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Radiofrequency ablation after selective internal radiation therapy with Yttrium90 microspheres in metastatic liver disease—Is it feasible?

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ABSTRACT

This retrospective study analyzes, whether patients suffering from extensive hepatic metastatic disease treated with SIRT can become suitable candidates for RFA.Within 38 months 46 patients (26 female, 20 male; age 32–75 years) bearing an extensive hepatic metastatic disease were treated with SIRT. Patients suffered from metastases of breast cancer (16/46), colorectal cancer (CRC) (21/46), neuroendocrine (3/46), and other primary carcinomas (6/46). The indication for SIRT was otherwise untreatable metastases confined to the liver. Forty-three patients received single-session whole-liver radioembolization treatment using Yttrium90 resin microspheres with a mean activity of 2.13 GBq. In 1 patient SIRT was confined to the left and in 2 patients to the right liver lobe. In 3 patients major complications (2/3 gastric ulceration and 1/3 oedematous pancreatitis) and in 24 patients minor complications occurred (acute abdominal/epigastric pain and/or nausea). Follow-up CT and/or MRI were obtained in 44 of 46 patients. In 5 of 44 patients tumor load decreased substantially (3/5 breast cancer, 1/5 CRC and 1/5 pancreatic cancer) making RFA feasible. The patients were referred for RFA after the first 3-month follow-up. RFA of the liver was successful in all cases in terms of complete ablation. In selected patients radioembolization is able to downstage liver metastases to an extent making a subsequent RFA suitable and therefore allows increasing the number of patients with a "complete response" after a minimally invasive therapy.

1. Introduction

Primary liver cancer and metastatic solid tumors within the liver represent one of the most common and most challenging situations in oncology. Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths in the United States [1], furthermore breast cancer is the most common cancer in females in Europe and in the US [2].

Up to one-third of all patients have metastatic disease at the time of cancer diagnosis, and half of the patients diagnosed and resected with early-stage primary tumor subsequently develop metastases preferentially in the liver. Liver resection in this situation is still regarded the only available treatment with an option of long-term survival. However, the resectability rate of metastases at the time of diagnosis is low. Therefore, only up to 20% of patients are suitable candidates for surgery due to size and location of the metastases or other contraindications [3]. A variety of other liver-targeted therapies are available including laser interstitial tumor therapy, radiofrequency or microwave ablation and cryotherapy. These techniques are applicable only in patients with limited metastatic involvement of the liver in terms of number and size of the metastases. For patients with liver metastases being no candidates for surgery or local ablative therapy and showing a progression under standard chemotherapy concepts, the radioembolization with Yttrium90 (Y90) resin microspheres may be a new and promising palliative treatment option.

Radioembolization combines the effects of interstitial high dose radiotherapy and arterial micro-embolization. For this new modality, SIR-Spheres® (SIRTEX medical, Lake Forest, IL, USA) are approved for the treatment of patients with non-resectable malignant liver disease in Europe. The resin microspheres (SIR-Spheres®) are labelled with Yttrium90. They serve as a radiation source and are infused into the hepatic arteries resulting in very high doses of radiation being selectively targeted to metastases via their arterial blood supply. According to present data, treatment with Y90 microspheres results in moderate to high response rates for

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patients with hepatocellular cancer (HCC) and CRC liver metastases [4,5].

Just as with other therapies there is an interest in combining SIRT with resection or RF ablation. The aim of those combinations is to eradicate all metastases to get the patient tumor free. The concept of this serial treatment consisting of SIRT first is to downsize tumors to diameters amendable to RF ablation. The aim is to create a "complete response" comparable to the desired R0 situation after surgical resection, which proofed to be of significant advantage for patients life expectancy [6].

There are already some reports [7,8] on downsizing HCC to a size and amount making resection, RFA or even liver transplantation feasible; however, no publication exists – to the best of our knowledge – reporting downstaging of liver metastases using radioembolization to a degree making further local ablative therapies feasible.

Therefore, the aim of this retrospective evaluation was to analyze, whether there is the possibility of downstaging liver metastases using radioembolization to a degree making local ablative therapy possible. Furthermore, since all patients were heavily pre-treated with different types of chemotherapy and radioembolization, another goal was to obtain knowledge, whether an additional RF ablation can be done at a reasonable low complication rate.

2. Materials and methods

2.1. Patients

Between 2002 and 2005 forty-six patients suffering from extensive hepatic metastatic disease were treated with SIRT. All these patients were heavily pre-treated with standard chemotherapeutical regimens and showed at least a no change situation or even progression under third or fourth line therapy. Therefore SIRT was considered to be a salvage therapy. All patients showed no extrahepatic tumor manifestation. Prior to treatment all cases were discussed in an interdisciplinary tumor board composed of at least an interventional radiologist, an oncologist, a surgeon and an expert in nuclear medicine. Due to the guidelines in our institution a vote from the local ethic committee is neither necessary for a treatment in a salvage situation nor for a retrospective analysis. At least 24 h prior to the treatment all patients or their legal guardians had to give written informed consent after explanation of the planned therapeutic intervention, alternative therapeutic options and possible complications.

2.2. Evaluations and staging

The pre-treatment evaluation included a medical history consisting in time course of the disease, chemotherapy, lab tests (in particular bilirubine, transaminases, renal function), demographic parameter and co-morbid diseases. At least 2 weeks prior to the radioembolization, patients had to undergo a diagnostic work up consisting of a PET/CT to rule out any extrahepatic disease, a contrast-enhanced MRI of the liver to calculate the liver to tumor ratio, to document the distribution of the tumors within the liver and to enable measurements according to the RECIST criteria. Furthermore, all patients had to undergo a meticulous angiography of the abdominal aorta, the mesenteric artery and the celiac trunk including the common hepatic artery followed by a selective catheterization of the right and left hepatic artery, to rule out any contraindications (e.g. high grade stenosis or occlusion) and to identify aberrant vessels with extrahepatic communication, which have to be embolized prior to therapy. During this procedure, 80–100 MBq of ^{99m}Tc-macroalbumine aggregates (MAA) were injected into the hepatic arteries (^{99m}Tc-MAA administered into the right and left hepatic artery according to the individual tumor load of each lobe) via the previously placed catheter. After angiography, planar thoracic and abdominal scans were acquired with a gamma camera to rule out any unexpected delivery of the activity (based on aberrant gastrointestinal flow) and to estimate the percentage of injected activity shunting from the liver into the lungs. Since the particle size of the ^{99m}Tc-MAA is quite comparable to that of the microspheres, the gamma scintigraphy provided valuable information concerning the predicted distribution of the therapeutic dose and allows for quantification of hepato-pulmonary shunts [9,10]. If hepato-pulmonary shunts were detected exceeding 20% of the applied ^{99m}Tc-MAA activity, the procedure was abandoned. In our patients population the median hepato-pulmonary shunt fraction was about 5% (range 2.4–9.5%).

2.3. Radioembolization

The anatomical condition that allows transarterial treatment strategies is based on the dual blood supply of the liver and the fact that a majority of hepatic malignancies derive their blood supply almost exclusively (more than 75%) from the hepatic arteries.

In contrast to the "classical" transarterial chemotherapies with and without embolization, radioembolization combines the effects of interstitial high dose radiotherapy and arterial microembolization. For this relatively new modality, SIR-Spheres® (SIRTEX medical, Lake Forest, IL, USA) are approved in Europe for the treatment of patients with non-resectable malignant liver disease. SIR-Spheres® are composed of Yttrium90 labelled resin microspheres which are infused into the hepatic artery resulting in very high doses of radiation being selectively targeted to tumors via their arterial blood supply.

Close to each treatment, a diagnostic angiography of the aorta, the mesenteric artery and the celiac axis was performed to determine the vascular anatomy of each patient and to identify potential aberrant vessels with a possible impact on hepatic blood flow or distribution of the spheres. Identifying such vessels is crucial for further planning of the infusion regimen during the intervention since aberrant injection of the microspheres has to be strictly avoided because it would result in serious adverse events such as actinic ulcerations and inflammation e.g. in the duodenum or the pancreas [11]. The radioactive material is delivered via the arterial blood supply of a tumor after directed catheterization.

The microspheres used for SIRT are labelled with Yttrium90, an artificial beta radiation emitting isotope. It has a physical half-life of 64.1 h and decays to stable Zirconium90. The beta radiation of Yttrium90 has an average energy of 0.935 MeV and an average penetration in tissue of approximately 2.5 mm. The isotope is embedded in insoluble and non-biodegradable resin microspheres with a mean diameter of 32 μm.

2.4. Treatment procedure

Diagnostic and therapeutic hepatic angiographic procedures were carried out by well-trained interventional radiologists with an experience of at least 5 years in interventional radiology. All procedures (diagnostic and therapeutic) were performed on a short-term hospitalization basis.

A diagnostic catheter was inserted via the common femoral artery for angiography and selective catheterization. This procedure was conducted to once more evaluate the individual vascular anatomy, to identify small visceral branches and to determine the appropriate position of the catheter tip for radioembolization. The angiography was performed by catheterization of each hepatic artery separately. To avoid ectopic implantation of spheres during therapy into the cystic artery, we placed the catheter tip distal to