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ORIGINAL ARTICLE

Appropriate patient selection and overall survival after transarterial radioembolization in colorectal adenocarcinoma liver metastases

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ABSTRACT

Background and Aim: The objective of this study was to describe the overall survival (OS) with transarterial radioembolization (TARE) for patients with colorectal adenocarcinoma liver metastases (CRLM) treated at an academic center with a dedicated multidisciplinary liver tumor board (MTB).
Methods: Single institution retrospective study of consecutive patients with CRLM undergoing TARE with mainly Y90 resin spheres between 01/2016-07/2020.
Results: Fifty-five patients were included in the study. Median age was 60 years (range 36–84), 61.8% were female, Eastern Cooperative Oncology Group 0–1 = 90.9%. The median time from diagnosis to first TARE was 16.4 months (1.7–95.6) and 36.4% were treated within the first 12 months of diagnosis. With a median follow-up of at least 2 years, the median OS from the date of diagnosis and first TARE was 43.2 months (29.5–68.7) and 16.7 months (9.9–35.2), respectively.
Conclusions: The observed OS in this cohort compares favorably to OS reported in contemporary Phase 3 trials and might indicate a benefit of TARE with appropriate patient selection at experienced centers with dedicated MTB.
Relevance for Patients: Oncologists treating patients with CRLM should consider referral to a tertiary treatment center with a multidisciplinary team and TARE treatment expertise.

1. Introduction

The liver is the most common site of distant metastasis in colorectal carcinoma (CRC) with 50–70% of patients developing colorectal liver metastases (CRLM) during the disease [1]. Liver failure is the main cause of death in CRC patients. Standard of care treatment for CRLM includes curative intent resection and systemic therapy [1]. However, surgery is only applicable in 10–20% of cases, and of patients who undergo resection, long-term remission is only achieved in 20% of cases [1]. Over the past two decades, there have been some advances in systemic therapy; however, control of liver metastases remains an unmet need. Transarterial radioembolization (TARE) using yttrium-90 spheres (Y90) has been shown to induce tumor responses and delay progression of CRLM across all lines of treatment [2]. However, randomized trials in first and second-line CRLM patients failed to show an overall survival (OS) benefit in unselected populations [3,4]. There is also a concern that early exposure to internal liver radiation might lead to early and/or delayed radiation-induced damage which could compromise long-term outcomes of patients [5]. The objective

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of this work was to describe the survival of consecutive patients with CRLM treated with radioembolization (Y90 SIRspheres and Theraspheres) at a single academic institution.

2. Materials and Methods

The institutional review board approved a retrospective single-institution study. Consecutive patients with CRLM treated at least once with TARE between 01/2016 – 07/2020 were included in the analysis. The sample size was based on all available patients seen at the institution within the time frame. The start date for data collection was determined as the time when all involved investigators became part of the multidisciplinary tumor board at the institution. The end date for data collection was determined as 24 months before the data analysis, hence allowing for at least 24-month follow-up for patient survival. This retrospective chart review study was conducted at a tertiary referral center, and patients' records were reviewed using institutional electronic medical records. Clinically relevant variables including dates of diagnosis and death, demographics, genomic analysis, primary tumor location, chemotherapy regimen, laboratory values, and Eastern Cooperative Oncology Group (ECOG) performance status were extracted from patient charts. OS was calculated from the time of Stage 4 CRC diagnosis to death. Liver progression-free survival (LPFS) was calculated from the date of the first TARE procedure until the date of documented disease progression or death. Radiographic response was based on RECIST v1.1. Patients still alive at the time of last available follow-up were censored. We performed descriptive analyses for relevant patient and tumor characteristics, Wilcoxon Signed-Rank Test for comparison of continuous variables, and Kaplan–Meier estimates for survival.

The majority of mCRC patients were treated with resin and a few with glass Y90 microspheres according to previously published methodologies [6-8]. Specifically, all cases were discussed at a multidisciplinary tumor board consisting of hepatobiliary surgeons, medical oncologists, interventional and diagnostic radiologists, radiation oncologists, and clinical research personnel. Once deemed appropriate candidate for radioembolization (i.e., unresectable disease and liver limited/dominant metastases), patients underwent a mapping angiogram to determine tumor vascular supply, identify extra-hepatic arteries that require embolization to avoid iatrogenic gastrointestinal radiation ulcers, and determine the tumor and treatment volumes as well as the lung shunting fraction with MAA administration.

The microspheres type (resin vs. glass) and the treatment type (lobar or segmental) affected the method of Y90 activity calculation. Moreover, the method evolved during the study period. For resin microspheres, the body surface area (BSA) method was almost exclusively utilized. The activity to be administered to the target lobe was based upon:

Prescribed activity (GBq) = (BSA-0.2) + ([Tumor mass/Total liver mass] × 100)

If patients had received several lines of chemotherapy, the BSA prescribed activity was reduced empirically by up to 30% to reduce the risk of radiation-induced liver disease.

For glass microspheres, the medical internal radiation dose (MIRD) model was used:

Prescribed activity (GBq) = (Target dose [Gy] × Liver mass [kg])/(50 × [1–Lung shunting fraction] × ├ [1–Percent residual after infusion])

The liver volume was determined by computed tomography (CT), magnetic resonance imaging, or cone-beam CT. No adjustments were made for prior cytotoxic chemotherapy. For segmental treatments, the activity was derived from calculating the dose for the entire lobe even though given to selectively to a single segment [9-11].

Routine imaging after completion of TARE was performed at 8 weeks. A positron emission tomography scan was performed post-Y90 treatment to evaluate treatment.

3. Results

A total of $n = 55$ patients were included in the study. Follow-up time for survival in the entire cohort was at least 24 months. Patient demographics and tumor characteristics are shown in Table 1. Baseline and post-TARE liver function tests are shown in Table 2. Median time from diagnosis to first TARE was 16.4mo (1.7–95.6) (Figure 1A). Of note, 36.4% of the patients ($n = 20$) were treated within the first 12 months of diagnosis. Eleven patients (20%) were re-treated with TARE. Median OS from diagnosis and first TARE was 43.2 months (29.5–68.7) and 16.7 months (9.9–35.2), respectively.

Median LPFS was not reached (95% CI: 4.8 months to not evaluable) (Figure 1B). In 48 patients with at least one follow-up scan post-TARE, two patients had a complete response and 20 patients had a partial response, that is, overall response rate of 45.8%. The clinical benefit rate (i.e., stable disease or better) was 65.6% (31 of 48 patients).

4. Discussion

Surgical resection is recommended for patients with CRLM and associated with long-term survival in a subset of patients [12]. However, only 10–15% of patients with CRLM are candidates for curative intent liver resection. While initially effective, resistance to multi-agent systemic treatment will invariably develop in virtually all patients with CRLM. Progression-free survival (PFS) decreases with each subsequent line of systemic treatment [1].

To address the unmet need of control of liver metastases in CRLM, two randomized Phase III trials tried to address the role of TARE in first-line and second-line treatment of CRLM [3,4]. Both trials failed to show an actual OS benefit, despite of higher objective response rate and liver PFS in both trials. It is unclear why no survival benefit was seen in both trials despite improvement of other endpoints. While patient selection (e.g., performance status, disease volume, and extrahepatic disease) and trial design (timing of TARE, choice, and dose of systemic treatment) might have contributed to the results, there remains a concern that acute and delayed liver toxicity from TARE might negate any initial positive effect of tumor control in the liver.

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Table 1. Patient and tumor characteristics

Total patients, *N* (%)	**55 (100)**
Age at diagnosis, years	
Median	60
Range	36–84
Gender, *N* (%)	
Male	21 (38.2)
Female	34 (61.8)
Ethnicity, *N* (%)	
Caucasian	30 (54.5)
Hispanic	9 (16.4)
Asian	9 (16.4)
Other	7 (12.7)
ECOG performance status, *N* (%)	
0	18 (32.7)
1	32 (58.2)
2	5 (9.1)
Tumor sidedness, *N* (%)	
Left	40 (72.7)
Right	13 (23.6)
Unknown	2 (3.6)
Primary tumor resected, *N* (%)	
Yes	50 (90.9)
No	5 (9.1)
TARE, *N* (%)	
Unilobar	13 (23.6)
Bilobar	42 (76.4)
Re-treatment	8 (14.5)
MSI-high, *N* (%)	
Yes	2 (3.6)
No	32 (58.2)
Unknown	21 (38.2)
RAS/RAF mutation presence, *N* (%)	
Yes	19 (34.5)
No	27 (49.1)
Unknown	9 (16.4)
Number of prior systemic treatments before TARE, *N* (%)	
1	21 (38.2)
2	20 (36.4)
≥3	12 (21.8)
Unknown	2 (3.6)
Number of total systemic treatments, *N* (%)	
1	6 (10.9)
2	14 (25.5)
≥3	29 (52.7)
Unknown	6 (10.9)
Type of prior systemic treatments before TARE, *N* (%)	
FOLFIRI±biologic	10 (18.2)
FOLFOX/CapeOx±biologic	23 (41.8)
FOLFOXIRI±biologic	19 (34.5)
Other	2 (3.6)
Unknown	1 (1.8)

Abbreviations: FOLFOX: Fluorouracil, leucovorin, and oxaliplatin; CapeOx: Capecitabine and oxaliplatin; FOLFOXIRI: Fluorouracil, leucovorin, irinotecan, and oxaliplatin

Table 2. Liver function parameters

	Baseline (range)	**Post-TARE (range)**	***P***
Alkaline phosphatase (U/mL)	112.0 (36.0–782.0)	198 (73–1442.0)	<0.001
Albumi*n* (g/dL)	4 (1.8–4.9)	3.55 (2.2–4.7)	<0.004
Bilirubi*n* (mg/dL)	0.5 (0.2–2.3)	0.8 (0.2–5.6)	<0.001
ALT (U/mL)	24 (8–149)	28.5 (9–173)	<0.004
AST (U/mL)	28.5 (13–100)	39.5 (12–121)	<0.001

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transaminase

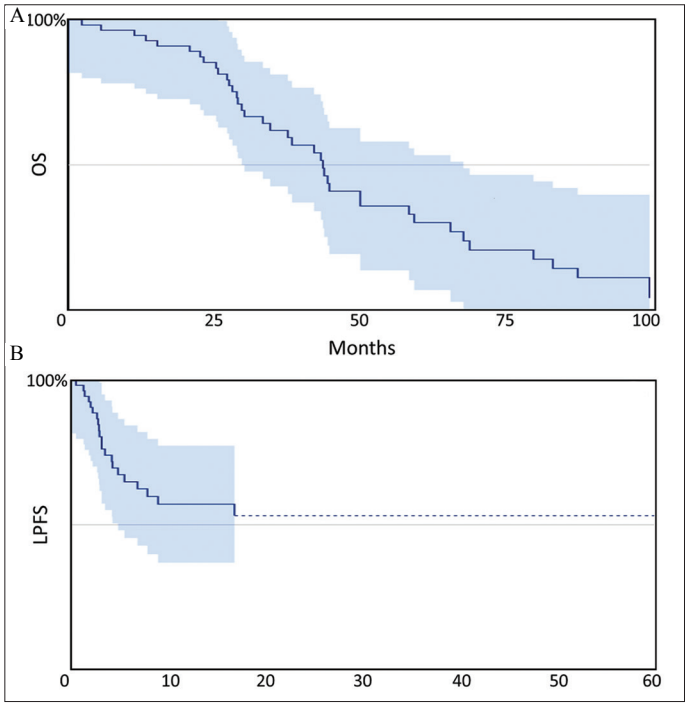

Figure 1. Overall survival of the population from the date of diagnosis (A) and liver progression-free survival from the date of first transarterial radioembolization (B). Blue area denotes the 95% confidence intervals.

The present study reports the outcome of a single-center consecutive cohort of CRLM patients treated with TARE. In this cohort of patients treated at an academic medical center with a multidisciplinary liver tumor board and experience in TARE, the mOS of more than 43 months does not appear to be diminished compared to results from contemporary mCRC trials with an estimated survival from initial diagnosis of stage IV mCRC of 30–40 months [13]. Importantly, more than a third of the patients were treated with TARE within 12 months of initial diagnosis with no observed detrimental longer-term effects. The minimum follow-up time was at least 24 months, hence long enough to show any potential delayed toxicity from early integration of TARE.

There are important differences between the design of the Sirflox trial in the first-line setting and the integration of TARE at our institution which might explain the favorable outcomes reported here. At our institution, patients with newly diagnosed CRLM are presented at the MDT. If the liver metastases are not deemed resectable initially, then patients are treated with full dose

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multiagent systemic treatment (two or three drug regimens) plus an appropriate biologic agent based on the tumors mutational status for 3–4 months. After this initial induction phase with reduction in the tumor burden, the patients are re-evaluated with repeat imaging at the MDT. If resectable, they will proceed at this stage with liver resection. However, patients deemed still unresectable by the MDT are evaluated for the absence of extrahepatic metastases, preserved performance status of ECOG 0-1, adequate kidney and liver function (including total bilirubin <2 mg/mL), and referred for TARE for consolidation. Maintenance single agent fluopyrmidine treatment is usually given before TARE and in between TARE treatments (i.e., both lobes of the liver, if indicated). The extent of TARE, dosing, and choice of spheres is based on the treating physician's discretion. After TARE, the patients continue maintenance chemotherapy, and about 2–3 months later are evaluated for response. At that time, those with further tumor response deemed resectable are referred for liver resection. In addition, if after about 6–8 months of treatment as outlined here the patients are in partial or complete remission, they are referred for resection of the primary tumor, hence rendering the patient disease-free.

Thus, the approach to incorporating TARE at our MDT is focused on appropriate patient selection which includes an intensive initial systemic tumor debulking and careful patient selection based on the clinical criteria above. This approach is very different from the Sirflox trial where patients were randomized to TARE within the first two cycles of chemotherapy and received suboptimal doses of systemic treatment during the first three cycles of systemic treatment. In addition, about a third of the patients had extrahepatic disease. Taken together, we believe these differences in patient selection and treatment might explain the survival outcomes in our cohort.

The main purpose was to focus on the major endpoint of OS, which can be objectively determined and hence is not biased by the frequency of scheduled diagnostic studies and their subjective interpretation. Furthermore, while there were no apparent differences in prognostic subgroups (e.g., by tumor sidedness; data not shown), it is important to note that due to relatively small numbers in each subgroup, the study did not have the power to detect potentially different outcomes based on clinical variables.

5. Conclusion

The herein presented data suggest that even relatively early integration of TARE in appropriately selected patients with CRLM who are reviewed by MDT and treated at an experienced academic center does not appear to negatively affect subsequent treatment or long-term outcomes.

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Conflicts of Interest

FD reports honoraria from Astrazeneca, Eisai, Exelixis, Servier, Sirtex, and Ipsen. NAJ has received research funding to the institution from Sirtex and Theraspheres. All other authors declare no disclosures.

Ethics Approval and Consent to Participate

This work was performed under an IRB approved protocol at the University of California Irvine.

Consent for Publication

Due to retrospective nature of the study, this protocol was deemed IRB exempt for obtaining patient consents.

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