Successful Right Hepatectomy After Four Treatments of Yttrium-90 Microspheres (SIR-Spheres®) and Concomitant FOLFOX as Bridging Therapy to Resection of Colorectal Liver Metastases

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Abstract. *The use of yttrium-90 microspheres is a novel interventional radiological procedure that has delivered promising results in the treatment of liver cancer. Multiple treatments in combination with systemic chemotherapy may be realised as an effective modality for unresectable colorectal liver metastases. This case study reports the first case of a patient who had a complete response of 7 out of 10 liver metastases following multiple doses of yttrium-90 microsphere therapy, who then underwent a curative hepatic resection. This case demonstrates the feasibility and potential use of this management strategy to expand the role of successful therapies that will bridge the road towards curative liver resection.*

Selective internal radiation treatment (SIRT) using yttrium-90 microspheres (SIR-Spheres®, Sirtex Medical Limited, Australia) is a promising new modality in the treatment of patients with hepatic colorectal cancer metastases. Recent data suggest that combining SIRT with systemic chemotherapy (chemo-SIRT) may improve response rates in patients with unresectable colorectal liver metastases (1, 2). The incorporation of radiation therapy has traditionally not been considered a viable neoadjuvant therapy modality because of the unacceptably high incidences of hepato-toxicity. However, the efficacy of chemo-SIRT may lead to a change in management paradigm. This case report describes the clinical course of a patient treated using the strategy of neoadjuvant chemo-SIRT for unresectable colorectal liver metastases.

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Brief Report

A fit and healthy 54-year-old gentleman complained of intermittent rectal bleeding with a sensation of a bulge in the rectum, and sought medical attention. Diagnostic work-up revealed a rectal tumour, with staging scans showing extensive involvement of the liver with at least 10 liver metastases each of about two to three centimetres in size. He underwent an anterior resection, total meso-rectal excision and formation of an ileostomy at a district hospital. Following resection, he was referred to the hepatobiliary service of St. George Hospital, Sydney, where the liver lesions were further characterized using computed tomography angiogram and positron-emission tomography (PET) scan. It was apparent that there was bilobar disease but without extrahepatic disease. The extent of liver involvement rendered a liver resection infeasible. Hence, the multidisciplinary medical team decided to pursue neoadjuvant systemic chemotherapy, with a view to resection using the modified FOLFOX 6 protocol (3).

After three cycles of chemotherapy, the patient developed a partial response of the liver lesions with more than 50% reduction of his carcinoembryonic antigen (CEA). He continued on chemotherapy; however, after completing the fifth cycle, there was a marginal elevation of CEA from 3.4 to 3.9. A PET scan was performed again which showed more than 12 lesions. He continued with chemotherapy, but in view of the rising CEA, and that resection was still not an option, other local therapy was required. The patient underwent yttrium-90 microsphere treatment with the dose divided into two amounts: 10% was delivered to the to the left and 90% to the right lobe of the liver. Response of the tumours to microsphere treatment was good and the patient went on to have three further treatments. At the completion of 12 cycles of FOLFOX-based chemotherapy and four treatments of microspheres, his bilirubin was level 28, albumin was 27, aspartate transaminase was 120, alanine transaminase 283, alkaline phosphatase was 182 and gamma glutamyl transpeptidase was 181. At this stage, response to both

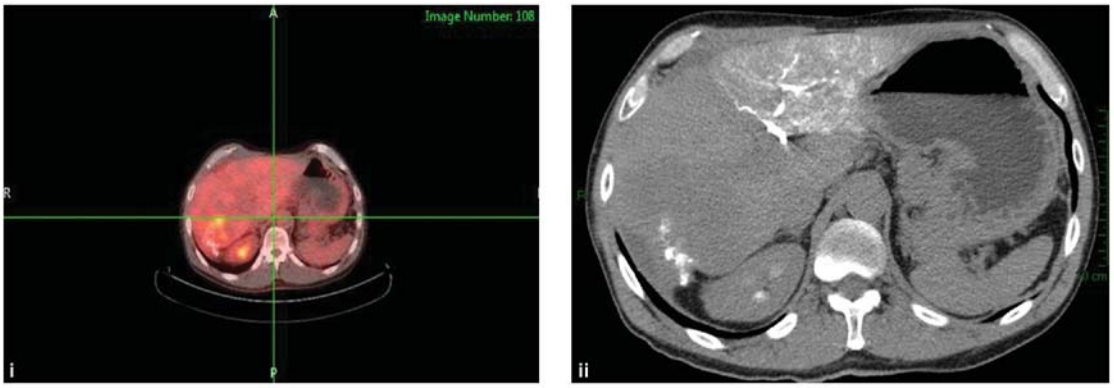

Figure 1. *Imaging after four treatments of yttrium-90 microspheres and 12 cycles of FOLFOX-6. (i) PET scan imaging; (ii) CT angiogram.*

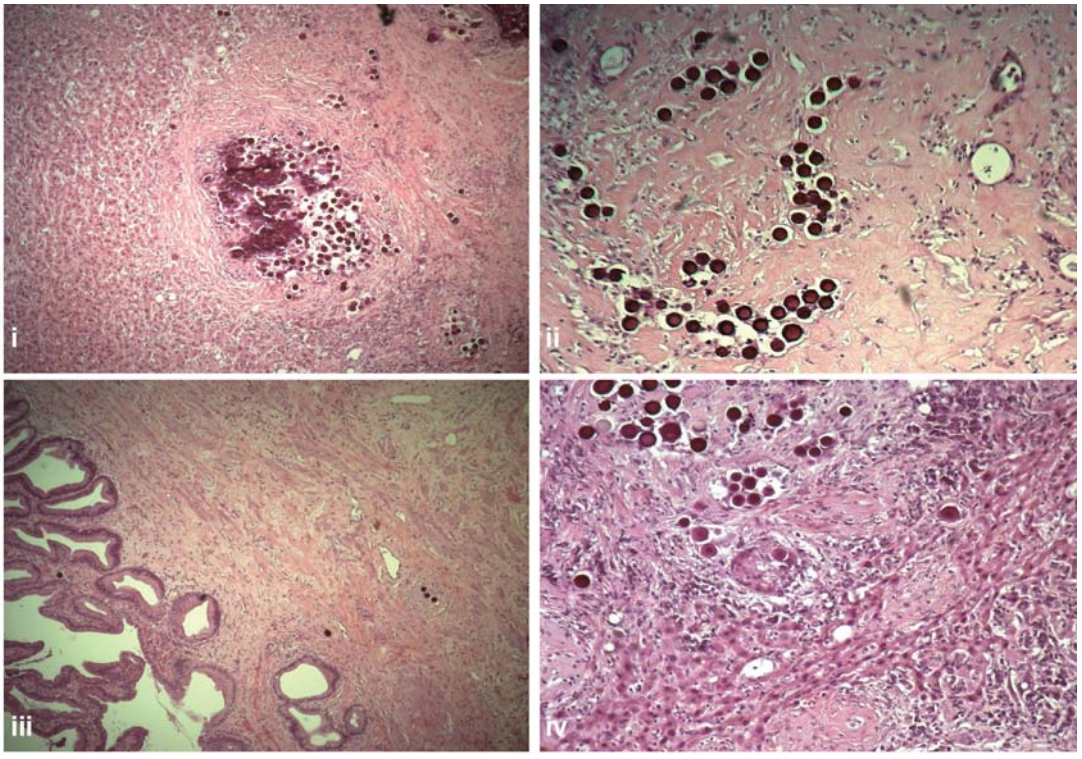

Figure 2. *Histopathology of resected liver metastases. (i) Granulomatous reaction to microspheres in a region with normal appearing hepatic architecture. (ii) Fibronecrotic reaction to microspheres with prominent tumour necrosis associated with fibrosis and calcification. (iii) Microsphere present within the gall bladder evoking a histiocytic reaction. (iv) Metastatic adenocarcinoma adjacent to an area containing microspheres.*

yttrium-90 microspheres and FOLFOX chemotherapy appeared to be good. PET scan revealed tumours present only in the right lobe (Figure 1). A decision was made at this stage for resection, and a portal vein embolization was performed to induce hypertrophy of the left lobe. An indocyanine green test demonstrated adequate functional reserve for a right hepatectomy. At surgery, many adhesions were found. Intraoperative ultrasound showed multiple tumours present within the atrophic right lobe and one area of scarring in the edge of segment three. The liver was mobilised through which necessitated a partial diaphragm resection. Cholecystectomy, and right hepatectomy were performed with cryoablation of a segment three lesion. A total clamp time of 22 minutes was applied in three applications.

Histopathological examination of the right lobe of the liver showed viable tumour present with fibronecrotic reaction to the microspheres (Figure 2). There were multiple deposits of metastatic adenocarcinoma consistent with the rectal primary

present in the right lobe of the liver. Numerous microspheres were present in the liver, with tumour necrosis and associated fibrosis and calcification present where the microspheres were located. In the non-involved area, the microspheres induced a foreign body giant cell reaction, with numerous mononuclear histiocytic reaction containing granular debris and portal fibrosis.

Postoperatively, the patient was transferred to the surgical intensive care unit for a day before being moved to the surgical ward. His postoperative recovery was uneventful and he was discharged postoperatively on day eight.

Discussion

This case report demonstrates that chemo-SIRT, in particular with multiple SIRT treatments to may be feasible as part of a multimodality treatment approach for patients with unresectable colorectal liver metastases. To the Authors' knowledge, this is the first reported case where multiple treatments with SIRT were performed in combination with systemic chemotherapy.

The targeted delivery of radiation treatment *via* the hepatic artery through SIRT allows a preferential distribution of microspheres to regions of higher blood flow which correlate to areas with increased vascularity due to tumour angiogenesis. Hence, a high radiation concentration in tumour compartments is achieved. The efficacy of this treatment in combination with FOLFOX chemotherapy changed the treatment aims for this patient from that of a palliative intent to being able to undergo curative liver surgery. Without doubt, the largest obstacle for such a patient would have been the ability to preserve adequate functional remnant liver volume given the numerous SIRT treatments. The patient's Child-Pugh score (4) was B. Preoperative portal vein embolization and indocyanine green test were performed.

Radiation damage to the liver from external beam radiotherapy involves the central vein. This causes clinical veno-occlusive disease with signs of cirrhosis, portal hypertension, ascites, and deterioration in liver function (5). Hepatocellular damage from radiation injury through SIRT is less pronounced and may further be kept at a minimum through dosimetric modification according to a patient's liver function. However, in the context of multiple treatments, the likelihood of radiation damage is invariably increased. As shown in the histopathology of the patient's liver (Figure 2(i)), associated hepatic injury included evidence of chronic inflammatory infiltrate, and fibrosis of the portal triads.

Patients with unresectable colorectal liver metastases have been reported, prior to the advent of modern agent systemic chemotherapy, to have an overall median survival of 7 months (6). The role of FOLFOX with or without targeted molecular therapies such as bevacizumab and cetuximab has dramatically improved median survival to approximately 20 months (7, 8). Given that hepatic resection is the only curative option in patients with colorectal liver metastases (9), bridging therapies that can downstage liver metastases to allow a complete resection are paramount to the success of managing this disease entity. Chemo-SIRT has shown promise, and this case report demonstrates that extensive liver metastases may be down-staged adequately such that a complete cytoreduction may be undertaken which may involve multiple treatment of SIRT and chemotherapy.

In a phase I trial by Sharma *et al*. (1), of 20 patients treated, partial responses were demonstrated in 18 (92%), amongst which, only two patients were adequately down-staged and underwent a partial hepatectomy. Multiple SIRT treatments may prove useful should a strategy of chemo-SIRT be employed as neoadjuvant therapy for unresectable colorectal liver metastases. Future trials investigating the role of chemo-SIRT should consider administering multiple SIRT treatments and incorporating an endpoint of adequate down-staging that allows a curative hepatectomy.

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