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Radiation segmentectomy using Yttrium-90 labelled resin microspheres in a case of relapsing colorectal liver metastasis after previous microwave ablation

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A 70-year-old male underwent routine oncologic follow-up at our out-patient clinic because of a history of colorectal cancer (CRC) with synchronous liver metastasis in segment 2. Patient had received neoadjuvant external beam radiation therapy (5x5 Gy) followed by laparoscopic low-anterior resection and resection of liver segments 2 and 3. Additionally, a metastasis in segment 7 was treated using microwave ablation. Two years later a metastasis was revealed at the same site of segment 7 (carcinoembryonic antigen, CEA 6.9 µg/L), and due to close relation with the diaphragm selective internal radiation therapy (SIRT) was chosen as treatment as a form of radiation segmentectomy (RS). Six months after SIRT, the patient remained in good clinical condition. His CEA had decreased to 3.6 µg/L. and MRI of the liver showed no signs of relapse at the treated site, nor new lesions in other parts of the liver.

Introduction

Only in recent years has RS been used as a neoadjuvant therapy concomitant with chemotherapy and monoclonal antibody therapy. Studies done with SIRT as a form of radiation segmentectomy on patients with mCRC are scarce due to this novelty. Preliminary studies regarding RS show that the procedure is safe and efficacious with minimal exposure to healthy liver parenchyma. Our case study demonstrates that RS is capable of complete tumour necrosis, even in the case of recurrent mCRC after previous microwave ablation, with no other suitable local treatment available.

Case

This case details a patient with relapsing colorectal liver metastasis after previous microwave ablation, who achieved complete response after treatment with Yttrium-90 resin microspheres.

A 70-year-old male underwent routine oncologic follow-up at our out-patient clinic because of a history of colorectal cancer (CRC) with synchronous liver metastasis in segment 2. Four years before, the patient underwent neoadjuvant external beam radiation therapy (5x5 Gy) at the site of the primary tumour, with subsequent laparoscopic low-anterior resection and resection of liver segments 2 and 3. Histology confirmed complete resection of both well-differentiated intestinal type adenocarcinoma (5.7 cm diameter) and the liver metastasis. The tumour was staged as pT3N0M1 due to evidence for invasion of the resected primary tumour into the pericolic fat and venous structures, but lacking lymph node metastases. Two years after the initial treatment, a liver metastasis in segment 7 was treated using microwave ablation, complicated by a subcapsular hematoma.

At routine oncologic follow-up, the patient was in good clinical condition and free from any complaints. Due to an increase of carcinoembryonic antigen (CEA) from 3.5 to 6.9 µg/L. the patient was referred for a fluorine-18 labelled fluorodeoxyglucose (^{18}F-FDG) PET/CT scan (Figure 1). This PET/CT revealed intense FDG accumulation at the mediodorsal edge of the ablation site in liver segment 7, suggesting relapse of the liver metastasis. Because of the close relation of the metastasis with the diaphragm, percutaneous re-ablation was considered unsuitable. Therefore, this patient was scheduled for selective internal radiation therapy (SIRT) to reduce tumour burden. Additional laboratory findings were: alkaline phosphatase 108 U/L, gamma-GT 100 U/L, alanine transaminase 24 U/L, aspartate transaminase 28 U/L, bilirubin (total) 10 µmol/L, albumin 49 g/L, prothrombin time 11.5 seconds.

Pre-therapy evaluation using Technetium-99m labelled macro-aggregated albumin (^{99m}Tc-MAA) SPECT revealed good targeting of the relapsing liver metastasis (Figure 2A). In addition, there was no significant extra-hepatic ^{99m}Tc-MAA accumulation, and pulmonary shunting was limited to 6.9 percent. The volume of segment 7 was approximately 167 mL. The remaining part of the right liver lobe was 1685 mL. The volume of the remainder of the left

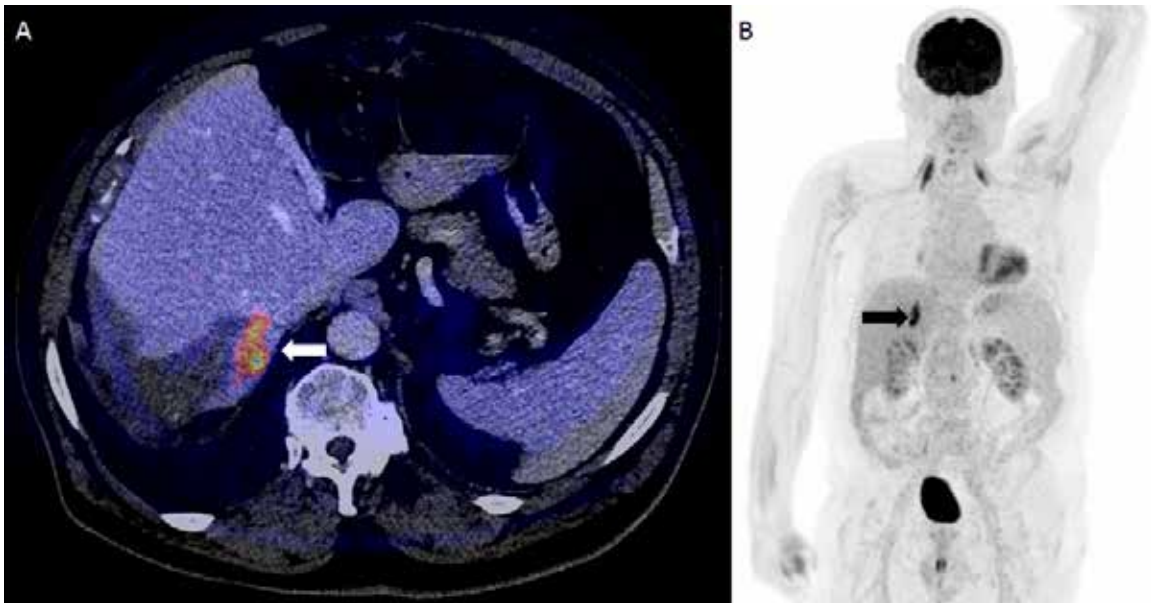

Figure 1. Transversal (left panel) and maximum intensity projection (right) of ^{18}F-FDG PET/CT. Arrows indicate the relapsing liver metastasis in segment 7, along the border of the ablation site.

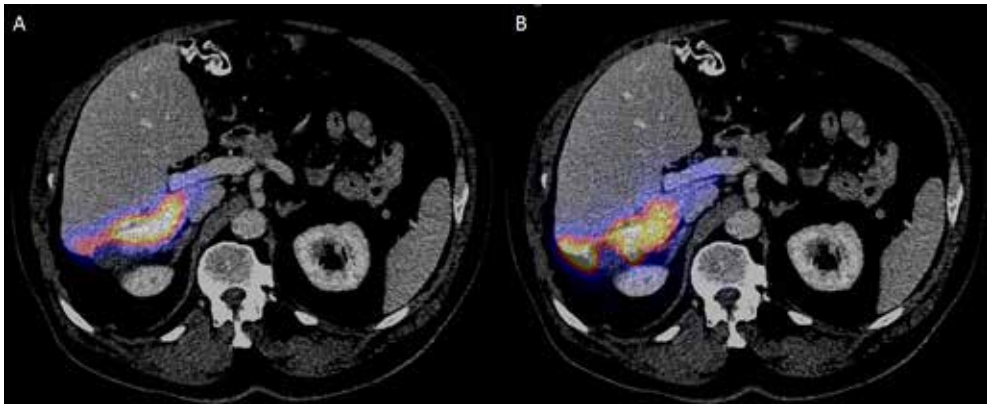

Figure 2. Transversal slices of pre-therapy ^{99m}Tc-MAA SPECT (A) and ^{90}Y post-therapy PET (B) images superimposed on the contrast enhanced CT scan. Close correlation of the distribution of MAA and resin microspheres.

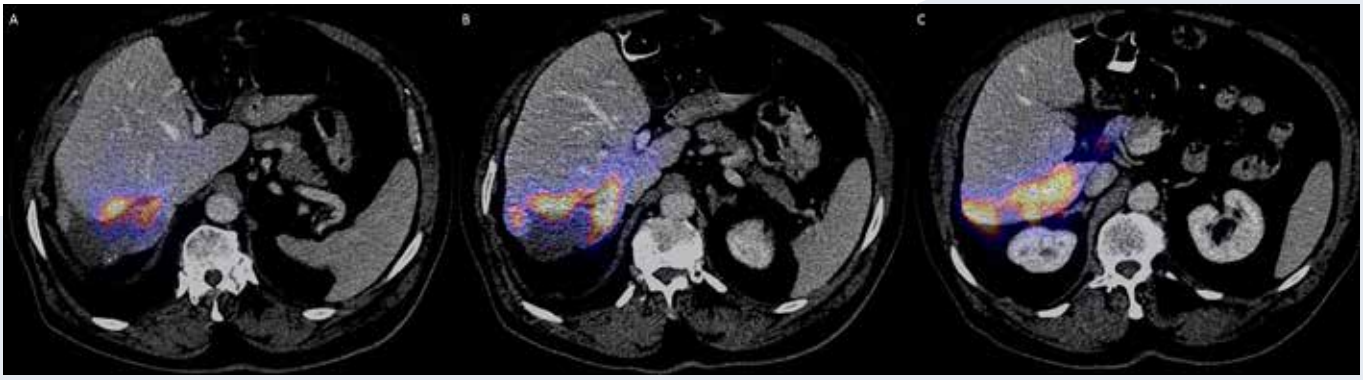

Figure 3. Different transversal slices of ^{90}Y post-therapy PET scan, from left to right in cranio-caudal direction through segment 7 of the liver.

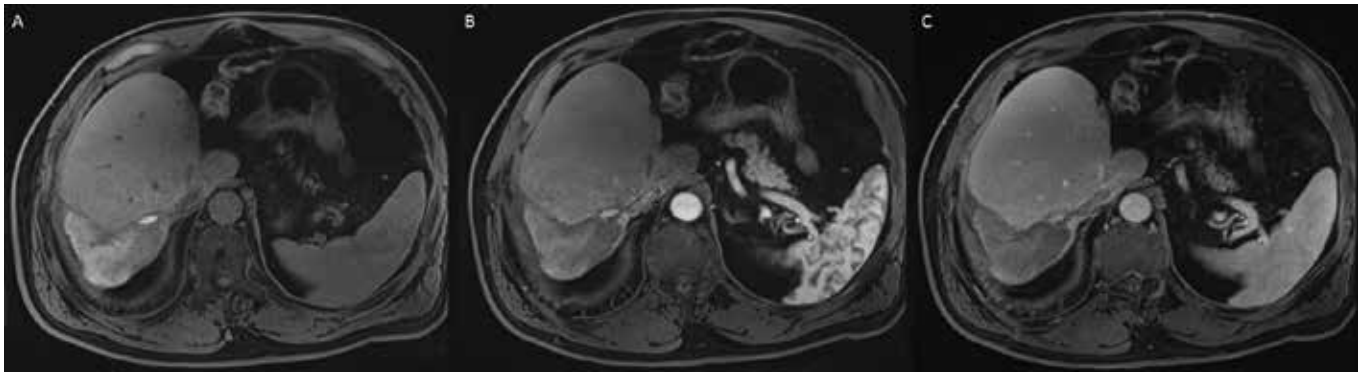

Figure 4. Transversal slice of MRI 6 months post-SIRT. Pre-contrast image (A) showing hyper-intense signal at the treatment site, and no new lesion on post-contrast series (B arterial phase, C portal-venous phase).

liver, consisting of segments 4A and 4B, was 150 mL. The treatment dose of Yttrium-90 (Y-90) resin microspheres (SIR-Spheres®, SIRTeX) to be delivered (A) was calculated by using: A (GBq) = [Desired Dose (Gy) x Liver Mass (kg)] / 50 (Gy kg GBq^{-1}). With a desired dose of 300 Gy at the site of the tumour, the activity was calculated to be: A = 300 x (0.167 L x 1.03 g/L) / 50 = 1.03 GBq of resin microspheres. The treatment dose was delivered through a super-selectively positioned microcatheter in the posterior branch of the right hepatic artery, in a slow and fractionated manner, resulting in saturation of the entire treated segment on post-therapy PET (Figure 2B and 3). The treatment was well tolerated, without clinical toxicity. The patient was discharged the day after the treatment.

Six months after SIRT, the patient remained in good clinical condition. His CEA had decreased to 3.6 µg/L. and MRI of the liver showed hyper-intense signals on pre-contrast series, indicating haemoglobin or protein rich content (Figure 4). There were neither signs of relapse at the treated site, nor new lesions in other parts of the liver.

Discussion

CRC is the third most common cancer with 50-60% of the patients developing liver metastases during the course of the disease (1). One study of 1325 patients with CRC reported that 8% developed metastases after resection of their primary tumour, as is the case with our patient (2). The recurrent nature of liver metastases remains a life-limiting factor for the majority of patients.

For these recurring metastases, loco-regional treatment such as SIRT can offer an additional way to achieve tumour necrosis, when systemic treatment, surgical resection or additional ablation is not an option.

SIRT is a form of internal radiation therapy where Y-90 labelled microspheres are injected into the hepatic artery to selectively target tumour cells while surrounding healthy liver tissue is left mostly unharmed. This is made possible because of the predominantly arterial blood supply of tumour sites, together with the dense microvasculature that is created by tumour-induced neovascularization.

Y-90 is a pure beta-emitter with a half-life of 2.67 days (64.2 h), decaying to stable Zirconium-90. The mean tissue penetration of Y-90 beta-radiation is 2.5 mm with a maximum range of 11 mm. The microspheres preferentially lodge in the neovascular rim of the tumour(s) and deliver tumouricidal doses of radiation (3). SIRT is suitable for those lesions that are hard to reach by CT-guided ablation, that are close to vascular structures or the diaphragm, or in heavily pre-treated patients.

Radiation segmentectomy (RS) is defined as the trans arterial lobar infusion of Y-90 labelled microspheres with the intention of segmental tissue ablation. This technique may induce growth in the contralateral, non-infused hepatic lobe, with the concomitant advantage of reducing or controlling size of the tumour (4). RS can act as a bridge to liver transplantation, or enable liver resection when there is insufficient future liver remnant (FLR).

An established neoadjuvant procedure designed to increase FLR is portal vein embolization (PVE). The PVE-procedure enables lobar hypertrophy by an acute redirection of portal blood flow by administration of embolic agents to the portal supply of the diseased liver lobe. RS might proof to be an alternative to PVE as it provides hepatic tumour control and the presence of a partial or complete necrotic tumour may potentially result in a lowered risk of dissemination during surgical manipulation. Noted is that the induced contralateral hypertrophy by RS is often substantial enough to enable surgical resection (5).

In the recent decade RS is used as a neoadjuvant therapy concomitant with chemotherapy (FOLFOX, FOLFIRI) and monoclonal antibody therapy (e.g. bevacizumab, cetuximab) (6). Studies done with SIRT as a form of radiation segmentectomy on patients with mCRC are scarce, as the technique was first described in 2011 (7). This landmark study of 84 patients receiving RS showed

that the procedure is safe and efficacious with minimal exposure to healthy liver parenchyma, although only patients with primary HCC were included.
A preliminary study with thirteen patients with unresectable liver tumours included one case of mCRC that showed sufficient contralateral hypertrophy enabling surgical resection (8). Another retrospective study of 83 cases detailed 7 patients undergoing RS because of mCRC, with two of those patients suffering from recurrent liver metastases following previous resection. One right-lobe mCRC patient displayed dramatic hypertrophy of segments 2/3, making the patient eligible for surgical re-resection. At three years follow-up, this patient is free of liver disease (9).
Four cases presented by Shah et al. included one patient that displayed complete pathological response without needing surgery at three-month follow-up (10). Another case study brought forward a patient who underwent RS while having unresectable and chemotherapy refractory tumours. After RS, serum CEA levels had decreased to 35.4 ng/mL (before second ^{90}Y-treatment: 295.1 ng/mL) showing partial response of the mCRC (11).
The patient in this case report experienced no side effects from the RS-treatment with ^{90}Y microspheres. According to the literature, RS is generally well tolerated although pain and nausea are common post-RS (12). In patients with mCRC, background liver parenchyma is usually free of underlying disease, therefore liver dysfunction is rare in post-SIRT mCRC patients, unless most of the liver is replaced by tumour. With promising early results and evidence that RS can be a truly ablative technique, it is becoming part of standard practice at centres offering SIRT (12). These reports show that although RS is feasible in patients with mCRC, no prospective or larger comparative trials have been performed using Y-90 labelled microspheres.
The patient in our case study demonstrates that RS is capable of complete tumour necrosis, even in the case of recurrent mCRC after previous microwave ablation, with no other suitable local treatment available.

Conclusions

Radiation segmentectomy with Y-90 labelled resin microspheres in case of relapsing colorectal liver metastasis after previous microwave ablation is feasible, well tolerated, and can result in good clinical outcome.

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