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Radioembolisation for liver metastases: Results from a prospective 151 patient multi-institutional phase II study

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Abstract ***Purpose:*** To investigate the safety, response rate, progression-free and overall survival of patients with liver metastases treated with ^{90}Y (glass) radioembolisation in a prospective, multicenter phase II study.

Methods: 151 patients with liver metastases (colorectal $n = 61$, neuroendocrine $n = 43$ and other tumour types $n = 47$) refractory to standard of care therapies were enrolled in this prospective, multicenter, phase II study under an investigational device exemption. Clinical/laboratory/imaging follow-up were obtained at 30 days followed by 3-month intervals for 1 year and every 6 months thereafter. The primary end-point was progression-free survival (PFS); secondary end-points included safety, hepatic progression-free survival (HPFS), response rate and overall survival.

Results: Median age was 66 (range 25–88). Grade 3/4 adverse events included pain (12.8%), elevated alkaline phospatase (8.1%), hyperbilirubinemia (5.3%), lymphopaenia (4.1%), ascites (3.4%) and vomiting (3.4%). Treatment parameters including dose delivery were reproducible among centers. Disease control rates were 59%, 93% and 63% for colorectal, neuroendocrine

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and other primaries, respectively. Median PFS was 2.9 and 2.8 months for colorectal and other primaries, respectively. PFS was not achieved in the neuroendocrine group. Median survival from ^{90}Y treatment was 8.8 months for colorectal and 10.4 months for other primaries. Median survival for neuroendocrine patients has not been reached.

Conclusion: Patients with liver metastases can be safely treated with ^{90}Y microspheres. This study is the first to demonstrate technical and dose reproducibility of ^{90}Y glass microspheres between centers in a prospective setting. Based on these promising data, three international, multicenter, randomised phase III studies in colorectal and hepatocellular carcinoma have been initiated.

1. Introduction

Hepatic metastases are common in a wide range of malignancies, primarily through the hematogenous mechanism of spread through the portal circulation. In the proper clinical setting, surgical resection is considered the only curative treatment.[1,2] However, less than 20% of patients with liver metastases qualify for resection because of tumour size, location, multifocality and/or inadequate hepatic reserve.[3] Consequently, there is a clinical need for advances in loco-regional liver-directed treatments in patients with liver metastases.

Currently, local therapies for liver metastases include hepatic arterial infusion chemotherapy, transarterial chemoembolisation and radiofrequency ablation–all with the intent of providing local control while preserving essential vascular structures, liver parenchyma and adjacent organs.[4–11] Radioembolisation is an emerging local transarterial approach that capitalizes on tumour hypervascularity to deliver high doses of radiation therapy while preserving normal parenchyma.[12–15] This treatment has been used in hepatocellular carcinoma (HCC), colorectal cancers (CRC), neuroendocrine tumours (NE) and a variety of other primaries.[16–24] However, the majority of these studies have been single center reports. Prospective, multicenter studies are lacking.

The purpose of our study was to investigate the safety and efficacy of ^{90}Y radioembolisation for liver metastases under a prospective, multicenter phase II paradigm. At the time (2007), the technical reproducibility and multicenter feasibility of clinical trials involving radioembolisation were unknown. The primary end-point of the study was progression-free survival (PFS). Secondary end-points included safety, response rate, hepatic PFS and overall survival.

2. Methods

2.1. Eligibility criteria

Between 17th January 2007 and 7th October 2009, 151 patients were treated with radioembolisation for liver metastases as part of a prospective, multicenter phase II trial. Protocol entry criteria included: (1) unresectable liver metastases with imaging-confirmed disease progression following standard of care therapy; (2) performance status 0–2; (3) ability to undergo angiography and selective visceral catheterisation and (4) liver function (bilirubin $<$2.0 mg/dL). Exclusion criteria included: (1) significant extrahepatic disease; (2) evidence of uncorrectable flow to the gastrointestinal tract observed on angiography or technetium-99 m macroaggregated albumin scan (^{99m}Tc-MAA); 3) risk of exposure $>$30 Gy delivered to the lungs and (4) concurrent chemotherapy or radiotherapy. Patients were not excluded based on perceived imaging or angiographic hypovascularity of metastatic lesions.

An investigational device exemption (IDE) was obtained from the United States Food and Drug Administration (FDA; IDE GO40148) with subsequent institutional review board approvals from all centers (Mayo Clinic, Albany Medical Center [AMC], Medical College of Wisconsin [MCW], Johns Hopkins University [JHU] and Northwestern University [NU]). The study was Health Insurance Portability and Accountability Act compliant, was registered (NCT00511862) and conducted under good clinical practices. The trial was closed on 31st March 2011, with the final report submitted to the FDA on 28th September 2011.

2.2. Patient evaluation

All patients underwent a complete history and physical examination. In particular, prior exposure to cytotoxic, cytostatic and/or hormonal agents was recorded. For the CRC cohort, the number of 'lines' of chemotherapy was determined post hoc by a board-certified medical oncologist (H.N.) using data from the case report forms. Patients underwent a pre-treatment angiogram with selective visceral catheterisation in order to assess hepatic vasculature, blood-flow dynamics, identify non-target vessels and determine lung shunt fraction.[12,25–28] Extra-hepatic vessels were prophylactically embolised when necessary. Finally, 4-5 mCi of ^{99m}Tc-MAA was injected in order to assess for non-target flow to the gastrointestinal tract and lung shunting fraction.[12–14]

2.3. Radioembolisation device

TheraSphere (Nordion, Canada) consists of 20–40 micron particles, where the ^{90}Y is an integral constituent

of the glass matrix. ^{90}Y is a pure beta emitter with a physical half-life of 64.1 h and mean tissue penetration of 2.5 mm. The partition method of calculating the required activity used for the protocol has been previously described.[12] The planned ^{90}Y dose was 120 Gy (±10%).

2.4. Treatment strategy and follow-up evaluation

Patients were classified as having either unilobar or bilobar disease. This translated into patients receiving one or more lobar infusions (separated by 30–40 days), depending on tumour distribution. No whole liver infusions were performed.

Following treatment, patients were contacted at 2 weeks by telephone and clinical toxicities were recorded. A formal clinic visit was performed 4 weeks after ^{90}Y, and subsequently at 3-month intervals for 1 year then every 6 months thereafter on protocol. Each follow-up visit consisted of repeat laboratory assessments, adverse event (AE) recording as well as imaging. AEs were assessed using Common Toxicity Criteria v3.0; data reported herein comply with the research reporting standards for ^{90}Y.[29] All toxicities that were recorded within 3 months of treatment with unknown relationship or possibly/probably related to treatment are reported herein. The attribution of AEs to radioembolisation was determined by an independent medical oncologist not involved in the study.

2.5. Data collection and outcome measures

Adverse events were recorded from the day of treatment until protocol exit or death. Patients exited from the protocol were followed for overall survival.

Central response assessment was performed by an independent radiologist with specific expertise in cross-sectional imaging. Response was assessed using response evaluation criteria for solid tumours (RECIST) v1.0 criteria.[30] Since ^{90}Y represents a liver-directed therapy, response methodology was adjusted to capture the local nature of radioembolisation and the fact that 35% exhibited extra-hepatic disease at baseline. Hence, the following conservative modifications were applied to RECIST criteria to assess hepatic PFS: (1) partial response (PR): hepatic response without extra-hepatic progression, (2) stable disease (SD): stable disease in both liver and extra-hepatic sites, (3) progressive disease (PD) and progression of the liver lesions with/without extrahepatic progression. Any extrahepatic progression (irrespective of hepatic response), whether present at baseline or not, was classified as PD. Disease control rate (DCR) was defined as complete response + PR + SD.

A progression-free survival (PFS) end-point was defined as either imaging progression or death from any cause. A hepatic progression-free survival (HPFS) end-point was defined as liver progression or death from any cause. Overall survival (OS) was defined as the time from first treatment until death (or censored to last follow-up).

2.6. Statistical analyses

Data were summarised using descriptive statistics (mean/standard deviation for continuous variables; count/frequency for categorical variables). Kaplan–Meier methodology was used to determine HPFS, PFS and OS.[31,32] Exploratory imaging and survival subanalyses were performed in patients with liver-only disease. All statistical calculations were performed using SAS software (version 9.1.3). There was no efficacy hypothesis; the intent was to demonstrate multicenter feasibility within a prospective, predefined feasibility design.

3. Results

3.1. Patient population

Table 1 presents baseline characteristics and prior exposure to systemic agents. The majority of patients exhibited advanced disease with multifocal (89%) bilobar (77%) tumours, extrahepatic metastases (35%), tumour burden >25% (35%) and performance status >0 (35%). Despite 35% of patients exhibiting limited extrahepatic disease at baseline, enrolment in this clinical trial using a liver-directed therapy was deemed appropriate by medical oncology, as the liver was the most immediate life-threatening site of disease. The origin of primary disease was colon ($N = 61$), neuroendocrine ($N = 43$) and various other primaries (cholangiocarcinoma, breast, ovarian, renal cell, bladder, pancreatic, oesophageal, lung and gastric; $N = 47$). 98% of colorectal patients had been exposed to prior systemic chemotherapy. None of the patients were on chemotherapy at the time of ^{90}Y treatment. For the NE group, 19 of 43 (44%) had been exposed to sandostatin, 3 had received ablation and 4 arterial embolisation. All centers contributed to patient recruitment (AMC $N = 32$, JHU $N = 27$, Mayo $N = 22$, MCW $N = 22$, NU $N = 48$).

3.2. Treatment and dosimetry

48 patients (32%) required coil embolisation of extrahepatic vessels to prevent non-target distribution, with the right gastric ($N = 24$), gastroduodenal ($N = 22$) and the supraduodenal ($N = 4$) being the most common (sum >48 since patients may have >1 vessels embolised). Table 2 depicts dose administered to the liver. Mean and median doses administered were comparable by disease states and centers. The mean (115.9 ± 7.35) and median (115.0 ± 10.3) dose delivered was >95% of the target

Table 1
Baseline characteristics.

Characteristic	Category	Patients N (%)
Age	Median	66 (range: 25–88)
Ethnic group	Caucasian	138 (91)
	African American	11 (7)
	Other	2 (1)
Gender	Male	84 (56)
	Female	67 (44)
Origin of primary	Colorectal	61 (40)
	Neuroendocrine	43 (29)
	Non-CRC/non-NE	47 (31)
Tumour burden	⩽25%	98 (65)
	26–50%	52 (34)
	>50%	1 (1)
Lobes affected	Unilobar	34 (23)
	Bilobar	117 (77)
Distribution	Solitary	16 (11)
	Multifocal	135 (89)
Limited extrahepatic metastases	Absent	98 (65)
	Present (lymph nodes, lung, peritoneum)	53 (35)
Bilirubin	⩽1.2 mg/dL	143 (95)
	>1.2 mg/dL	8 (5)
Albumin	>3.5 g/dL	69 (46)
	⩽3.5 g/dL	82 (54)
ECOG performance status	0	78 (52)
	1	66 (44)
	2	7 (5)
Prior systemic therapy	Colorectal	60/61 (98)
	5 FU or capecitabine	57 (93)
	Irinotecan	38 (62)
	Oxaliplatin	48 (79)
	Cetuximab	23 (38)
	Bevacizumab	42 (69)
	Panitumumab	2 (3)
	Neuroendocrine	10/43 (23)
	Non-CRC/non-NE	33/47 (70)

Abbreviations: CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; NE, neuroendocrine cancer; FU and fluorouracil.

dose. The rate of treatment completion (unilobar and bilobar) was 95.1% ($N = 58$), 83.7% ($N = 36$) and 89.4% ($N = 42$) for CRC, NE and non-CRC/non-NE, respectively. This resulted in an on-protocol treatment completion rate of 90.1%.

3.3. Safety

All patients were treated on an outpatient basis, with discharge 2–6 h following treatment. Table 3 lists (alphabetically) grade ⩾3 toxicities: pain (12.8%), elevated alkaline phospatase (8.1%), deaths (7.4%), hyperbilirubinemia (5.3%), lymphopaenia (4.1%), ascites (3.4%) and vomiting (3.4%). All grade 5 toxicities were attributed to disease progression (not device-related) by independent medical oncology assessment. The solitary ulcer responded to conservative management.

3.4. Tumour response and progression analyses

Table 4 summarises response outcomes data stratified by CRC, NE and others. 147 of 151 (97%) patients were evaluable for response assessment. For CRC, a PR rate of 5.2% was observed, with 53.4% exhibiting SD; this translates to a DCR of 58.6%. Median PFS was 2.9 months (95% confidence interval [CI]: 1.3–3.1); median HPFS was 3.0 months [CI 2.0–5.8]. For NE, a PR rate of 20.9% was observed, with 72.1% exhibiting SD, translating to a DCR of 93.0%. Median PFS was not achieved; median HPFS was 17.9 months [CI 13.5–19.5]. Non-CRC/non-NE patients demonstrated a PR

Table 2
Total liver dosing (Gray).

By type of metastases				
	CRC ($N = 61$)	NE ($N = 43$)	Non CRC/non-NE ($N = 47$)	All patients ($N = 151$)
Mean (SD)	115.3 (7.61)	116.2 (7.42)	116.3 (7.04)	115.9 (7.35)
Median (IQR)	114.3 (11.4)	115.0 (10.5)	115.7 (9.0)	115.0 (10.3)
Min, Max	100, 134	103, 138	97, 133	97, 138

By treating center					
	Site 1	Site 2	Site 3	Site 4	Site 5
Mean (SD)	112.2 (5.9)	116.3 (5.4)	117.3 (5.5)	119.9 (8.1)	111.7 (5.9)
Median (IQR)	111.7 (7.1)	117.4 (6.7)	116.7 (8.3)	119.6 (10.7)	110.7 (7.9)
Min, Max	102, 124	105, 126	108, 126	97, 138	104, 130

Abbreviations: CRC, colorectal cancer; IQR, inter-quartile range; Max, maximum; Min, minimum; NE, neuroendocrine cancer and SD, standard deviation.

rate of 6.5%, with 56.5% exhibiting SD, resulting in a DCR of 63.0%. Median PFS was 2.8 months (CI: 1.3–3.3); median HPFS was 2.9 months [CI 1.5–3.3].

3.5. Survival

Overall survival (stratified by disease) is listed in Table 4. Median survival for CRC was 8.8 months (CI: 6.6–11.9). Patients with non-CRC/non-NE survived a median of 10.4 months (CI: 6.6–14.6). Median survival was not reached in the NE cohort; 2-year progression-free and survival rates were 67.4% and 79.1%, respectively. Median follow-up time was 30 months (CI: 26.4–33.8).

3.6. Exploratory Response and Survival Subanalyses (liver-only disease ± low disease burden – Table 5, Supplementary Tables 1–5)

In the CRC cohort, DCR was 63.9%. This was associated with 3.0 month median HPFS and PFS. Median survival was 10.5 months (CI: 6.6–14.1) in patients with liver-only disease and 11.8 months (CI: 6.5–14.1) in those with liver-only disease and $\leqslant$25% tumour burden. When analyzed from the time each lobe was treated, lobar HPFS ranged from 5.1–6.2 months (Supplementary Table 4). Survival by lines of chemotherapy, time from initial diagnosis and time of chemotherapy to treatment are described in Supplementary Table 5. The survival from radioembolisation of 6.6–9.8 months after $\geqslant$2 lines of prior chemotherapy and the median time of 28.2–29.2 months from initial diagnosis to radioembolisation confirm that the cohort was comprised of well-selected, chemorefractory patients.

Table 3
Clinical and biochemical toxicities.

Adverse event	No. of patients	Percent (%)
Grade 3		
Ascites	5	3.4
Alkaline phosphatase	12	8.1
Alanine transaminase	1	0.7
Aspartate transaminase	3	2.0
Bilirubin	6	4.0
Creatinine	1	0.7
Dehydration	2	1.3
Dyspnoea	2	1.3
Fatigue	4	2.7
GI-obstruction/stricture	4	2.7
Gastrointestinal – ulcer (endoscopy confirmed)	1	0.7
Heartburn	1	0.7
Haemoglobin	1	0.7
Hyperglycaemia	2	1.3
Hypoalbuminaemia	4	2.7
Hypokalaemia	3	2.0
Hypoxia	1	0.7
Infection Grade 3 or 4, unknown absolute neutrophil count	5	3.4
International normalised ratio	1	0.7
Leukocytes	1	0.7
Lipase	1	0.7
Lymphopaenia	5	3.4
Mucositosis	1	0.7
Muscle weakness	2	1.3
Nausea	2	1.3
Neuropathy	1	0.7
Neutrophils	1	0.7
Obstruction – genitourinary	1	0.7
Pleural effusion	2	1.3
Pulmonary other	1	0.7
Pain	18	12.1
Structure anastomotic – genitourinary	1	0.7
Tumour Lysis Syndrome	1	0.7
Vomiting	5	3.4
Grade 4		
Acidosis	1	0.7
Alanine transaminase	1	0.7
Asparate transaminase	1	0.7
Bicarbonate sodium – low	1	0.7
Bilirubin	2	1.3
Cardiac Ischaemia	1	0.7
Hyperkalaemia	1	0.7
Hyponatraemia	1	0.7
Infection	3	2.0
Pain	1	0.7
Leukocytes	1	0.7
Lymphopaenia	1	0.7
Neutrophils	1	0.7
Platelet	2	1.3
Grade 5		
Death	11	7.4
Liver dysfunction	1	0.7
Infection	1	0.7
Thrombosis/thrombus/embolism	1	0.7

In the liver only NE cohort, DCR was 90.9%, with a median HPFS of 19.5 months. Median PFS was not reached.

Table 4
Response/survival outcomes.

Response				
Response by RECIST	CRC ($N = 58$) N (%)	NE ($N = 43$) N (%)	Non CRC/non-NE ($N = 46$) N (%)	All patients ($N = 147$) N (%)
CR	0	0	0	0
PR	3 (5.2)	9 (20.9)	3 (6.5)	15 (10.2)
SD	31 (53.4)	31 (72.1)	26 (56.5)	88 (59.9)
PD	24 (41.4)	3 (7.0)	17 (37.0)	44 (29.9)
Disease control: CR + PR + SD	34 (58.6)	40 (93.0)	29 (63.0)	103 (70.1)
Time-to-end-point analyses (median)				
	HPFS (95% CI)		PFS (95% CI)	OS (95% CI)
CRC	3.0 months (2.0–5.8)		2.9 months (1.3–3.1)	8.8 months (6.6–11.9)
NE	17.9 months (13.6–N.C.)		67.4%*	79.1%**
Non-CRC/non-NE	2.9 months (1.5–3.3)		2.8 months (1.3–3.3)	10.4 months (6.6–14.6)

Abbreviations: CI, confidence interval; CRC, colorectal cancer; CR, complete response; N.C., not calculable; NE, neuroendocrine; OS, overall survival; PR, partial response; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumours; SD, stable disease and PD, progressive disease.

* Percentage that had not progressed at 2 years.

** Percentage alive at 2 years.

4. Discussion

A large number of patients with metastatic disease to the liver either do not respond to systemic chemotherapy or ultimately become chemo-refractory. For these patients, liver-directed therapies may provide an effective alternative. The purpose of this open-label phase II was to assess the safety and efficacy of radioembolisation in this patient population.

The safety profile of radioembolisation in this heavily pretreated population was acceptable. The reporting of moderate to severe pain in 12.8% was lower than previously reported in uncontrolled series, with other reports ranging from 50% to 60%.[20,33] The 5.3% hyperbilirubinemia rate was also acceptable, given the significant exposure to prior chemotherapy and end-stage status. The gastrointestinal ulcer rate was also lower than prior reports, likely a result of standardised meticulous angiography adopted by all centers.[26–28] The ability to standardise and uniformly deliver prescribed doses at all centers with this device has been demonstrated. With a median dose delivered of >95%, the intended dose can predictably be delivered by all centers. Overall, this study was able to reproduce previous safety findings in prior radioembolisation studies.[34]

A majority of the CRC patients were exposed to $\geqslant 2$ lines of chemotherapy. The objective response rate was (5.2%). When compared to prior reports (response 35–45%), this was lower than expected possibly due to heavy pretreatment in the population.[20,22] The effect of targeted agents anti-VEGF bevacizumab and anti-EGFR cetuximab on the vasculature is unknown; there have been several reports of attenuated hepatic vasculature in patients chronically exposed to targeted agents possibly leading to less efficiency.[35] Several other clinical parameters may have contributed to the low response rates. First, 69% received bevacizumab; the effect of hepatic vasculature is unknown. Second, some patients only received treatment to the initial lobe. Several did not have complete treatment given progressive disease; it was not deemed appropriate for the patients to undergo completion of treatment to the other lobe given clinical progression. Third, although several patients did exhibit PR in the treated lobe, this was made in association with progressive extrahepatic metastases; in this setting, despite radioembolisation resulting in treated tumour size reduction or stabilisation, patients were categorised as PD per oncology reporting standards. Finally, it is well-recognised that response assessment following locoregional therapies (in particular ^{90}Y) may be confounded by post-treatment peri-tumoural oedema and swelling; this could translate into an artificially low response rate when size criteria are used without considering tumour necrosis.[36,37]

In the CRC cohort, a DCR of 58.6% was achieved; this signal is worthy of further investigation given this

Table 5
Colorectal cancer survival subanalyses.

Survival from ^{90}Y treatment (median)	95% confidence interval	
	Lower	Upper
Patients with liver-only disease (N = 36)		
10.5 months	6.6	14.7
Patients with liver-only disease and Tumour Burden 0–25% (N = 27)		
11.8 months	6.5	14.7
Patients with stage 4 disease at diagnosis (N = 39)		
7.4 months	5.3	10.1
Patients with liver-only disease and stage 4 disease at diagnosis (N = 25)		
9.4 months	4.7	11.9

cohort's advanced stage. These patients also exhibited a median HPFS and PFS of 3.0 months, further supporting the advanced nature of disease at protocol enrolment and aggressive tumour biology. Extrahepatic disease contributed to the low PFS. This translated to an overall survival of 8.8 months, similar to a recent report by Hendlisz, where advanced CRC patients were randomised to 5FU ± ^{90}Y and achieved median survival of 7.9–10 months.[23] Interpretation of survival in this study was limited by crossover of the control group to ^{90}Y at progression. Furthermore, although comparison to other studies should be undertaken cautiously, PFS and median survival were comparable to outcomes achieved in heavily pretreated CRC patients treated with cetuximab, panitumumab or regorafenib compared to placebo in randomised trials, which reported PFS of 1.4–2 months and overall survival of 6.1–6.6 months.[38–40] Finally, the CRC cohort exhibited promising survival, further supporting the continuum of care strategy in advanced colorectal cancer with exposure to multiple treatment regimens over time resulting in incremental benefit and potentially longer survival.

For NE patients, response rate was higher (20.9%). This is in keeping with prior reports of high response rates and is expected given the hypervascular nature of NE metastases.[21] The DCR of 93% was also noteworthy, especially given the documented imaging progression prior to trial enrolment. These findings support the well-known high response rates of trans-arterial treatments.[6,41–44] Although direct comparisons should be undertaken cautiously, recent targeted agents have shown PR rates of 5.0–9.3% and a PFS of 11.0–11.4 months.[45,46] The NE cohort exhibited HPFS of 17.9 months. There are no detailed reports or controlled investigations of PFS in NE treated with ^{90}Y; comparison to other series is challenging. Survival was promising, with a 2-year survival rate of 79%.

Conclusions that can be drawn from the non-CRC/non-NE cohort are limited. Patients with liver metastases from various primaries could be treated safely with a DCR of 70.1%. Disease states such as cholangiocarcinomas and metastatic breast cancer were eligible for treatment under this protocol given progression on standard therapies. Assessed as a group, we did not identify any areas of concerns such as toxicity from treatment with radioembolisation.

Interesting findings were derived from exploratory imaging and survival subanalyses in the CRC patients with liver-only disease. Despite HPFS and PFS both being 3.0 months, survival from first ^{90}Y treatment was 10.5 months. This was further improved to 11.8 months in those patients with burden $\leqslant$25%. The long survival observed in these subgroups suggests the ability of ^{90}Y to control the disease (despite being heavily pre-treated) and delay extrahepatic dissemination, despite the low PFS. This is supported by the observation that many of the PD end-points were due to size progression rather than extrahepatic metastases. It also highlights the differences in response assessment in local therapies compared with systemic agents, where disease control, time to progression and PFS have been correlated with long-term survival.[47–50]

The successful completion of this study demonstrating the safe and standardisable application of radioembolisation on strict protocol has set the stage for 3, international multicenter randomised trials investigating the role of ^{90}Y glass microspheres in colorectal and hepatocellular carcinoma (HCC). The first trial investigating colorectal cancer is a 360 patient, prospective, international randomised phase III clinical trial **E**valuating TheraSphere in **P**atients with metastatic colorectal carcinoma **O**f the liver who have failed first line **Ch**emotherapy (EPOCH; NCT01483027). This ongoing trial randomises patients who have failed first line therapy to receive standard of care 2nd line chemotherapy ± ^{90}Y. The second trial is a 400 patient, international, prospective, randomised phase III clinical trial of intra-arterial Thera**S**phere in the **T**reatment **O**f **P**atients with unresectable **H**epato**C**ellular **C**arcinoma (STOP-HCC; NCT01556490). This ongoing study randomises advanced HCC patients to receive standard of care sorafenib ± ^{90}Y. The 3rd trial is a 328 patient, prospective, international randomised phase III trial of ^{90}**Y** trans-arterial radio**E**mbolisation versus **S**orafenib for the treatment of advanced HCC in patients with **P**ortal vein thrombosis (YES-P; clinical trial number pending). This study will directly compare radioembolisation to sorafenib in patients with portal vein invasion. As a group, these three trials investigate the role of local therapy in the form of radioembolisation with systemic treatments and, if positive, have the potential to challenge current paradigms and redefine standards of care.

There are strengths to this study. First, this is one of very few prospective, multi-center device studies in oncology, thereby validating the feasibility and reliability of dose delivery in multi-center clinical trials with radioembolisation. Second, imaging outcomes were determined by independent central imaging review. Third, data collection was comprehensive and verified by a dedicated contract research organisation. There are limitations. First, this was a non-randomised trial in a heterogeneous cohort. Generalisability of findings (other than safety) is limited. Second, there was no comparator arm. However, surgical resection of similarly heterogeneous patients has been reported to be beneficial.[51–54] The closest comparison of patients having failed systemic therapy for CRC treated with supportive care has previously demonstrated an overall survival of 6 months.[38,47] Third, many of these patients were treated following exposure to systemic biologics, potentially impacting vascularity and microsphere delivery.[35] Stratification to prior anti-VEGF therapy exposure may be

needed in future trials. Fourth, although it was the intent of locoregional therapy to delay progression and liver dissemination, the long survival rate noted in CRC patients receiving ⩽1 line of chemotherapy may have been partly attributable to early treatment in patients that were chemotherapy intolerant. Lastly the lack of biomarker analysis (BRAF/KRAS) in our small CRC cohort may have masked the identification of a specific genomic subset that may benefit the most from our treatment approach.

5. Conclusion

Radioembolisation was found to be safe in this 151 patient heavily pre-treated cohort with disease refractory to standard of care therapies. Treatment was well-tolerated with acceptable toxicities when performed using careful embolisation techniques and standardised methodology. Data were reproducible between centers. Based on these findings, three prospective randomised international phase III trials using glass microspheres are underway investigating the role of ^{90}Y in patients with liver malignancies.

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Conflict of interest statement

ABB, JFG, MFM, WR, RJL and RS are advisors to Nordion. JC, BH and MR are employees of Nordion. None of the other authors report a conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.05.012.

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