Selective intraarterial radionuclide therapy with Yttrium-90 (Y-90) microspheres for hepatic neuroendocrine metastases: initial experience at a single center

Selektivno intraaratterijsko radionuklidno lečenje primenom mikrosfera sa itrijumom-90 kod neuroendokrinih metastaza u jetri: prvo iskustvo u jednom centru

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Abstract

Background/Aim. Selective intraarterial radionuclide therapy (SIRT) with Yttrium-90 (Y-90) microspheres is also known as radioembolization and delivers high doses of radiation to hepatic tumors with minimum healthy liver exposure. The aim of this study was to present our preliminary experience in the role of liver directed radiotherapy with Y-90 microspheres for the treatment of unresectable hepatic metastases from neuroendocrine tumors (NET). Methods. The results of SIRT in 10 patients (5 males, 5 females; mean age 48.7 years; age range 24–73 years) with metastatic liver disease from NETs during the period from April 2008 through August 2010 were reviewed. All patients had meticulous pre- and post-imaging studies as a part of their work-up procedure, as well as serologic tests of liver function to determine the extent of liver function damage. The patients who were eligible for SIRT had pretreatment visceral angiography to define and occlude non-target arteries. Results. The mean ± SD administered SIR-Spheres® activity was 1.49 ± 0.42 GBq (range 0.72–2.21 GBq) in all the patients. These treatments delivered a dose of 99.73 ± 66.36 Gy (range 49–420.8 Gy) to the target tumors. The estimated dose to the lungs and normal liver was 4.45 ± 1.95 Gy (range 2.4–8.5 Gy) and 26.73 ± 14.19 Gy (range 5–58.9 Gy), respectively. Overall response rate of 90% and patient tolerance was satisfactory for most patients. Conclusion. From our limited experience, we can conclude that SIRT with Y-90 microspheres is a safe and efficacious treatment option for patients with liver metastasis of NET without any serious side effects.

Key words: neuroendocrine tumors; liver; neoplasm metastasis; injections, intra-arterial; yttrium; prognosis.

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Introduction

One of the most important prognostic factors that dramatically affects survival of a patient with neuroendocrine tumor (NET) is the presence of liver metastasis. It has been shown that patients with liver metastasis have a worse survival rate compared to those without liver involvement in all types or digestive NETs. Liver metastasis has a negative impact on survival with a 10–20% 10-year survival compared to 90–100% without liver metastases. Unfortunately, the majority of patients with NETs (up to 60–75%) already present with liver metastases. In particular, patients with non-functioning tumor (without hormonal symptoms) mostly present with liver disease in up to 50% of the cases. Besides that, patients with liver metastases present an overall poor prognosis compared to those without liver metastases for all NETs regardless of the primary.

Although surgical resection remains the gold standard in the treatment of liver metastases achieving a survival rate of 60–80% at 5 years with low mortality (0–5%) and acceptable morbidity (close up to 30%), only a limited number of patients can meet the minimum requirements for curative surgical procedures. Another possible therapy option for carefully selected patients with diffuse unresectable liver metastases or who suffer from severe hormonal disturbances refractory to medical therapy is liver transplantation. However, a long-term cure from the disease by transplantation will be an exceptional event even in this highly selected subgroup.

Local ablative techniques such as radiofrequency ablation (RFA), selective hepatic transcatheter arterial embolization (TAE) or chemoembolization (TACE) with hepatic artery occlusion, can be employed in the treatment of unresectable liver metastases from NETs regardless of the origin of the primary tumor. Nonetheless, these ablative therapies as well as some others such as laser therapy, ethanol injection or cryotherapy are applicable to a small proportion of patients with few tumors.

Symptoms related with hormonal hypersecretion are frequent in functional tumors with liver metastases. Somatostatin analogues (with or without interferon) are often effective and helpful in controlling these symptoms. However, medical therapies with somatostatin analogues and/or interferon have weak antiproliferative effects. Systemic chemotherapy with streptozotocin achieves modest response rates of limited duration and is better for pancreatic NETs compared with metastatic carcinoid tumors. A randomized study using doxorubicin with fluorouracil or streptozocin followed by dacarbazine in the patients at disease progression of metastatic carcinoids demonstrated response rate of 8.2% with significant treatment related toxicity. On the other hand, peptide receptor related radionuclide therapy may be used in the treatment of metastatic NETs, with YDOTATOC and Lu-DOTATOC revealing particular promise.

Radioembolization with Yttrium-90 (Y-90) labeled microspheres has shown promise for the treatment of patients with nonsurgically resectable primary and metastatic liver metastatic disease. It is known that hepatic tumors receive 80–100% of blood supply from the hepatic artery. Since liver tumors are fed mainly by arterial rather than portal venous blood, a selective intraarterial radionuclide therapy (SIRT) via hepatic arterial administration of Y-90 microspheres may deliver high radiation doses to tumor tissue with minimal effect to the surrounding normal liver parenchyma. In SIRT, Y-90 microspheres are used to both embolize and irradiate tumors in the liver by delivering the microspheres through the hepatic artery. In this study, we presented our initial experience with early follow-up results of SIRT with Y-90 microspheres for hepatic neuroendocrine metastases.

Methods

We retrospectively evaluated the data from 10 patients (male/female 5/5, mean ± SD age 48.7 ± 16.63 years; age range 24–73 years) between April 2008 and August 2010, who had SIRT with Y-90 microspheres (SIR-Spheres® Sirtex Medical, Lane Cove, Australia) for biopsy–proven progressive unresectable hepatic NET metastases.

All patients were neither suitable nor responsive to other local treatment options and showed inadequate response to systemic chemotherapy. Prior to the treatment, all patients were discussed in an interdisciplinary tumor board composed of medical oncologist, interventional radiologist, radiation oncologist, surgeon and an expert in nuclear medicine. All patients had to give a formal written informed consent after explanation of the whole treatment steps, alternative therapeutic options and possible complications.

The pretreatment evaluation included a medical history compatible with time course of the disease, chemotherapy, somatostatin analogues and/or interferon, laboratory tests and comorbid disease. All patients had FDG-PET scan at least 4 weeks prior to SIRT at least 4 weeks before to determine the extent of disease. Besides that, In-111 OctreoScan whole body scan results were evaluated if available. Other imaging studies, such as chest radiography, computed tomography (CT) scan of chest and abdomen, abdominal ultrasound and a bone scan are also done in determination of disease extent.

 Adequate coagulation parameters and sufficient pulmonary function to undergo arterial catheterization, and adequate liver function [total bilirubine (TB) level less than 2 mg/dL and alanine transaminase (ALT) or aspartate transaminase (AST) levels less than five times of upper limit of normal] were required in all patients. Patients who had previous external beam radiation therapy to the liver, ascites or were in clinical liver failure, markedly abnormal synthetic and excretory liver function tests (LFTs), complete portal vein thrombosis, life threatening major extra hepatic metastases, and those with expected survival < 3 months were not considered for SIRT.

All patients with sufficient lab results had pretreatment meticulous visceral angiography of the abdominal aorta, the mesenteric artery and the celiac trunk including the common hepatic artery. Moreover, a selective catheterization of the

right and left hepatic artery was done to identify and occlude non-target arteries with extrahepatic communication while ruling out any high grade stenosis or occlusion which would be contraindication for SIRT. Subsequently prophylactic embolization of extrahepatic vessels such as the right gastric, gastroduodenal or falciform artery was performed (Figure 1). Noncorrectable flow to gastrointestinal tract was an exclusionary criteria for SIRT. Technical details for performing mesenteric angiography prior to SIRT have been described in the literature 28.

Following initial angiographic evaluation with/without necessary prophylactic embolization of non-target extra hepatic vessels, 150 MBq (4mCi) Technetium-99m Macro-Aggregated Albumin (Tc-99m MAA) was injected via the hepatic artery catheter or implanted port to assess the fraction that passes through the liver to the lungs and the relative distribution of MAA (and hence SIR-Spheres®) between tumor and normal liver. Anterior and posterior scintigraphic images of the abdomen and thorax, and right lateral images of the abdomen were obtained 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. Regions of interest are drawn around the whole of lung fields and the whole of liver field on planar (A) Tc-99m MAA perfusion scan; SPECT (B) images were also obtained for simulation of Y-90 radiomicrospheres distribution before SIRT (note the faint gastric and salivary uptake due to free Tc-99m-pertechnetate).

\[
\text{LSF} = \frac{\sqrt{\text{Counts Lung (Anterior)} \times \text{Counts Lung (Posterior)}}}{\sqrt{\text{Counts Lung + Liver (Anterior)} \times \text{Counts Lung + Liver (Posterior)}}}
\]

Since the particle size of the 99mTc-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 the quantification of hepato-pulmonary shunts 23, 26. If the LSF is between 10–15% and 15–20% then a SIR-Spheres® dose reduction of 20% and 40% was done respectively. Although it was not the case in our patients, LSF more than 20% would be an absolute contraindication (with a dose to the lungs > 30 Gy) for SIRT. Additionally, there was no need for reduction in shunting <10%.

Selective intraarterial radionuclide therapy procedure was done in 2 to 3 weeks following the completion of the above-mentioned procedures. Treatment of one side of the liver was done for patients with disease limited to one lobe on CT and/or FDG PET-CT scan. Treatment of both sides of the liver was done by selective administration of Y-90 radiomicrospheres into the right and left hepatic vascular bed sequentially in the same session. A specially designed plexiglas delivery box provided by Sirtex Medical (Wilmington, MA) was used for SIRT procedure (Figure 3). The body surface area (BSA) method was used to calculate the prescribed SIR-Spheres® activity according to the following formula 26, 29:

\[
\text{Activity (GBq)} = \frac{(\text{BSA}-0.2) \times \text{TumorVolume}}{\text{LiverVolume}}
\]

Immediate medication consisting of antiemetics and analgesics were prescribed for all patients. Additionally, light
diet and sufficient hydration before and after SIRT were maintained. The patients were discharged after one night stay, and received a preventive gastric antisecretory treatment (proton pump inhibitors) for 1 month and low dose corticosteroids for one week to overcome flu-like reaction.

Since Y-90 is a pure beta emitter, Bremsstrahlung imaging is the only method for post treatment localization study of radiomicrospheres. According to the patients’ clinical stability, post-therapeutic Bremsstrahlung imaging was performed to confirm and document the distribution of SIR-Spheres® in all patients between 2 to 24 hours after SIRT (Figure 4).

All patients continued on low-dose steroids and proton-pump inhibitors for 1 week and 4 weeks after SIRT, respectively. Complete blood count, liver function tests, and routine biochemical tests were obtained at 24th hour after SIRT, and then at every 4 weeks for the next 3 months. Tumor response was assessed using RECIST criteria on CT. Moreover, FDG PET scan was performed at 10 to 12 weeks after SIRT for the evaluation of metabolic response and to differentiate viable components of the tumor from necrotic tissue.

The quantitative data was analyzed using the Wilcoxon Signed Ranks Test. Quantifiable data was given as mean ± standard deviation (SD) (if no otherwise specified). A statistically significant difference was considered when \( p \) values < 0.05. All calculations were performed using SPSS for Windows, Version 9.01.

Results

Sixteen SIRT procedures were carried out in 10 patients with metastatic hepatic disease from NETs during a 24-month period between April 2008 and May 2010. Out of the 10 patients, the primary NET site was the bronchus in 3 patients, the stomach in 1 patient, the medullary thyroid in 1 patient, the pancreas in 2 patients, the kolon/rectum in 2 patients and of unknown origin in 1 patient. The primary NETs were classified as carcinoid in 8 patients, medullary thyroid cancer in 1 patient and well differentiated unknown NET in one patient (Table 1).

Nine out of 10 patients had multifocal metastases in both lobes of the liver. Only one patient had multifocal disease in the right lobe of the liver. Of the 10 patients, 6 patients had whole liver treatments, and the other 4 patients had unilobar treatments initially. While 6 out of the 10 patients had single SIRT procedure, 2 patients had SIRT twice and 2 patients had SIRT for three times (Table 1). Whole liver treatments were administered either via common hepatic artery for bilobar disease or by the administration of 2 separate doses into the right and left hepatic arteries (after adjusting the dose according to the volume of the right and left hepatic lobes).

Because of the differences in the FDG avidity of NETs, we used a combined approach for the calculation of tumor volumes and normal livers. For the calculation of SIR-Spheres® activity to be administered, the total volume of the all FDG avid hepatic metastases, and also normal liver volumes were initially computed from the contoured and thresholded region by counting the number of voxels in the three-dimensional region and automatically multiplying by the known volume of a voxel using MIM® Software (MIM-vista Corp., USA). Secondly, we reviewed the CT scans and calculate the volumes of non FDG avid tumor sites with positive radiologic findings for hepatic metastases using the same software. Calculated mean ± SD liver involvement was 31.1 ± 10.43% (range 10–45%).

None of the patients showed marked pulmonary activity on Tc-99m MAA scan. The mean ± SD pulmonary shunt was 6.04 ± 2.47% (range 3.4–10.03%). There was no scintigraphically detectable extrahepatic uptake on planar Tc-99m MAA scan. Furthermore, we did not observe any additional extrahepatic uptake on SPECT in the patients (4/10) where available.
The mean ± SD administered SIR-Spheres® activity was 1.49 ± 0.42 GBq (range 0.72–2.21 GBq) in all patients. The 4 patients with bilobar disease were treated with whole liver administration of SIR-Spheres® with the activity of 1.62 ± 0.26 GBq (range 1.40–2.20 GBq) at a single session. The other 6 patients had unilobar treatment initially with the activity of 1.40 ± 0.52 GBq (range 0.7–2.02 GBq) initially. Three out of these 6 patients with unilobar injection had opposite lobe treatment in the follow-up. These treatments delivered a dose of 99.73 ± 66.36 Gy (range 49–420.8 Gy) to the target tumors. The estimated dose to the lungs and normal liver was 4.45 ± 1.95 Gy (2.4–8.5 Gy) and 26.73 ± 14.19 Gy (range 5–58.9 Gy) respectively (Table 1).

We experienced difficulty in the administration of SIR-Spheres® in 2 patients because of vessel spasm during the procedure. Both of the 2 patients were planned to have whole liver treatment (Cases 8 and 10). But both of them had left hepatic vessel spasm, shifting to treatment procedure from whole liver to only right lobe therapy. They had similar celiac axis with no definitive anatomic variation. The first patient had retreatment to the opposite lobe 4 weeks later. The second one is still on follow-up and scheduled for the left lobe treatment.

In our study group, there was no patient with portal vein thrombosis. The mean ± SD follow-up time for SIR-Spheres® therapy was 6 ± 2.8 months (range 3–28 months). Although, almost all patients reported some degree of mild-to-moderate abdominal pain, nausea, lethargy, anorexia, and fever from 1 week to 1 month after the treatment, no one needed intravenous narcotics and antiemetics. Liver function tests during the follow-up period were stable in all patients. However, we experienced mild-to-moderate increase in ALT, AST, GGT, and serum alkaline phosphatase (ALP) levels in 70% of all patients. Among these parameters, post treatment AST, GGT and ALP levels were significantly higher than baseline values (Table 1). On the other hand, the increase in ALT and TB levels were not statistically significant. The patient with medullary thyroid cancer developed transient elevation of serum amylase which resolved in 48 hours without any medication. There was no case with radiation pneumonitis or radiation induced liver disease (RILD).

Of the 10 patients, 3 showed complete response (CR), 5 showed partial response (PR) and one showed stable disease (SD) of the target lesions according to RECIST criteria (Figures 5a and 5b). One patient showed progressive disease (PD) on follow-up. One of the patients with PR for hepatic tumors died of extensive bone, soft tissue and solid organ metastases 18 month after SIRT (Table 1). The data representing the extent of hepatic involvement, administered activities, estimated tumor doses with tumor responses are presented in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Liver tumor on FCR PET</th>
<th>Liver tumor on CT</th>
<th>Estimated tumor dose (Gy)</th>
<th>Cumulative administered SIR-Spheres® activity (GBq)</th>
<th>Cumulative estimated normal liver dose (Gy)</th>
<th>Cumulative estimated lung-dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobe 1</td>
<td>Lobe 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lobe</td>
<td>Left lobe</td>
<td>9.6 ± 3.9</td>
<td>5.8 ± 2.1</td>
<td>4.6 ± 1.5</td>
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Neuroendocrine tumors are heterogeneous group of neoplasms with endocrine metabolism and special histological structure. Despite the lack of private residential areas, 90% of NETs is derived from the gastroenteropancreatic system. They are generally low grade malignancies and tend to grow slowly. Although metastases from NETs are rare in tumors less than 2 cm, presence of liver metastases is one of the worst prognostic factors. Resection and successful local treatments can be related with long term survival, but the treatments are seldom curative, and the 5-year survival rate for patients who have unresected liver metastasis is between 25% and 50%. Therefore, if metastases are limited to the liver and the surgical resection is not possible, other local interventional treatment options should be considered, even in the presence of extrahepatic metastases. Although, TAE, TACE or RFA may be one of the local treatment options, each of them has its own restrictions in the appropriate patient selection, and also in application which limits their effectiveness as a single therapy.

SIRT, a form of intraarterial brachytherapy, is a technique in which glass (TheraSphere®) or resin (SIR-Spheres®) particles are labeled with Y-90. The radioisotope Y-90 is a pure β emitter with no primary gamma radiation. SIR-Sphere, a permanent implant, is not metabolized or excreted and it stays permanently in the liver in the form of biocompatible particles, measuring approximately 20 to 60 microns. The mean energy of the particles is 0.9367 MeV, has a mean tissue penetration of 2.5 mm, and has a maximum penetration of 10 mm. In therapeutic use, requiring the isotope to decay to infinity, 94% of the radiation is delivered in 11 days. Administration of radiomicrospheres is performed via a catheter placed in the hepatic artery delivering the spheres to the capillary bed where they are fixed and decay with the physical half-life of Y-90 (64 h). Malignant liver tumors are fed mainly by hepatic arterial system rather than portal venous blood. Therefore, the dominant arterial flow of
malignant tissue allows the delivery of high doses of radiation to tumors while keeping the exposure of the healthy liver at minimum with selective microsphere distribution.

At our institution, 48 SIRT procedures were carried out in 38 patients during a 28-month period between April 2008 and August 2010. Of the 38 patients, 10 patients suffering from extensive hepatic metastatic disease from NET were included in this study. Although, there are some physical differences in quality, size and particle number, Tc-99m MAA is the current standard for the evaluation of hepatic arterial flow. Since all aberrant and non-target vessels were coiled prior to Y-90 therapy in all patients, we did not observe any extra hepatic activity on Tc-99m MAA scan. Moreover, we observed great concordance with pre-SIRT Tc-99m MAA scan and post-therapeutic Bremsstrahlung imaging. We performed Bremsstrahlung imaging as soon as possible, but no later than 24 hours after the radioembolization as recommended in the literature. Although we did not observe any hormonal crisis, we experienced vasospasm during Y-90 radiomicrosphere injection in 2 patients. As reported before, vessel spasm is not unusual during the Y-90 infusion. Therefore, it may be crucial to use microcatheter injections as recommended, particularly if the vessels are small in caliber or demonstrate significant tortuosity. Moreover, it may be helpful to use short acting somatostatin analogs for symptomatic patients presenting with carcinoid related symptoms before local treatment procedures. Most of our patients, except cases N° 1 and 10, were on somatostatin treatment during the SIRT procedure.

As RECIST are commonly used to evaluate the success of a treatment, we used CT scan data to document therapy response. Of the 10 patients, 5 had both hepatic and extra-hepatic metastases on pre-SIRT FDG PET scan (Table 1). One out of 10 patients showed PD for hepatic metastases despite SIRT. Of the 10 patients, 5 showed PR after SIRT. One patient with PR for hepatic metastases showed new bone and soft tissue metastatic sites on follow-up (case N° 3) and died of systemic spread of metastatic disease 18 months after SIRT while on streptozotocin and somatostatin treatment. The other 3 patients showed CR for hepatic metastases. The patient with medullary thyroid cancer (case N° 1) had bilateral cervical lymph node metastases, and had lymph node dissection after SIRT. The patient with bronchial carcinoid tumor (case N° 2) had external radiotherapy for bone metastases concomitantly with SIRT. Fortunately, the bone and hepatic metastases completely resolved on follow-up in this patient. The other patient with bronchial carcinoid tumor (case N° 10) showed CR to SIRT at the beginning. However, we observed new mediastinal lymph nodes and solitary lung nodule, showing markedly increased FDG uptake, very suspicious for recurrence on the recent FDG PET-CT in the same patient 4 months after completing the therapy.

The tolerability of SIRT for all patients was very good. We observed minor side effects (fatigue, nausea, transient elevation in serum liver enzymes and abdominal pain) which resolved in 1 week. No severe side effect, treatment related mortality, radiation hepatitis or veno-occlusive liver failure was seen in our patient population. The common side effect was a slight increase in serum ALP and GGT levels. These results are concordant with the procedure guidelines and previously published reports.

The response rates in this preliminary study are consistent with previously published data on large series of patients. According to the CT data, we observed 90% response rate (CR – 30%; SD – 10%; PR – 50%). PD was observed in 10% (1/10) of all patients on CT scan. However, patients with PD or SD on CT, have either stable or decreased FDG uptake values on FDG PET study. Therefore, from our limited experience we may conclude that FDG-PET-CT and quantitative FDG data such as SUVmax, SUV mean, and Tissue Lesion Glycolysis (TLG) may have a crucial role in the evaluation of response to SIRT in future.

The results of this study should be considered preliminary and exploratory by nature in this study involving a limited number of patients. Moreover, not having serum tumor markers such as Chromogranine A, Neurokinin-A or HIAA, and In-111 OctreoScan in all patients, are the main drawbacks of this study. We still need to improve our practice and knowledge regarding radiation dosimetry and fractionation, including more than one application of microspheres, imaging and follow-up guidelines and long-term results.

Conclusion

From our limited experience, SIRT with Y-90 radiomicrospheres for liver metastases from NETs seems to be safe and efficacious with limited toxicity. However, there is a need to combine Y-90 radiomicrospheres treatment with systemic therapeutics for the patients with extra hepatic metastases to control the disease.

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