (B), and hepatic-progression-free survival (C)
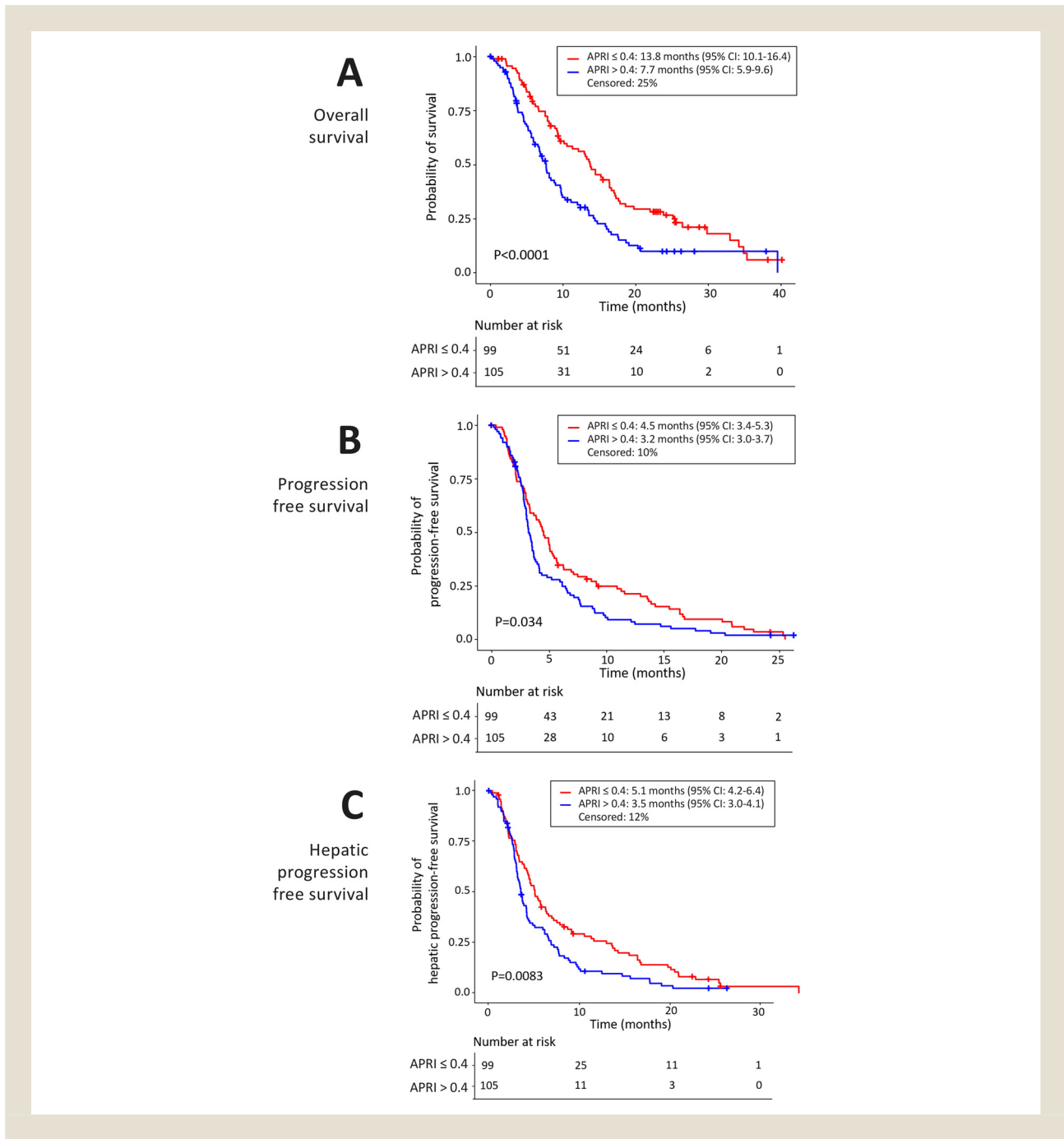
ology predicted neither hepatic PFS nor overall progression free survival.

Safety

During the study, 95 of 237 (40.1%) patients experienced 197 adverse events, with 28 of 237 (11.8%) patients having a grade 3 or higher adverse events: abdominal pain 4 of 237 (1.7%), nausea 1 of 237 (0.4%), gastrointestinal ulceration 2 of 237 (0.8%), gastritis 2 of 237 (0.8%), radiation cholecystitis 1 of 237 (0.4%); 18 of 237 (7.6%) patients experienced 29 all-cause "other" grade 3 to 4 adverse events. (Supplemental 7).

Discussion

The current dataset from the prospective multicentre observational CIRT study represents the real-world patient population treated with Y90 resin microspheres for liver dominant mCRC in

Table 4 | **Multivariable Analysis for Overall Survival, Progression-free Survival and Jepatic Progression-free Survival**

Variable	Threshold	HR (95% CI)	P Value
Overall survival			
Extra-hepatic disease prior to treatment (vs. no)	Yes	1.48 (1.02-2.15)	.0391
Prior locoregional procedures (vs. no)	Yes	0.34 (0.17-0.71)	.0037
Prior surgery (vs. no)	Yes	1.99 (0.91-4.34)	.0830
Dose methodology (vs. BSA/mBSA)	Partition Model	0.45 (0.24-0.84)	.0120
APRI (vs. ≤0.40)	>0.40	2.28 (1.56-3.33)	<.0001
INR (vs. ≤1)	>1	1.67 (1.15-2.45)	.0078
Progression-free survival			
APRI (vs. ≤0.40)	>0.40	1.42 (1.01-1.98)	.0416
Ablation (vs. no)	Yes	0.59 (0.36-0.96)	.0323
ALBI (vs. A1)	A2	1.36 (0.97-1.90)	.0720
	A3	3.24 (1.00-10.55)	.0506
Hepatic progression-free survival			
Number of tumor nodules (vs. 1)	2-5	0.42 (0.21-0.85)	.0148
	>5	0.56 (0.30-1.06)	.0772
	Uncountable	1.00 (0.54-1.85)	.9877
Prior locoregional procedures (vs. no)	Yes	0.87 (0.50-1.51)	.6303
Prior surgery (vs. no)	Yes	1.18 (0.64-2.19)	.5918
ALBI grade (vs. A1)	A2	1.43 (0.98-2.09)	.0653
	A3	5.29 (1.56-17.97)	.0075
APRI (vs. ≤0.40)	>0.40	1.50 (1.06-2.11)	.0207

P values are from the Cox model. The proportional hazard function of the Cox model was verified.
ALBI = Albumin-Bilirubin; ALT = Alanine Aminotransferase; APRI = Aspartate Aminotransferase to Platelet Ratio Index; AST = Aspartate Aminotransferase; BSA = Body Surface Area; HR = Hazard Ratio; INR = International Normalized Ratio.

Figure 2 | **Kaplan-Meier graph comparing overall survival outcomes for patients whose prescribed activity was calculated with partition model dosimetry compared to (modified) Body Surface Area.**
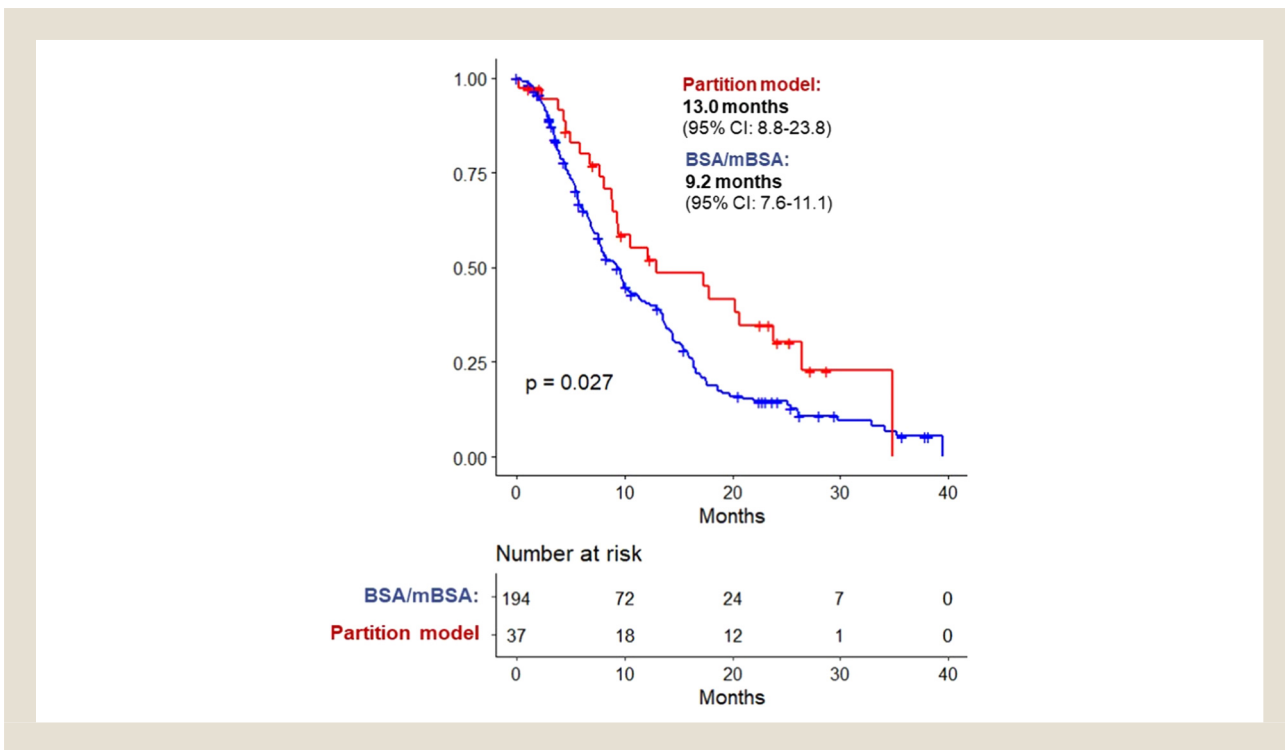
Europe. Our results underline the importance of blood value-based markers for predicting the outcomes of TARE: APRI is a strong predictor for OS, PFS and hPFS in patients receiving TARE, while INR predicted OS and ALBI predicted hPFS outcomes. Furthermore, partition model should be considered to optimize treatment outcomes.

In the mCRC patient population of CIRT, we have found an OS of 9.8 months (95% CI 8.3-12.9), a PFS of 3.4 months (95% CI 3.1-4-1) and a hepatic PFS of 4.2 months (95% CI 3.4-4.7). Kennedy et al. published a retrospective series of 208 mCRC patients and described a median OS of 10.5 months in responding patients and 4.5 months in nonresponders[27] while Cianni et al. found an OS of 11.5 months and a PFS of 9.1 months in 41 patients.[28] Despite the similarities in OS, our low median PFS may be due to our heterogeneous patient population, which includes patients at various stages of the disease and treatment pathway. Both cohorts reported that TARE was well-tolerated by patients with an acceptable toxicity (7% and 3% SAEs, respectively) similar to our findings (11.8%). Other studies evaluating safety data observed that the occurrence of SAEs can range from 3% to 15%.[29-33] The dataset from the French prospective multicentre observational study CIRSE Registry for SIR-Spheres in France (CIRT-FR) reported 27% SAE occurrence in 63 mCRC patients treated with TARE (data forthcoming).

Despite many promising efficacy signals from above studies, the SIRFLOX and FOXFIRE randomized controlled trials remained without any significant survival benefit for first line mCRC patients compared to chemotherapy.[18,19] With TARE as second line treatment combined with systemic therapy, the recent randomized controlled EPOCH trial reported a significant improvement in PFS and hPFS compared to systemic therapy alone (HR 0.69; 95% CI 0.54-0.88; 1-sided $P = .0013$ for PFS and HR 0.59; 95% CI 0.46-0.77; 1-sided $P = .0001$ for hPFS)), but no improvement in OS (HR 1.07; 95% CI 0.86-1.32; 1-sided $P = .7229$ for the TARE and chemotherapy group).[20] At the same time, patients enrolled in the EPOCH trial experienced poorer results in right-sided tumors, while patients from the SIRFLOX and FOXFIRE Global trials had better efficacy results in right-sided tumors. It was proposed that this discrepancy may indicate different optimal time points of TARE in the continuum of care of left- and right-sided tumors.[20] In a broader sense, it is testimony to the fact that, despite the experience in clinical use of TARE in mCRC patients, there is a demand to optimize the treatment application and a need to identify better prognostic markers.

Prognostic Factors

Our mCRC cohort suggests that laboratory values indicative of liver status and potential liver damage are strong predictors of reduced survival after TARE. Our multivariable analysis found INR >1 ($P = .0078$) and APRI >0.40 ($P< .0001$) to be independent prognostic factors for reduced overall survival. APRI >0.40 predicted reduced PFS and hPFS ($P = .0416$ and $P = .0207$) and ALBI grade 3 was significantly associated with shorter hPFS ($P = .0075$). A prognostic scoring system for TARE in mCRC, developed by Damm et al., identified tumor load, CEA levels, CA 19-9 levels and Karnofsky index as predictive variables,[34] while Kurilova

et al. used CEA level, baseline ALT and albumin levels, tumor size, and differentiation level and number of extrahepatic sites to estimate outcomes after TARE.[35] Our cohort is the first to show the importance of APRI, ALBI and INR as possible predictive markers for survival outcomes after TARE in mCRC and it is recommended that future predictive models further evaluate and validate these variables.

ALBI and APRI are already well-established prognostic parameters in HCC prior to interventional procedures.[23-26,36] APRI specifically has been utilized as a noninvasive score to predict liver fibrosis.[37] However, an understanding of the underlying mechanisms shows that APRI can also be a signifier of general liver injury, whereby elevated AST correlates with injury of hepatocytes and reduced platelet counts mainly correlate with a reduction in thrombopoietin production in damaged liver tissue.[38,39] Such liver injury can be caused by oxaliplatin or irinotecan, common chemotherapeutic agents in first line mCRC, and Pereyra et al. have demonstrated that the combination of APRI and ALBI score can predict the presence of this chemotherapy-associated liver injury in this patient group.[23] Similarly, the ALBI score was developed by Johnson et al. to evaluate liver function in patients with virus induced HCC[40] and is considered superior to Child-Pugh in its predictive value in HCC.[36] Although ALBI has been shown to predict outcomes in HCC patients undergoing TARE,[41] to our knowledge our study is the first to identify ALBI as an independent marker for hPFS in mCRC, albeit only in grade 3 patients. INR, a marker of liver synthesis capacity, has shown prognostic value in a univariable analysis in mCRC patients undergoing TARE[42] and has here been shown for the first time as an independent predictor for OS. Our results therefore suggest that adding the easy-to-collect laboratory markers APRI, ALBI and INR to routine practice can be valuable in identifying the mCRC patients that may benefit the most from TARE and should be considered in future predictive models.

Dose Planning

In addition to blood value-based markers we investigated whether dose planning methods had any predictive relevance in mCRC patients, by comparing standard BSA models with partition model. To our knowledge, there is no publication comparing dosimetry methods and outcomes for Y90 resin microspheres in mCRC. Following multivariable analysis and propensity score analysis, the data from our prospective cohort shows that patients undergoing partition model display a significantly longer OS. In brief, partition model dosimetry uses lung, tumoral and targeted non-tumoral liver volumes derived from pre-treatment Technetium 99mTc macroaggregated albumin (Tc-99m MAA) SPECT/CT leading to a tumoral-to-nontumoral ratio to predict tumoral volume and targeted nontumoral liver absorbed dose.[43] It has been demonstrated that partition model dosimetry leads to a higher tumor-absorbed dose[44] which has been shown to have a positive efficacy outcome in patients with HCC.[45] The DOSISPHERE-01 trial investigating standard dosing (120 +/- 20Gy to the perfused lobe) against personalized dosimetry (≥205Gy to the index lesion) revealed a longer OS of patients receiving personalized dosing.[46] One analysis with glass microspheres, published as an abstract only, showed a significant dose-response relationship in patients receiving higher tumor-absorbed

doses with an identical safety profile[47] and a small prospective study on 24 patients with 57 mCRC lesions found a significant relationship between mean tumor-absorbed dose an OS (HR 2.6, 95% CI 0.98-7.00, p=0.012).[48] Interestingly, dose methodology was not a predictor for PFS or hPFS in our cohort and is potentially not fully understood. Nevertheless, our data suggests that dose estimation based on body surface corrected with a total liver to tumor ratio (BSA model) might be insufficient, not only regarding efficacy but probably also toxicity, especially in our heavily pre-treated mCRC patient population.

Overall, this prospective study further augments the body of evidence supporting TARE treatment in liver dominant mCRC. We identified several new independent prognostic markers in mCRC patients undergoing TARE: APRI, INR and dose methodology for overall survival, and APRI and ALBI for progression free survival and hepatic progression-free survival. To our knowledge, these independent predictive variables have not yet been described outside HCC in the context of TARE.

Limitations

A limitation of the study is the observational study design, whereby important confounding factors may not have been accounted for. The heterogeneity of the patient population and the single-device aspect of the study make a comparison to other treatment modalities difficult. However, it allowed us to evaluate real-life factors that independently influence effectiveness outcomes and thus inform future predictive models for mCRC patients, leading to optimal patient selection for TARE. Furthermore, the study was designed to explore the clinical outcome of TARE and, therefore, less focused on dosimetry-specific data. This meant, unfortunately, that retrospectively important data points such as precise injected dose and tumor-absorbed dose were not included in the evaluation at the time of study design. Additionally, no data on tumor markers relevant to mCRC, such as CEA and CA 19-9 levels, or molecular characteristics such as RAS, BRAF or MSI status were collected.

Although selection bias cannot be ruled out, regular remote monitoring and contractual agreements were put in place to reduce selection bias. Sites were encouraged to follow-up with patients when follow-up visits happened with the patient's referring physician, instead of on site. Remote monitoring was done to improve data quality; however, no source data verification was performed. Investigators evaluating imaging data instead of a central image review could have introduced bias concerning PFS or hPFS and should be considered when interpreting this data. We attempted to collect quality-of-life data – on a voluntary basis for the patient – at the time of treatment and at every follow-up until the study exit. The relevance of the collected dataset is currently being evaluated. The relatively high number of censored patients of OS (62/237, 26.2%) and PFS (27/237, 11.4%) is comparable to other studies in oncology and reflects the clinical reality of patients being treated in larger institutions having access to multiple treatments and studies.[49] Despite our promising results when comparing partition model with body surface driven dosing models, it must be noted that only 42/237 (17.7%) patients received TARE dosage calculated using partition model. This imbalance in dose calculation methods needs to be considered when interpreting the results. Nevertheless, it

is encouraging that both the multivariable analysis and the propensity score analysis were consistent in pointing towards the survival benefits of partition model dosimetry. Finally, it cannot be ruled out that post-TARE treatments impacted the effectiveness results, although this subset of patients was too small to perform meaningful statistical analyses (Supplement 3).

Conclusion

This large prospective real-world study in patients with liver dominant mCRC demonstrates that TARE with Y90 resin microspheres can be applied safely and lead to encouraging effectiveness outcomes. Our results identified new predictive markers for this patient population (INR, APRI and ALBI), and highlight the need for advanced dose methodology techniques to optimize the outcome of TARE in mCRC patients. Partition model dosimetry has shown here a clear overall survival benefit in this patient population compared to body surface driven dosing models. These findings are of utmost importance as they can help optimize patient care by informing routine clinical practice as well as future trial designs.

Clinical Practice Points

- Transarterial radioembolizaton is a treatment option for patients with colorectal cancer liver metastases due to its tolerability by patients and local tumor control. However, selecting the optimal patients for this treatment is challenging. Several predictive models for effectiveness outcomes exist using a combination of blood values, tumour characteristics and spread of the disease.
- Our study identified several predictive markers not included in previous models, especially APRI >0.40, which was a strong independent predictor of worse overall survival, progression-free survival and hepatic-progression free survival. Other independent predictive factors for overall survival were blood markers such as ALBI and INR, as well as previously identified factors such as the presence of extra-hepatic disease and the performance of locoregional treatments prior to transarterial radioembolizaton.
- This study also showed for the first time in patients with colorectal cancer liver metastases that partition model dosimetry results in better overall survival than dose calculations using the standard body surface area model – previously only shown in hepatocellular carcinoma.
- Blood values used to calculate APRI and ALBI are, together with INR, routinely taken in patients with colorectal cancer liver metastases and are here shown to be indispensable in determining the optimal treatment pathway for patients with colorectal cancer liver metastases. Furthermore, optimizing the dosimetry methods of transarterial radioembolizaton can improve the effectiveness of the treatment.

Authors' Contributions

Acknowledgments

Disclosure

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clcc.2022.09.002.

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