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ORIGINAL ARTICLE

Single-institution experience with selective internal radiation therapy (SIRT) for the treatment of unresectable colorectal liver metastases

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Abstract

Background Liver metastases are the commonest cause of death for patients with colorectal cancer. Growing evidence supports the use of selective internal radiation therapy (SIRT) in combination with conventional chemotherapy regimens for liver-only or liver-dominant unresectable metastatic colorectal cancer.

Aims To measure and evaluate outcomes of the first 20 consecutive patients with unresectable colorectal liver metastasis selected for SIRT in addition to their chemotherapy at a single Irish institution.

Methods Retrospective case series was performed. Patient charts and medical records were reviewed.

Results All 20 patients (100%) selected for angiographic workup were subsequently successfully treated with radioembolization. All patients were discharged 1 day post-SIRT. At initial imaging evaluation, 12 (60%) had a partial response in their liver, 2 (10%) had stable disease, and 6 (30%) had liver-specific progressive disease. Median follow up was 10 months (range 6–26). At last follow up, 14 (70%) patients were alive and 6 (30%) deceased. Most recent imaging demonstrated 2 (10%) with a complete response, 7 (35%) had a partial response, 2 (10%) had stable disease, and 9 (45%) had progressive disease within their liver. One patient was downstaged to hepatic resection, and one with a complete hepatic response had his primary sigmoid tumor resected 11 months post-SIRT.

Conclusions SIRT is a safe and effective therapy for certain patients with unresectable colorectal liver metastases. This case series supports our opinion that selected patients should be offered SIRT in concert with their medical oncologist, concomitant with their chemotherapy. Larger multi-center studies are required to more clearly define the patient groups that will derive most benefit from SIRT.

Keywords Colorectal liver metastases · Cytoreduction · Interventional oncology · Interventional radiology · Intra-arterial brachytherapy · Localized therapy · Molecular genetics · Radioembolization · Radiosensitization · Radiotherapy · Regional therapy · SIRT · Unresectable liver metastases

Introduction

Colorectal cancer (CRC) is the third most common cancer in Ireland for both males and females [1]. It is a diagnosis that carries substantial morbidity and mortality, accounting for 13 and 10% of cancer deaths in Irish men and women, respectively, or 1018 deaths per year in 2011–2131. Hepatic metastases contribute to the high mortality rates observed in these patients [2, 3] with about 50–60% of patients developing hepatic metastases during the course of their disease [4]. Furthermore, approximately one third of patients with CRC present with hepatic metastases at initial diagnosis [5, 6] and approximately half of patients with early CRC develop metastases after resection of their primary colonic lesion [6, 7].

Liver resection offers the best chance of cure for patients with liver metastases, with 5-year survivals of 30–50%; however, surgery is available to fewer than 20% of these patients [8–11]. Percutaneous thermal ablation can also be effective in treating select patients with low-volume liver disease [12]. First-line chemotherapy regimens such as 5-fluorouracil (5-

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FU) combined with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) and the addition of a biologic agent can increase median survival time up to 30 months [2]. However, after failing first-line chemotherapy, the response rate to second-line agents ranges from about 20 to 35% [13, 14]. Many patients therefore either do not respond to systemic chemotherapy or ultimately develop chemorefractory disease. There is clearly an unmet need for treatment options for patients with CRC and hepatic metastasis.

For these reasons, loco-regional or liver-directed therapies may be an important addition to the armamentarium in the fight against CRC liver metastases. Intra-arterial therapies use the dual blood supply to the liver to their advantage. Normal liver parenchyma has a predominantly portal vein source of blood supply while liver cancers derive their blood supply almost exclusively from hepatic arteries [15]. This allows small particles infused into the hepatic arteries to effectively select tumor cells for treatment with relative sparing of normal liver parenchyma. Second, neovascularization induced by hepatic neoplasms results in the formation of dense microvasculature at the periphery of the lesions, compared with the capillary bed of normal liver parenchyma [16]. Yttrium 90 radioembolization or selective internal radiation therapy (SIRT) delivers a targeted radiation dose to the liver via the hepatic artery. Yttrium 90 particles release tumoricidal beta rays. Beta rays have a mean range of 3–4 mm and a maximum range in tissue of 11 mm. Growing evidence [17–22] supports its use in combination with traditional chemotherapy regimens for liver-only or liver-dominant unresectable metastatic colorectal cancer.

The purpose of this study is to measure and evaluate outcomes of the first 20 consecutive patients with unresectable CRC liver metastasis treated at a single institution with hepatic arterial radioembolization (SIRT) using resin microspheres.

Methodology

Patient selection

Institutional Review Board approval was obtained for this retrospective review of all patients who had a planning angiogram with a view to radioembolization of CRC liver metastases in the Mater Misericordiae University Hospital (MMUH), Dublin, Ireland from March 2015 to December 2016. Patients were referred from oncology services both within MMUH and other centers nationwide. All patients were discussed at a multi-disciplinary team (MDM) meeting at their referring hospital or at MMUH. All were seen in an outpatient setting by the Consultant Interventional Radiologist who subsequently performed the planning angiogram and SIRT treatments.

All patients eligible for SIRT had histologically confirmed adenocarcinoma of the colon [with or without primary in situ] and liver-dominant unresectable metastatic disease. Additionally, they were required to have performance status [Eastern Cooperative Oncology Group Score of 0/1] and normal serum bilirubin levels [see table below]. Demographic, laboratory, imaging, and dosimetry data were collected. Chemotherapy regimens, including adjunctive biological agents, to date were recorded. Patients were classified as receiving first-line or salvage chemotherapy at the time of SIRT. If patients were on Bevacizumab, this was omitted in the 6 weeks prior to SIRT. Based on a prior dose escalation study [23], oxaliplatin dose was reduced from 85 to 60 mg/m^2 for three courses at the time of SIRT treatments. Otherwise, patients' current chemotherapy regimens were continued through their radioembolization treatment. Post-treatment technical and clinical outcomes were analyzed. All SIRT treatments were performed with Yttrium90 (Y90) resin microspheres (SIR-Spheres, Sirtex Inc., Cosgrove, Australia).

Radiological technique

Vascular planning angiography involved celiac and superior mesenteric artery angiography with access via the right common femoral artery. Aberrant vascular anatomy was identified. Arterial supply in the distribution of the common hepatic artery susceptible to reflux or non-hepatic distribution of the radioembolization resin microspheres on the day of therapy were prophylactically coil embolized. Albumin labeled with Technetium-99m (Tc-99m) was then injected into the right and left hepatic arteries in order to simulate future planned therapy.

Following the planning angiogram, the patient proceeded immediately to the nuclear medicine department for a single positron emission computed tomography (SPECT)CT (Fig. 1). This allowed calculation of the lung shunt fraction and distribution of the Tc-99m. Lung shunt fraction determined dose reduction as follows. Lung shunt < 10%: no dose reduction. Lung shunt 10–15% 20% dose reduction. Lung shunt 15–20% 40% dose reduction. Lung shunt > 20%: no treatment. Any other unexplained extrahepatic uptake was a contraindication to treatment.

In line with international standards [24], recent cross-sectional imaging was reviewed to establish intrahepatic tumor burden and distribution, extrahepatic disease, and hepatic arterial anatomy. The body surface area method was used to calculate the administered dose of Y90 resin microspheres. This requires calculation of liver and liver tumor volume from 3D-reconstructed CT images. The formulas to calculate the treatment dosage are described in the Sirtex Medical training manual [25], for SIR-Spheres.

The SIRT procedure was then performed between 2 and 3 weeks after the angiographic workup. This involved hepatic artery angiography and whole liver therapy. The SIRT procedure, also performed under local anesthesia, included correct

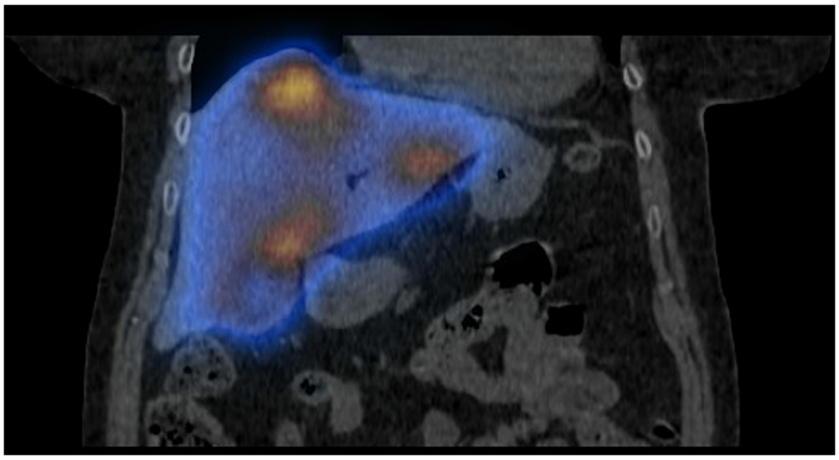

Fig. 1 Sixty-eight-year-old female with unresectable colorectal liver metastases. SPECT CT immediately after planning angiography and injection of Technetium 99M labeled albumin into the right and left hepatic arteries. Increased uptake of radioisotope within tumor in both lobes of the liver is predictive of good ytrrium90 microsphere uptake at time of selective intra-arterial radiation therapy (SIRT) treatment

positioning of the tip of the microcatheter within the hepatic artery/arteries at the same position as the injection of Tc-99m during workup. All patients were admitted for one night observation and PRN analgesia. Bremsstrahlung imaging was performed the next morning. This was done using a SPECT-CT scanner. The scanner measures scattered gamma rays produced by the Y90 beta rays as they "decelerate" within the body. This helps confirm appropriate placement of microspheres within the liver and allows for early identification of potential complications.

All patients were discharged with appropriate analgesia (non-steroidal anti-inflammatory as required), a proton pump inhibitor to prevent gastrointestinal side effects, low-dose oral steroids to prevent fatigue and chronic liver injury, and ursodeoxycholic acid in an attempt to minimize the incidence of radioembolization-induced liver disease (REILD) defined as jaundice and ascites appearing 1 to 2 months after SIRT in the absence of tumor progression or bile duct occlusion [26].

Post-procedure

Patients were followed by their referring medical oncologist for biochemical testing, monitoring of complications, continuation of chemotherapy, and follow-up imaging [3–4 months post-radioembolization]. Follow-up imaging involved at least a restaging contrast-enhanced CT thorax, abdomen, and pelvis. This was used to categorize response to therapy although some patients also had MRI liver and/or 18F-fluoro-2-deoxy-D-glucose (18FDG) CT positron emission tomography (CT PET). Follow up in clinic by the interventional radiologist who performed the procedure was offered to all patients. Results from outside referring institutions were shared with our institution to evaluate procedural outcomes. This review involved a retrospective analysis of electronic medical records, including outpatient clinic letters, biochemical tests, imaging, and procedural reports. Referring oncologists from outside institutions were contacted for additional data when required. Follow-up imaging was assessed using RECIST criteria (version 1.1) [27].

Results

All 20 patients (100%) selected for angiographic workup were subsequently successfully treated with radioembolization. Six (30%) of patients were on first-line chemotherapy when referred for radioembolization. The remaining 14 (60%) were on salvage chemotherapy.

Patient demographics are summarized in Table 1.

Prior to SIRT therapy, one patient had a left hepatectomy. Two other patients had prior wedge resections of colorectal hepatic metastases, and one patient had main portal vein thrombosis. All patients had serum total bilirubin levels within normal parameters (< 20 μmol/L). Other tumor characteristics are summarized in Table 2. Patient systemic therapies are summarized in Table3.

The mean ± SD pulmonary shunt was 5.5 ± 1.9% [range 2.8–8.6] on initial planning angiogram. No patient required a dose reduction because of a lung shunt percentage of more than 10%. All 20 patients had their entire liver treated at a single session. The mean ± SD tumor volume percentage of total liver volume was 23.9 ± 18.8% (range 3–73%).

Eighteen (90%) of patients had vessels prophylactically embolized at planning angiography. This included the right gastric artery ($N = 12$), the gastroduodenal artery ($N = 9$), small accessory branches to segment IV ($N = 4$), supraduodenal branches ($N = 4$), small branches of a gastrohepatic trunk to the peri-esophageal region ($N = 3$), the falciform artery ($N = 2$), and the cystic artery ($N = 1$).

Mean ± SD implanted dose to the right lobe was 1.33 ± 0.28 GBq. Mean ± SD implanted dose to the left lobe was 0.52 ± 0.13 GBq. The mean ± SD implanted dose to the entire liver was 1.83 ± 0.36 GBq [range 1.21–2.61]. Three (15%) patients had a 20% dose reduction because tumor volume was less than 10% of total liver volume. The median length

Table 1 Patient demographics

Variable	Statistic	Total ($N = 20$)
Male	*N* (%)	14 (70%)
Female	*N* (%)	6 (30%)
Age	Mean (±SD)	61 ± 10.7
	Range	34–76 years of age
Eastern Cooperative Oncology Group Performance status (ECOG)	0/1	16/4

of time from SIRT to first follow-up imaging was 80 days (range 42–160).

Early complications [< 48 h]

Seven patients (35%) had mild abdominal pain in the 12 h following their procedure that responded to PRN diclofenac oral analgesia. Three (15%) had nausea that was relieved with a single injection of ondansetron 4 mg iv. There were no immediate National Institutes of Health (NIH) grade 3 complications, and all patients were discharged 1 day following their SIRT procedure.

Late complications [> 48 h]

No patients developed symptomatic gastric or duodenal ulcerations, and there were no cases of pancreatitis. Four patients (20%) developed neutropenia within 30 day of SIRT therapy. All four of these patients were on concomitant FOLFOX chemotherapy. No patients developed radioembolization-induced liver disease (REILD). Thirty-day mortality was zero.

One patient (5%) suffered from a chest port-site infection 3 weeks following the procedure. He was not neutropenic and so the infection was deemed likely related to port-site access. The same patient developed cholecystitis 3 months post-SIRT therapy requiring a cholecystectomy. This patient had gallstones and so the etiology of the cholecystitis is unclear. One patient was admitted with confusion 12 days post-SIRT. This was thought to be unrelated to SIRT and responded to a change in medications. There were no other late [> 48 h] NIH grade 3 complications recorded.

Outcomes

Mean follow up was 13 months (range 6–26). At time of last follow up, 14 (70%) patients were alive and 6 (30%) deceased. Of the 6 deceased, all died from diffuse progressive disease. Four had extrahepatic metastases (two with peritoneal lymph nodes and two with peritoneal lymph nodes and lung metastases) at the time of SIRT.

Hepatic response

At initial imaging evaluation, 12 patients (60%) had a partial response in their liver, 2 (10%) had stable disease, and 6 (30%) had liver-specific progressive disease. Table 4 demonstrates a local disease control rate (partial response + stable disease) of 70%. Table 5 demonstrates response rates for different tumor sub-types.

At most recent follow up, two patients (10%) had a complete response, seven (35%) had a partial response, two (10%) had stable disease, and nine (45%) had progressive disease within their liver (Table 5).

Overall response

Overall partial response was seen in nine patients (45%), stable disease in two (10%), and nine (45%) had overall progressive disease. Three patients (15%) had extrahepatic progressive disease on initial follow-up staging CT despite having a partial response within their liver. Five out of 8 (63%) patients with extrahepatic metastases at the time of SIRT had progressive disease at initial follow-up staging CT. This compares to 4 out of 12 (33%) patients without extrahepatic metastases at SIRT.

At most recent follow-up, overall complete response was seen in 2 patients (10%), partial response in 3 patients (15%), 2 (10%) had stable disease, and 13 had overall progressive

Table 2 Tumor characteristics

	Statistic	Total ($N = 20$)
Primary tumor		
Right-sided colorectal primary	*N* (%)	5(25%)
Left-sided colorectal primary	*N* (%)	15(75%)
Primary in situ at time of SIRT	*N* (%)	12(60%)
Metastases		
Bilobar liver metastases	*N* (%)	20(100%)
Isolated liver metastases	*N* (%)	12(60%)
Liver and extrahepatic metastases	*N* (%)	8(40%)

Table 3 Previous chemotherapy/biological agents

	Statistic	Total ($N = 20$)
Chemotherapy		
Previous FOLFOX	*N* (%)	14 (70%)
Current FOLFOX	*N* (%)	5 (25%)
Previous FOLFIRI	*N* (%)	9 (45%)
Current FOLFIRI	*N* (%)	2 (10%)
Previous biologicals		
Bevacizumab	*N* (%)	5 (25%)
Cetuximab or panitumumab	*N* (%)	8 (40%)

Table 4 Initial post-SIRT imaging response [RECIST criteria]

	Partial	Stable	Progressive
Hepatic response—overall ($n = 20$)	12/20	2/20	6/20
Hepatic response—1st line ($n = 6$)	5/6	1/6	0/6
Hepatic response—salvage ($n = 14$)	7/14	1/14	6/14

disease. Therefore, four patients (20%) had a hepatic response to therapy but had progressed outside their liver.

One of the patients with a complete response on most recent imaging was a 51-year-old male with moderately differentiated sigmoid colon adenocarcinoma (KRAS wild type). Initial imaging (Fig. 2) including CT PET and liver MRI demonstrated more than 15 metabolically active small liver metastases with lesions in both lobes of the liver. The patient was treated with SIRT and FOLFOX chemotherapy followed by maintenance 5FU and leucovorin. CT PET and MRI liver 11 months post-SIRT demonstrated no residual liver metastases, but the primary sigmoid cancer was increasingly metabolically active on PET. After further MDM, the primary sigmoid cancer was resected 12 months post-SIRT. Six months after this surgery, there was no evidence of recurrent or metastatic disease on imaging and the patient is doing well on a chemotherapy holiday on last follow up.

The other patient with a complete response on most recent imaging (Fig. 3) is a 62-year-old male who had a T3N1 sigmoid cancer (KRAS wild type) resected. Subsequent MRI and CT PET demonstrated multiple bilobar hepatic metastases deemed unresectable at MDM. Again, decision was made to proceed with SIRT and FOLFOX chemotherapy. Five months later, MRI demonstrated a solitary 12 mm subcapsular segment IV hepatic lesion. The patient proceeded to planned laparoscopic liver wedge resection; however, no metastases were evident 4 weeks later at surgery despite focused laparoscopic ultrasound. Latest CT PET demonstrates no residual disease.

Discussion

SIRT is a targeted treatment, whereby a tumoricidal dose of radiation is directly delivered to the liver tumor site via selective hepatic arterial administration. SIR-Spheres® yttrium 90 resin microspheres is a form of SIRT that is approved as a medical device (CE marked). Unlike other transarterial therapies such as chemoembolization, the aim is not to induce ischemic necrosis but rather function as a form of intrahepatic brachytherapy. SIR-Spheres Y-90 resin microspheres are designed to be 20–60 μm in diameter and are labeled with yttrium-90, a high-energy beta emitter with no primary gamma emission. The microspheres pass through the arteries and become preferentially lodged in the smallest blood vessels of the tumor where they release radiation to surrounding tissue. The lower size limit prevents microspheres from passing through the tumor vasculature and into the venous circulation. The biocompatible microspheres are non-biodegradable and remain permanently implanted.

External beam radiation therapy is challenged by the sensitivity of normal liver to radiation. The dose to treat a liver tumor is estimated at 70 Gy, while the liver tolerance dose is 20–35 Gy [28–30]. Due to the hepatic artery-dominant blood supply of CRC liver metastases, the Yttrium-90 microspheres preferentially flow to the tumors. Pathological studies have confirmed the distribution of the microspheres [16]. This technique helps to overcome the radiosensitivity of the liver parenchyma, maximizing tumor coverage while minimizing radiation exposure to healthy liver parenchyma and avoiding exposure of non-tumor sites to potentially harmful radiation. Selective intra-arterial delivery enables doses over 120 Gy to target the tumor without reaching the liver toxicity threshold. As the half-life of Yttrium-90 is 64.8 h, the particles are radioactive for a period of about 14 days but most of the radioactivity is delivered over 5 days.

There are three main contraindications to SIRT prior to angiographic assessment. These are a poor performance status (ECOG > 0–1), a rising serum bilirubin or ascites, and significant extrahepatic disease not responding to therapy [31]. All patients in this case series were discussed at MDM in their referring institution or the institution performing the procedure, and all were seen in an outpatient setting by the Interventional Radiologist performing the procedure. Patient selection process was therefore appropriate and consistent with international standards of best practice [32].

Table 5 Initial post-SIRT imaging response [RECIST criteria]

	Partial	Stable	Progressive
Hepatic response—overall ($n = 20$)	12/20	2/20	6/20
Hepatic response—right-sided tumors ($n = 8$)	4/8	2/8	2/8
Hepatic response—left sided tumors ($n = 12$)	8/12	0/12	4/12
Hepatic response—KRAS mutant ($n = 9$)	4/9	1/9	4/9
Hepatic response—KRAS wild type ($n = 11$)	8/11	1/11	2/11

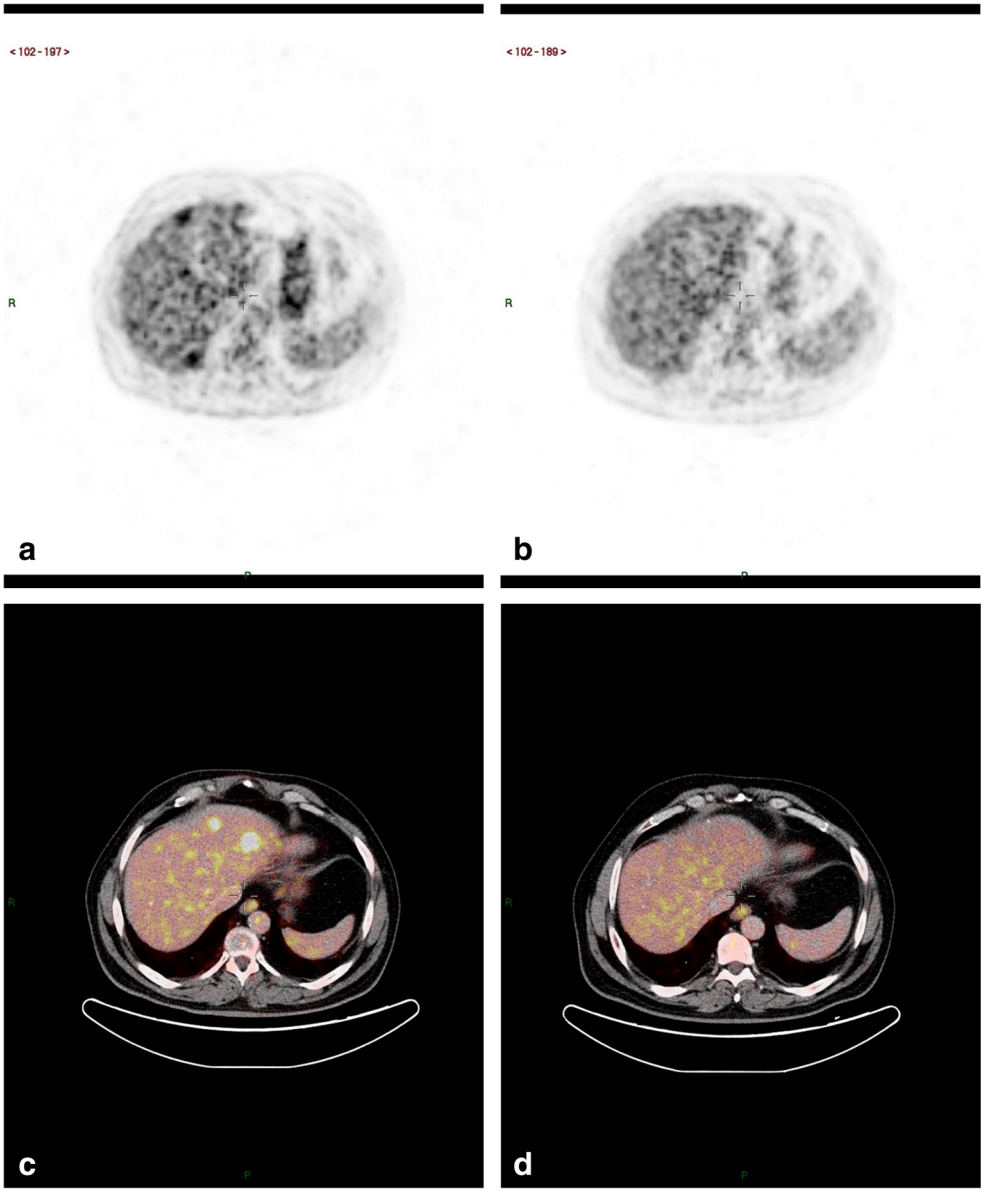

Fig. 2 Fifty-one-year-old male with sigmoid colon adenocarcinoma. Pre-SIRT and chemotherapy PET (**a**) and CT PET fusion (**c**) images at different axial levels demonstrate metabolically active bilobar unresectable colorectal liver metastases. PET (**b**) and CT PET fusion (**d**) images 21 months post-SIRT demonstrate a complete response to treatment. Only normal background FDG uptake in the liver is present in **b** and **d**. This patient had potentially curative resection of his primary sigmoid tumor 16 months post-SIRT

There are two further main contraindications for treatment after planning angiography. These are a lung shunt fraction of the administered technetium of more than 20% or extrahepatic uptake of radionucleotide on SPECT CT due to hepatofugal or retrograde flow. The latter can be avoided with meticulous angiography ± prophylactic embolization of the potentially offending vessels. Eighteen (90%) of patients had prophylactic embolization of arteries at planning angiography. All patients who elected to go forward with a planning angiogram subsequently received the SIRT treatment. There were no immediate NIH grade 3 or severe (defined as a treatment-related adverse event requiring further therapy, increased level of care, or prolonged hospitalization) complications.

The radiation dose was calculated by the body surface area method rather than calculating an empiric dose as this is thought to carry higher rates of toxicity [33]. In patients treated with SIRT, REILD consists of a constellation of anicteric non-malignant ascites, hepatomegaly, and mild transaminitis in relationship to the bilirubin, which is markedly elevated. This occurs in the absence of hepatic metastatic progression or obstructive liver disease. Patients who have received chemotherapy prior to SIRT [34] or have abnormal liver function tests [33] are at higher risk for REILD. A transient elevation of liver function tests are considered as a normal toxicity of the treatment, and it is normal for geographical areas of change in liver parenchymal signal on post-SIRT MRI. REILD has been reported to occur in up to 4% of patients [33]. No patients in this case series developed REILD.

Gastric or duodenal ulceration have been reported in up to 5% of cases [22]. No patients in this study developed

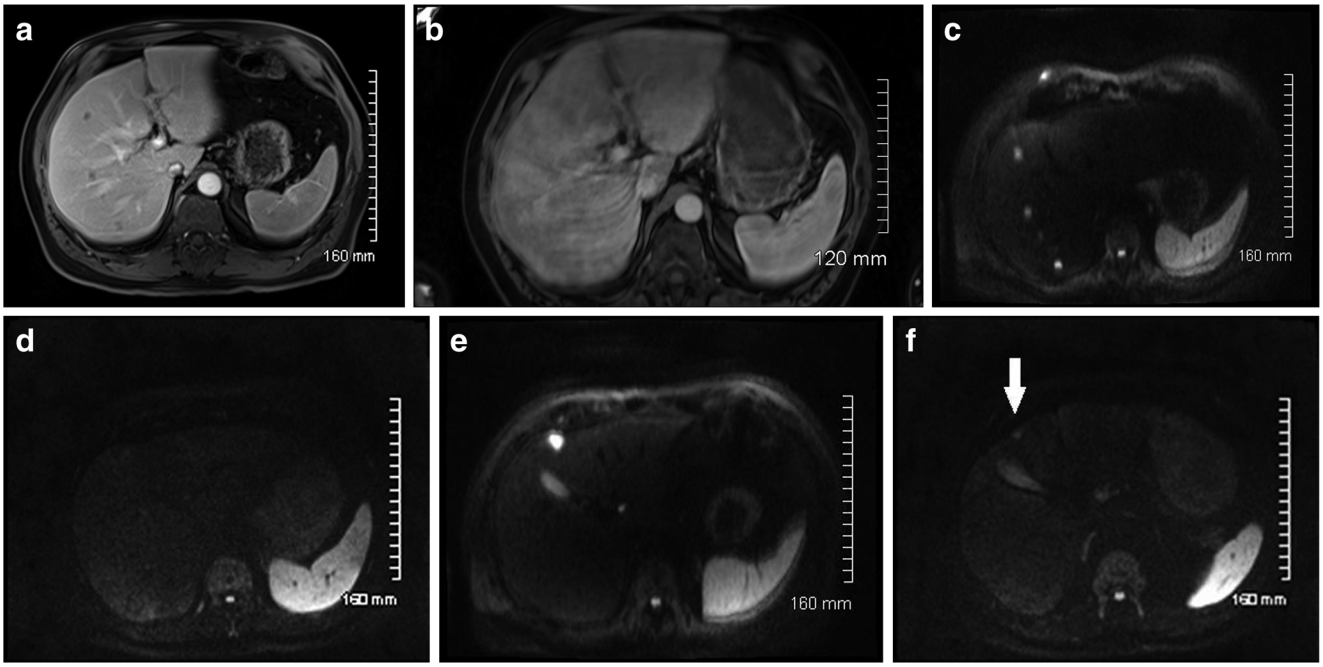

Fig. 3 Sixty-two-year-old male with sigmoid colon adenocarcinoma. Arterial phase contrast-enhanced MRI of the liver (**a**) pre-treatment demonstrates multiple small liver metastases. B800 diffusion imaging of the liver pre-treatment (**c**, **e**) demonstrate restricted diffusion (high signal) within the liver metastases. Arterial phase contrast-enhanced MRI of the liver (**b**) 3 months post-SIRT demonstrates resolution of liver metastases. There is a geographical pattern of liver parenchymal enhancement consistent with chemotherapy and radiation effect on normal liver. B800 diffusion imaging of the liver 3 months post-SIRT (**d**, **f**) demonstrate restricted diffusion (high signal) within the liver metastases has almost completely resolved. There was concern that one small focus of persistent subcapsular restricted diffusion (arrow) could represent viable tumor. Patient proceeded to planned laparoscopic wedge resection 5 months post-SIRT, but no residual tumor was evident at surgery

gastrointestinal ulceration or pancreatitis. One patient may have developed radiation-induced cholecystitis. The retrospective nature of this study limits evaluation for post-procedural pain, fever, nausea, or malaise, but no patients stayed more than 1 night in hospital or were readmitted for these symptoms in the weeks following SIRT. SIRT is a safe procedure with much less toxicity than chemoembolization [35, 36]. Overall complications in this study were within international accepted thresholds for standards of good practice [32]. The low morbidity associated with this procedure is an important consideration for these patients with metastatic cancer.

Beyond first-line, SIRT is a well-established therapy for CRC liver metastases. There are multiple prospective studies and retrospective analyses which show encouraging effects of SIR-Spheres Y-90 resin microspheres on time to progression (TTP), progression-free survival (PFS) (overall and liver), and overall survival (OS). This can be when added as consolidation of first-line chemotherapy (i.e., in patients deemed unresectable 12–26 weeks after first-line chemotherapy) [37], when combined with chemotherapy in patients who have already failed at least first-line chemotherapy [38, 39] and in heavily pre-treated patients who are chemorefractory and have failed standard of care [17, 18]. Several other single-arm studies of SIR-Spheres Y-90 resin microspheres as salvage therapy have demonstrated median survival of approximately 10–12 months [19, 40–42]. As such, the National Comprehensive Cancer Network (NCCN) guidelines (category 2A) in the USA and the European Society for Medical Oncology (ESMO) guidelines (IIB) recommend SIRT in the chemotherapy-refractory setting [43].

The role of SIRT and where it fits in the treatment algorithm in first-line therapy is less clear and is still being determined. Early small randomized controlled trials demonstrated efficacy of Y-90 resin microspheres when added to intrarterial chemotherapy [44] or intravenous fluorouracil and leucovorin [45] as first-line chemotherapy for patients with mCRC (with improved objective response rate [ORR] and TTP). One of these studies also showed a significantly increased OS with the addition of SIR-Spheres Y-90 resin microspheres to chemotherapy [45]. Later results such as the combined analysis of FOXFIRE, SIRFLOX, and FOXFIRE-global studies [46] comparing SIRT in first line in combination with FOLFOX chemotherapy to FOLFOX chemotherapy alone demonstrated an increase in liver-specific PFS but did not show an increased OS (primary end-point) or overall PFS in the SIRT arm. Therefore, the use of SIRT in combination with chemotherapy in unselected patients with metastatic colorectal cancer as first-line therapy cannot be recommended.

The location of the primary tumor is emerging as a major prognostic factor and predictor of response to treatment. Patients with right-sided colon tumors have an inferior

response to treatment, a worse prognosis [47] and fewer treatment options [48] compared with those with left-sided primary tumors. Intriguingly, further data presented from the SIRFLOX/FOXFIRE-global studies at the ESMO World Congress on Gastrointestinal Cancer [49] (WCGIC) and later confirmed in publication of subgroup analysis [46] demonstrated a statistically significant ($p < 0.007$) and clinically meaningful (Hazard Ratio 0.64) improved OS for patients with right-sided colon tumors treated with SIRT and FOLFOX chemotherapy in first line compared to FOLFOX alone.

In this study, 4 out of 9 patients (44%) with a KRAS mutation had an initial partial response in their liver (Table 5) compared to 8 out of 11 (73%) without a KRAS mutation. Both patients with a complete response on latest imaging had no KRAS mutation. To our knowledge, no study has examined if patients with different molecular profiles respond differently to SIRT. It is possible that the molecular genetics and the side of the original tumor can alter the radiosensitivity of these tumors. Further studies are required to help elucidate answers to these questions.

One patient in this study was downstaged to hepatic resection, and one patient with a complete response in his liver had his primary colon lesion removed surgically. Further analysis of the SIRFLOX trial suggests the addition of SIRT to FOLFOX(±bevacizumab)-based chemotherapy significantly increased the gain in surgical resectability of primarily unresectable CRC liver metastases compared with chemotherapy alone in first-line treatment [50]. Prior studies have demonstrated the morbidity and mortality associated with hepatic resection in patients after SIRT are similar to those that have not received SIRT [51]. The role of SIRT as consolidation therapy if first-line chemotherapy fails to downstage to hepatic resectability is another area that requires further investigation.

The small numbers of patients in this study, its retrospective design and the heterogeneity of patients in terms of tumor location, presence of extrahepatic metastases, molecular genetics, and prior courses of chemotherapy make it difficult to draw definitive conclusions. The rational for treating patients with extrahepatic metastases is that it is thought that many patients with hepatic dominant liver metastases ultimately are more at risk of dying of liver failure rather than their extrahepatic disease [52]. There was a trend in this study towards improved response in patients with no extrahepatic metastases. Toxicity and morbidity were low across the patient cohort. Importantly, two patients (10%) initially diagnosed with unresectable CRC liver metastases have had a radiological complete response sustained at 18 and 8 months after their SIRT.

This study, our experience and the published literature informs the authors opinion that selected patients should be offered SIRT in concert with their Medical Oncologist, concomitant with their chemotherapy. Furthermore, ESMO guidelines [43] recommend its consideration in the salvage setting. SIRT has cost-effectiveness data in the salvage setting [53, 54] demonstrating a cost of less than 30,000 Euro per quality life year (QALY); however, as the agents used for SIRT are classified as a medical device and not a pharmaceutical, funding or reimbursement difficulties can be encountered. As the landscape of anti-cancer therapies evolves, mechanisms that allow fair cost-effectiveness assessment of novel therapies such as SIRT are required in all modern health systems, including Ireland.

In conclusion, this case series demonstrated safety and efficacy of SIRT for patients with unresectable colorectal liver metastases. It supports the published literature that SIRT has the potential for tumor shrinkage and down-staging with little associated morbidity. This study adds to the knowledge base and supports the evidence that modern healthcare systems should offer this therapy as part of the armamentarium against metastatic colon cancer. Further studies are required to better stratify which patients with unresectable CRC liver metastases will benefit most from SIRT.

Compliance with ethical standards

All procedures performed in studies involving human participants were 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.

All patients consented to their procedures.

For this type of study, formal (research participation) consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

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