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INTERVENTIONAL

Robust evidence for long-term survival with ^{90}Y radioembolization in chemorefractory liver-predominant metastatic colorectal cancer

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Abstract

Objectives Our aim was to provide further evidence for the efficacy/safety of radioembolization using yttrium-90-resin microspheres for unresectable chemorefractory liver metastases from colorectal cancer (mCRC).

Methods We followed 104 consecutively treated patients until death. Overall survival (OS) was calculated from the day of the first radioembolization procedure. Response was defined by changes in tumour volume as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.0 and/or a ≥30 % reduction in serum carcinoembryonic antigen (CEA) at 3 months.

Results Survival varied between 23 months in patients who had a complete response to prior chemotherapy and 13 months in patients with a partial response or stable disease. Median OS also significantly improved (from 5.8 months to 17.1 months) if response durability to radioembolization extended beyond 6 months. Patients with a positive trend in CEA serum levels (≥30 % reduction) at 3 months post-radioembolization also had a survival advantage compared with those who did not: 15.0 vs 6.7 months. Radioembolization was well tolerated. Grade 3 increases in bilirubin were reported in 5.0 % of patients at 3 months postprocedure.

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Conclusions After multiple chemotherapies, many patients still have a good performance status and are eligible for radioembolization. This single procedure can achieve meaningful survivals and is generally well tolerated.

Key Points

- *After multiple chemotherapies, many patients are still eligible for radioembolization (RE).*
- *RE can achieve meaningful survival in patients with chemorefractory liver-predominant metastatic colorectal cancer (mCRC).*
- *Tumour responsiveness to prior systemic treatments is a significant determinant of overall survival (OS) after RE.*
- *Radioembolization in patients with a good performance status is generally well tolerated.*

Keywords Liver metastases · Radioisotope brachytherapy · Treatment efficacy · Safety · Palliative care

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer worldwide and is the cause of 11.6 % and 13.0 % of all cancer deaths in men and women, respectively [1]. For patients with unresectable metastatic disease (mCRC), palliation with fluoropyrimidine in various combinations and schedules with oxaliplatin and/or irinotecan and new biological agents have evolved to provide substantially improved median survivals [2] and a meaningful window for localized control of liver metastases [especially if extrahepatic disease (EHD) appears to have an indolent clinical course]. Metastases in the liver is a common presentation [3] and is prognostic for mortality in these patients [4].

Liver-directed approaches are used to treat either discrete visually targeted tumours (using resection, ablation, irreversible electroporation, stereotactic body radiation therapy) or more widespread multinodular disease in the liver using radioembolization (or selective internal radiation therapy) or transarterial chemoembolization (either conventional or with drug-eluting beads) [5–10]. There is encouraging evidence to suggest that there might be a potential synergy between systemic therapy and the use of locoregional approaches to improve outcomes in liver-predominant mCRC [11–13], and the value of a multidisciplinary approach employing the skills of the interventional radiologists and radiation oncologists in this setting is recognized by the most recent guidelines from the European Society for Medical Oncology [14] .

The aim of this paper is to provide further evidence for the efficacy and safety of radioembolization based on the long-term follow-up of >100 patients with unresectable chemorefractory liver metastases from CRC.

Materials and methods

Patients

Consecutive patients with unresectable chemotherapy-refractory liver metastases from CRC who received radioembolization were retrospectively analyzed. All patients had documented progression, mainly in the liver, following prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based regimens with or without antiepidermal growth factor receptor (EGFR) and antivascular endothelial growth factor therapies (VEGF).

Suitable candidates for radioembolization were selected by our interdisciplinary tumour review board, and written informed consent was provided for analyses of these data. Patients were eligible for radioembolization if they had an absence of significant progressive extrahepatic disease, a tumour burden in the liver of <50 % of total liver volume, and hepatic arterial anatomy that would enable safe delivery of radioembolization to the liver only. Patients with limited hepatic reserve, ascites, or other clinical signs of liver failure (total bilirubin level >2.0 mg/dl in the absence of a reversible cause; serum albumin <3.0 g/dl), compromised bone marrow or renal function, or other severe comorbidities (e.g., chronic obstructive or chronic restrictive pulmonary disease, including dyspnea at rest from any cause) were generally considered unsuitable for radioembolization.

Radioembolization

Yttrium-90 (^{90}Y) is a pure beta emitter that decays to stable zirconium-90 with an average energy of 0.94 MeV (half-life 2.67 days), with a mean tissue penetration of 2.5 mm and a maximum range of 11 mm. The principle of radioembolization is based on the preferential vascular distribution of radioactive microspheres within the tumour vasculature, which allows delivery of high doses of ^{90}Y with relative sparing of normal liver parenchyma.

Before the radioembolization was undertaken, meticulous coeliac and superior mesenteric angiography was conducted to map the hepatic arterial tree and to detect and occlude, using microcoil embolization, every collateral vessel that arose from the hepatic artery that could lead to extrahepatic deposition of microspheres.

At a second hepatic arterial catheterization conducted separately after the therapy-planning arteriography, ^{90}Y resin-microspheres (SIR-Spheres; Sirtex Medical Ltd, Sydney, Australia) suspended in sterile water were injected under intermittent fluoroscopic visualization, alternating with contrast medium, to assess for preserved antegrade hepatic arterial flow. The prescribed activity, calculated using the body surface area method based on target volumes of tumour and liver for each patient [15], was administered as either whole liver,

lobar, or sequential lobar treatment according to tumour burden [16]. Within 24 h of therapy, single photon emission computed tomography (SPECT) scans were performed to confirm microsphere target deposition.

Data collection and analysis

Results from hematologic, liver function, blood biochemistry tests, and physical examination were recorded prior to the first radioembolization procedure (baseline) and at all subsequent follow-up visits. Patients resumed a routine schedule of laboratory tests and clinical examination at day 1-3 after 1, 6, 12, and 24 weeks. The nature and severity of any changes in liver function recorded and any other clinically significant grade ≥3 adverse events using the National Cancer Institute Common Toxicity Criteria Adverse Events version 3.0 (CTC v3) [17]. Survival was calculated from the day of the first radioembolization procedure to the day of death or last follow-up. Patients were censored at the time of last follow-up if their status could not be established. Response was defined according to the RECIST criteria in 3-month intervals using computed tomography (CT) and magnetic resonance imaging (MRI) and additionally as a ≥30 % reduction in serum carcinoembryonic antigen (CEA) at 3 months compared with pretreatment values according to RECIST [18].

Statistical analyses were conducted using SAS version 9.2 XP Pro statistical analyses software (SAS Institute Inc., Cary, NC, USA). Variables of interest were calculated using descriptive statistics. Summary statistics for continuous variables included mean, median, standard deviation (SD), interquartile range (IQR), minimum and maximum, and 95 % confidence intervals (CI), as appropriate. Categorical data were summarized by frequency distributions with percentage-based on nonmissing data. Nonparametric estimates of median survival and 95 % CI were computed using Kaplan-Meier product-limit method. Univariate proportional hazards models were utilized to estimate the effects of covariates on time-to-event, as determined by the hazard ratio and 95 % CI.

Results

Patients and treatment

In this analysis, 104 consecutive chemorefractory patients with mCRC received radioembolization for progressive disease in the liver; 52.3 % of patients also had evidence of limited extrahepatic disease progression at the time of radioembolization (Table 1). All patients were followed up until death. Prior chemotherapy consisted mostly of

Table 1 Baseline characteristics

	Parameter	Number (%)
Gender, *n* (%)	Male:Female	73 (70.2): 31 (29.8)
Age, years	Mean ± SD (range)	64.0 ± 10.3 (37.0–82.0)
Diagnosis, *n* (%)	Cecum, colon, small bowel	73 (70.2)
	Rectum	31 (29.8)
Metastases	Synchronous	75 (72.1)
Diagnosis to SIRT, months	Median (IQR)	26.0 (21.0)
Liver metastasis to SIRT, months	Median (IQR)	22.4 (15.0)
Extrahepatic metastases, *n* (%)	Yes	57 (54.8)
	With progression	55 (52.9)
Tumour: liver involvement, *n* (%)	<25 %	66 (63.5)
	≥25 %	35 (33.7)
Prior bevacizumab or cetuximab, *n* (%)	Yes	48 (46.2)
Laboratory measurements, median (IQR)	Alk phosphatase U/L	166.0 (202.0)
	GGT, U/L	188.5 (231.0)
	Bilirubin, mg/dl	0.7 (0.7)
	AST, U/L	50.0 (33.0)
	ALT, U/L	36.0 (23.0)
	LDH, U/L	384.0 (261.0)
	Cholesterol, mmol/L	7.0 (2.6)
	Platelets, $\times 10^3$ /μl	243.0 (119.0)
	WBC $\times 10^3$ / μl	7.6 (4.2)

Alk phosphatase alkaline phosphatase, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *GGT* gamma-glutamyl transferase, *LDH* lactate dehydrogenase, *IQR* interquartile range, *WBC* white blood cell count

fluoropyrimidine-based treatment combined with oxaliplatin or irinotecan. In addition, 46.2 % of patients had received prior treatment with bevacizumab and/or cetuximab.

A median of 94.6 % of the planned ^{90}Y activity [1.6 GBq (IQR 0.5) of 1.8 GBq (IQR 0.4)] was delivered to patients, mostly as a whole-liver treatment. Mean ± SD lung shunting was 4.9 % ± 2.3 (range 1.0–12.0 %).

Overall survival

Median OS was 10.2 months (95 % CI 7.8–13.0), which did not differ significantly by gender or age. Median OS was similar regardless of duration (≥ or <24 months) between diagnosis of CRC (or liver metastases) and radioembolization (Table 2). However, the presence of extrahepatic disease or substantial tumour liver involvement (<25 % vs. ≥ 25 %) at the time of radioembolization were adverse prognostic factors, although there was only a trend toward reduced OS in patients with extrahepatic disease ($p = 0.052$).

Median OS post-radioembolization was significantly prolonged in patients who had a good response to prior chemotherapy, defined by either changes in tumour volume (according RECIST 1.0) or CEA (response or stable disease vs. no response) (Fig. 1). Moreover, if durability of response to radioembolization extended to ≥6 months (as in 45 of 104 patients; 43.3 %), median survival was 17.1 months (95 % CI 13.7–23.7) compared with 5.8 months (95 % CI 13.7–23.7) in patients who had disease progression within 6 months of treatment. Median OS also significantly improved (from 5.8 months to 17.1 months) if the durability of response to radioembolization extended >6 months.

Kaplan-Meier analysis showed that median OS decreased significantly with increasing severity of pretreatment laboratory parameters (beyond CTC grade 0) for aspartate transaminase (AST), gamma-glutamyl transferase (GGT), and total bilirubin, although patients with total bilirubin (beyond pretreatment CTC grade 0) were in the minority (27.5 % of patients) compared with AST (49.5 %) or GGT (89.2 %).

Safety and tolerability

Radioembolization with ^{90}Y resin microspheres was generally well tolerated. The most commonly reported observed adverse event the days after the procedure were fatigue (14.4 %) and abdominal pain (8.7 %). Gastric ulcer due to the suspected extrahepatic deposition of microspheres was reported in three patients (2.9 %) and cholecystitis in two (1.9 %); all occurred early following radioembolization and resolved with treatment. Regarding liver-related events, raised bilirubin (all grades) was recorded in 26.9 % of patients at baseline, increasing to 50.0 % of patients at month 3 post-radioembolization. Clinically significant radioembolization-induced liver disease (REILD) was not reported, and grade 3 increases in bilirubin were reported in a minority (5.0 %) of patients at month 3. Raised AST levels (all grades) were more common events at both baseline (43.9 %) and at month 3 (72.0 %) than changes in bilirubin; however, grade 3 increases in AST were reported in only 1.3 % of patients at month 3.

Discussion

This analysis provides further evidence for the safety and efficacy of radioembolization in liver-predominant mCRC. Our findings equate to the observations from centers in the USA [19, 20], Europe [21], and Australia [22], which reported median OS following radioembolization were consistently ≥10 months in patients who had exhausted most, if not all, conventional chemotherapy options.

Uniquely, our analysis also showed that tumour responsiveness to prior systemic treatment (and not duration since diagnosis of mCRC) was a significant determinant of median OS after radioembolization; OS varied between 23 months in patients who had a complete response to prior chemotherapy and 13 months in patients with a partial response or stable disease (according to RECIST). These data suggest that response to chemotherapy is a useful clinical marker of tumour biology [4]. Median OS also significantly improved (from 5.8 to 17.1 months) if the durability of response to radioembolization extended >6 months. Patients with a positive trend in CEA serum levels (≥30 % reduction) at 3 months post-radioembolization also had a survival advantage compared with those who did not. This fits with the fundamental premise of liver-directed therapies, in which the aim of treatment is to slow the course of disease in the liver, which may be predictive of prolonged survival [23]. Several previously published studies on radioembolization have demonstrated the value decreasing CEA as a marker of reduced tumour metabolic function, correlating with findings from positron emission tomography (PET)-CT, and decreased tumour load [24, 25].

Pretreatment markers of disease progression in the liver characterized by changes in liver-cell function (as measured by albumin and AST) and in the biliary tract (as measured by alkaline phosphatase (ALPase, GGT, and bilirubin) are not only prognostic for OS following radioembolization but predictive of treatment outcome with chemotherapy [26–28].

Of interest in the contemporary management of mCRC is the value of radioembolization as either an alternative, or as an add-on therapy, to either EGFR or VEGF receptor inhibitors. Our analyses showed a trend toward improved survival in patients who had not received prior bevacizumab or cetuximab (16 vs. 10 months). Data from the recent

Table 2 Kaplan-Meier analysis of survival by baseline characteristics

Characteristic	Category	Overall survival, months			*P* value
		No.	Median	95 % CI	
All Patients	Total	104	10.2	(7.8–13.0)	NA
Gender	Female	31	10.7	(7.7 –14.7)	0.917
	Male	73	9.5	(6.7 –13.3)	
Age	<65 years	49	7.8	(6.1 –10.8)	0.503
	≥65 years	54	12.2	(8.8–15.0)	
Diagnosis	Cecum, colon, small bowel	73	11.0	(8.8–14.1)	0.031
	Rectum	31	7.8	(4.7–11.0)	
Metastases	Metachronous	24	11.6	(4.4–17.0)	0.498
	Synchronous	75	10.4	(8.1–13.7)	
Best response to prior treatment	Complete response	6	22.6	(8.8–29.5)	0.221
	Partial response	22	13.2	(6.6–23.7)	
	Stable disease	9	13.3	(2.5–22.0)	
	Progression	14	4.9	(3.1–11.0)	
CEA responder	Response	27	15.0	(11.0–25.9)	0.014*
	Stable	24	15.5	(11.0–20.3)	
	No Response	25	6.7	(5.2–10.1)	
Tumour: liver involvement	<25 %	66	12.3	(9.5–15.2)	<0.001*
	≥25 %	35	5.9	(4.7–9.2)	
Extrahepatic disease	No	44	13.5	(8.2–16.4)	0.052
	Yes	57	8.7	(7.4–10.7)	
Bevacizumab or cetuximab	No	11	16.0	(10.9–33.5)	0.126
	Yes	48	10.4	(5.2–14.7)	
Diagnosis to RE	<24 months	42	11.0	(8.2–15.0)	0.104
	≥24 months	57	10.1	(7.4–13.7)	
Liver mets to RE	<24 months	53	11.0	(6.7 –14.3)	0.397
	≥24 months	46	10.2	(7.6 –14.7)	
RE to mets progression	<6 months	45	5.8	(4.7–7.8)	<0.001*
	≥6 months	38	17.1	(13.7–23.7)	
Activity	<1.5 GBq	20	12.5	(6.6– 20.3)	0.911
	≥1.5 GBq	42	12.0	(5.8–16.0)	
Lung shunt	<5 %	29	14.7	(10.1–24.9)	0.075
	≥5 %	32	9.9	(4.6–15.2)	
ALT CTC grade	0	77	11.0	(8.2–14.1)	0.405
	1	23	8.7	(4.4–16.0)	
	3	1	2.8		
AST CTC grade	0	52	14.2	(10.9–17.3)	<0.001*
	1	47	7.7	(5.1–10.1)	
	2	3	2.8	(1.5–4.4)	
GGT CTC grade	0	11	14.3	(5.7–30.4)	<0.001*
	1	26	15.3	(10.9–20.3)	
	2	35	10.4	(5.2–15.0)	
	3	30	7.3	(4.6–10.1)	
Total bilirubin CTC grade	0	74	12.3	(9.1–15.0)	0.036*
	1	23	7.4	(4.3–10.7)	
	2	5	7.6	(1.3–10.8)	
WBC CTC grade	0	98	10.6	(7.8–13.3)	0.892
	1	3	15.2	(7.6 –30.4)	
	2	1	6.7		

CI confidence interval, *NA* not applicable, *Alk phosphatase* alkaline phosphatase, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *CEA* carcinoembryonic antigen, *CTC* National Cancer Institute Common Toxicity Criteria, *GGT* gamma-glutamyl transferase, *IQR* interquartile range, *LDH* lactate dehydrogenase, *RE* radioembolization with ^{90}Y resin microspheres, *WBC* white blood cell.

* Median survival calculated by Kaplan-Meier analysis

Randomized phase III trial comparing first-line mFOLFOX6 ± bevacizumab (bev) versus mFOLFOX6 + selective internal radiation therapy (SIRT) ± bev in patients (pts) with metastatic colorectal cancer (mCRC) (SIRFLOX) study indicate that the combination of bevacizumab with chemotherapy and radiotherapy was an effective and well-tolerated strategy in prolonging the time to tumour progression in the liver compared with chemotherapy plus bevacizumab alone. Moreover, radioembolization may also be a potentially useful therapy as an alternative to EGFR receptor inhibitors (especially in patients with *KRAS* mutant genotype).

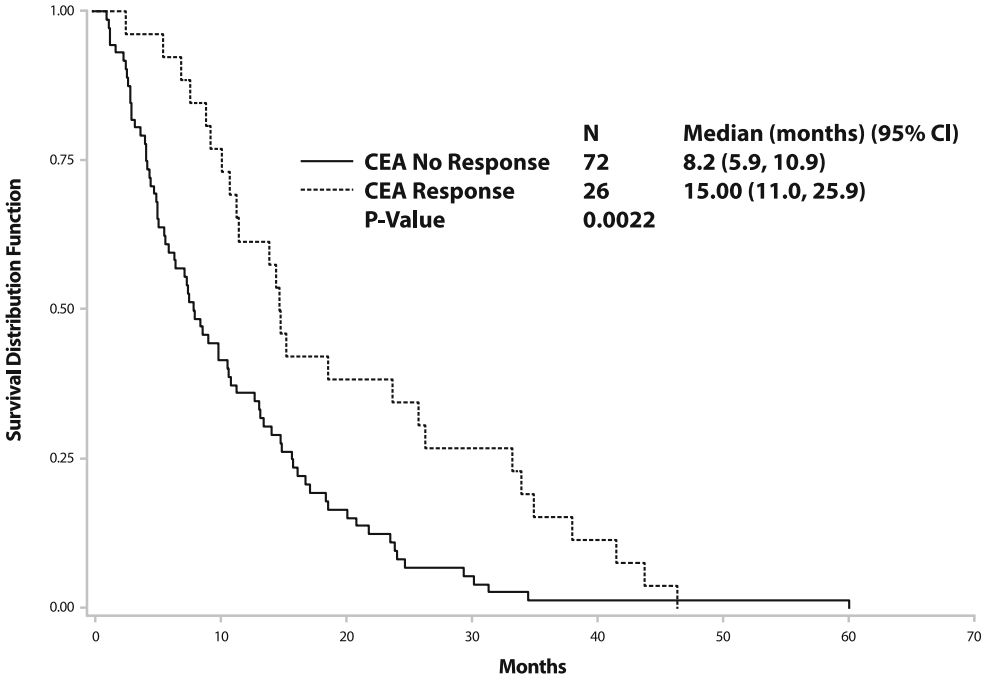

Fig. 1 Kaplan-Meier survival curve of patients treated with Y-90 resin microspheres stratified by carcinoembryonic antigen (CEA) response at 3 months

REILD to normal liver reserve is transient and not fatal; however, some deaths have been reported in patients with progressive liver failure attributed to REILD and not tumour progression. The likelihood of this potentially fatal event can be ameliorated by appropriate selection of patients and correct delivery and calculation of ^{90}Y activity. In our analyses of 104 patients, clinically significant REILD was not reported, and grade 3 increases in bilirubin were evident from routine laboratory investigations only in a minority (5.0 %) of patients at 3 months posttreatment. This is consistent with recent findings from the Metastatic Colorectal Cancer Liver Metastases Outcomes after RadioEmbolization (MORE) case-control study at 11 US centers, where REILD was an uncommon event using today's carefully defined treatment protocols (all grades, 1.7 %; grade ≥3, 0.5 %) [29].

There remains limited published evidence on the efficacy and safety of transarterial chemoembolization [both conventional and irinotecan-loaded drug-eluting beads (DEBIRI)] in mCRC, making comparison with radioembolization in this setting difficult. To date, a two-armed prospective clinical trial has been published by Fiorentini and colleagues involving 74 patients randomly assigned to receive either DEBIRI ($n = 36$) or conventional 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) therapy ($n = 38$) [9, 30] and a single-arm study [31] of DEBIRI ($n = 50$). Data from these studies are encouraging, but variability of enrolment criteria (first line, second line, salvage) and significant differences in technique and dose intensity of IRI (high variation of the dose of irinotecan loaded on particles) impede interpretation of these data [8]. Our own limited experience of DEBIRI, a finding also reflected in the literature [32], is that this technique is not as well tolerated by patients as radioembolization and so is viewed less favorably in the palliative setting.

Although our analysis provides robust evidence for patient OS following radioembolization, the analysis has a number of limitations due to its retrospective nature. Notably, however, all data were collated prospectively in consecutive patients receiving radioembolization and so are representative of the usual candidates for this procedure in clinical practice. However, our analysis does not detail all prior chemotherapy regimens and also lacks the rigor of a clinical trial in terms of reporting adverse events.

In conclusion, there remains a high medical need for effective treatments in the chemorefractory setting. Even after multiple lines of chemotherapy, many patients still have a good performance status and are fit and eligible for radioembolization. In our view, this single treatment procedure affords substantial benefits and is generally well tolerated.

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