Eur J Nucl Med Mol Imaging (2016) 43:1425–1431
DOI 10.1007/s00259-015-3264-6

ORIGINAL ARTICLE

Selective internal radiation therapy in patients with progressive neuroendocrine liver metastases

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Received: 31 August 2015 / Accepted: 10 November 2015 / Published online: 3 December 2015

Abstract
Purpose To evaluate the safety and efficacy of selective internal radiation therapy (SIRT) in patients with unresectable liver metastases from neuroendocrine tumours (NETLMs).
Methods This retrospective study included 40 patients with progressive NETLMs (22 women, 18 men, mean age 61.6 years) who underwent SIRT with ^{90}Y-labelled resin microspheres. Tumour response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) on CT or MR images. Medical records were reviewed.
Results In the 40 patients, 54 evaluable SIRT procedures were performed, 33 to the right liver lobe (mean activity 1.31 GBq), 13 to the left lobe (mean activity 0.85 GBq), and 8 to both lobes (mean activity 1.61 GBq). Late follow-up imaging (mean 20 months) was performed after 44 of the treatments. Objective tumour response and disease control rates were 54 % (29 of 54 treatments) and 94 % (51 treatments), respectively, at the early follow-up examination (mean 3 months) and 34 % (15 treatments) and 57 % (25 treatments), respectively at the late follow-up examination. Mean overall survival from the first SIRT was 34,8 months and survival rates at 1, 2, 3 and 5 years were 76 %, 59 %, 52 % and 35 % respectively. Adverse effects were generally mild and easily manageable, except in one patient who died from radiation-induced liver failure. Of the 45 patients, 18 (45 %) had received peptide receptor radionuclide therapy (PRRT) prior to SIRT.
Conclusion SIRT with ^{90}Y-labelled resin microspheres is a safe and effective treatment for patients with progressive NETLM, and also for those who have received prior PRRT.

Keywords Selective internal radiation therapy · Neuroendocrine liver metastases · Transarterial · Yttrium

Introduction

Neuroendocrine tumours (NETs) are uncommon, usually slow-growing neoplasms originating from the gastrointestinal tract, pancreas, lungs, thymus, adrenal glands, or paraganglia. Liver metastases from NETs (NETLM) are common [1] and progressive NETLMs with subsequent liver failure is an important cause of death in these patients. About one-third of NETs produce peptide hormones or biogenic amines causing disabling endocrine syndromes. In many patients, NETLMs appear before hormonal symptoms. However, the endocrine syndrome may precede NETLMs particularly in patients with insulinoma or ectopic Cushing's syndrome. Medical treatment with somatostatin analogues, sometimes combined with alpha-interferon, is widely used to decrease hormone secretion and consequently endocrine symptoms. Tumour burden can be reduced with surgery, radiofrequency ablation (RFA), systemic chemotherapy, peptide receptor radionuclide therapy (PRRT), hepatic transarterial bland embolization [2, 3] or chemoembolization [4, 5].

Selective internal radiation therapy (SIRT) is a recently developed technique in which ^{90}Y-labelled microspheres are deposited in the hepatic artery. Two types of microspheres are currently used: glass microspheres (TheraSphere™; BTG

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Biocompatibles Ltd, Farnham, UK) and resin microspheres (SIR-Spheres™; Sirtex Medical, Sydney, Australia). They differ in size, density [6], and activity per microsphere [7]. SIRT has been shown to slow down disease progression and to improve survival in patients with hepatocellular carcinoma and liver metastases from colorectal cancer [8]. Increasing evidence supports the use of SIRT in NETLMs [9, 10] and metastases from breast cancer [8]. The aim of the present study was to evaluate the safety and efficacy of SIRT in patients with unresectable NETLMs.

Materials and methods

Patients

After approval from the local ethics board, consecutive patients with histologically verified NETLM who underwent SIRT between June 2005 and September 2014 at Uppsala University Hospital were identified. Those who had a post-treatment CT or MRI scan of the liver were included in the present study. Indications for SIRT were unresectable NETLM that were progressing despite antitumoral therapy, ability to undergo angiography and catheterization, and adequate haematological, renal and hepatic function. Patients with extrahepatic disease or previous or ongoing NETLM treatment were not excluded. Previous PRRT (four to six treatments with 7.4 GBq ^{177}Lu-DOTA-octreotate) was allowed. All patients had a pretreatment CT or MRI scan.

SIRT procedure

SIRT was performed in a standard manner [11]. Depending on tumour burden and location unilobar or bilobar infusion was performed.

Two weeks prior to SIRT angiography was performed by an interventional radiologist for therapy planning. The vascular anatomy was thoroughly defined. If necessary, coiling of gastric vessels was performed and finally ^{99m}Tc-macroalbumin was injected into the hepatic artery selected for SIRT.

Within 30 min of the ^{99m}Tc-macroalbumin injection planar scintigraphy was performed to determine the lung shunting fraction. A SPECT scan combined with a low-dose CT scan (SPECT/CT) was performed consecutively over the abdomen and the uptake in the metastases and in extrahepatic tissue were assessed by a specialist in nuclear medicine.

^{90}Y resin microspheres (SIR-Spheres™) were used. The activity was determined and prescribed by a specialist in nuclear medicine and oncology based on the body surface area method [11] taking into account CT findings, risk factors and relevant clinical information. The microspheres were infused by an interventional radiologist with the catheter positioned in a location identical to that used in angiography for therapy planning.

Medication

The evening before SIRT, all patients were given 20 mg omeprazole orally and the morning before SIRT they were given 8 mg betamethasone and 5 mg tropisetron intravenously or orally, and 10 mg morphine and 10 mg diazepam orally. Patients with small-bowel NETs and carcinoid syndrome received an infusion of octreotide, 50 – 100 μg/h, starting after SIRT and continuing for 24 – 48 h. All patients were prescribed 20 mg omeprazole daily for 1 month after SIRT as ulcer prophylaxis.

Table 1 Baseline characteristics of the 40 patients comprising the study population

Characteristic	Value[a]
Sex	
Male	18 (45 %)
Female	22 (55 %)
Age (years), median (range)	63.1 (43 – 81)
Tumour type	
Small-intestinal NET	31 (77 %)
Pancreatic NET, nonfunctioning	4 (10 %)
Bronchial NET	3 (7 %)
Insulinoma	1 (3 %)
Gastrinoma	1 (3 %)
ENETS grade[b]	
1 (Ki-67 ≤2 %)	20 (50 %)
2 (Ki-67 3 – 20 %)	15 (37 %)
3 (Ki-67 >20 %)	4 (10 %)
Previous treatment	
Resected primary tumour	29 (73 %)
Cholecystectomy	15 (37 %)
Somatostatin analogues	36 (90 %)
Alpha-interferon	30 (75 %)
Chemotherapy	11 (27 %)
Peptide receptor radionuclide therapy	18 (45 %)
Everolimus	4 (10 %)
Hepatic arterial embolization with particles	6 (15 %)
Radiofrequency ablation	6 (15 %)
Stereotactic radiotherapy to the liver	1 (3 %)
Ongoing treatment	
Somatostatin analogues	32 (80 %)
Distribution of metastases	
Bilobar liver	39 (97 %)
Extrahepatic	28 (70 %)

[a] Values are number (%) of patients, except age in years as median (range)

[b] Ki-67 was not available in one patient

Retrospective analysis

CT or MR images that had been obtained before SIRT (baseline) were retrospectively compared with the first available images after SIRT (early follow-up) and with the most recent images available (late follow-up). In patients with progressive disease (PD), late follow-up was performed at the first imaging occasion when progression was seen. In patients undergoing PRRT with ^{177}Lu-DOTA-octreotate after SIRT, late follow-up was performed at the last imaging occasion before PRRT was started.

Imaging response

Assessment was performed by two experienced radiologists in consensus. Tumour response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [12]. An objective response (OR) was defined as complete remission (CR) plus partial response (PR), and disease control (DC) was defined as CR+PR plus stable disease (SD). The liver lobe size was measured and visually assessed on axial images in the portal plane. Differences in size between baseline and follow-up were scored as follows: *0* no difference, *1* <25 % difference, *2* 25 – 50 % difference, and *3* >50 % difference.

Biochemical response

Medical records were reviewed and biochemical markers from the same time as the CT or MRI examinations were identified. The available markers from each occasion were reviewed by an experienced endocrine oncologist. A decrease in at least one marker by >50 % was considered as a PR; an increase in at least one marker by >50 % was considered PD; and any difference of <50 % was considered SD. The radiologists who assessed the CT or MR images and the endocrine oncologist who assessed the biochemical markers were blinded to each other's results.

Statistical analysis

StatView 5.0.1 (SAS Institute, Cary, NC) was used for statistical analyses. The Mann-Whitney *U* test was used to evaluate the relationship between the delivered activity and the occurrence of liver size differences. The same test was used to evaluate the relationship between ENETS tumour grade and response. Spearman's rank correlation was used to evaluate the relationship between imaging and biochemical response. The Cox proportional hazards model and the Kaplan-Meier method were used to estimate survival starting from the day of first SIRT treatment. The significance level was set at 0.05 in all analyses.

Table 2 Selective internal radiation therapy parameters

Parameter	Value
Volume treated (54 procedures), *n* (%)	
Right lobe	33 (61)
Left lobe	13 (24)
Bilobar	8 (15)
Activity (^{90}Y) delivered (GBq)	
Right lobe	
Mean	1.31
Median (range)	1.30 (0.55 – 2)
Left lobe	
Mean	0.85
Median (range)	0.90 (0.1 – 1.4)
Bilobar	
Mean	1.61
Median (range)	1.60 (1 – 2.1)

Results

Between June 2005 and September 2014, 45 patients with NETLM were treated with SIRT. Five of these who did not have a post treatment CT or MRI (because they had either left the country or had died from extrahepatic disease) were excluded. The remaining 40 patients (22 women, 18 men, mean age 61.6 years) constituted the study population of the present study. Their baseline characteristics are presented in Table 1.

In these 40 patients, 56 SIRT treatments were performed. No imaging was performed after two of the treatments, leaving 54 SIRT treatments for which response could be evaluated. The volumes treated and the activities delivered are presented in Table 2. Treatment-related toxicity and adverse

Table 3 Toxicity and adverse effects following selective internal radiation therapy

Toxicity/Adverse effect	No. (%) of treatments (*n*=54)
Toxicity	
None	11 (20)
Transient transaminase increase	32 (60)
Fatigue	10 (18)
Nausea	15 (28)
Pain	27 (50)
Fever	10 (18)
Gastritis symptoms	2 (4)
Gastric ulcer	1 (2)
Liver failure	1 (2)
Adverse effects	
Groin abscess	1 (2)
Urinary tract infection	5 (9)

Table 4 Liver size differences per patient at early and late follow-up examinations compared to baseline on CT or MR images

Patient no.[a]	Early follow-up (mean 3 months)		Late follow-up (mean 20 months)	
	Treated lobe (decrease)	Contralateral lobe (increase)	Treated lobe (decrease)	Contralateral lobe (increase)
1	1	1	3	1
3	1	1	3	2
6	0	0	1	1
9	0	0	2	1
11	1	1	1	2
23	0	0	1	0
25	1	0	1	0
26	1	2	3	2
29	0	0	1	1
31	0	0	1	1
32	1	1	2	2
35	0	0	1	1

0 no difference, *1* <25 % difference, *2* 25 – 50 % difference, *3* >50 % difference

[a] Only patients in whom a difference was observed. In all of them the right liver lobe was treated. The contralateral lobe was not treated during this time interval

events are presented in Table 3. One patient died from radiation-induced liver failure (radioembolization-induced liver disease, REILD) 3 months after bilobar SIRT treatment. This patient had not discontinued interferon alpha medication as prescribed, which was revealed 2 months after the SIRT procedure.

Late follow-up imaging (mean 20 months, median 12 months, range 12 – 77 months) was performed after 44 of the SIRT treatments (in 36 patients).

The size of the treated liver lobe had decreased in 15 % of patients (6/40) at the early follow-up examination (mean/median 3 months, range 1.6 – 7 months) and in 33 % of patients (12/36) at the late follow-up examination. In most of these patients the size of the contralateral lobe had increased. In three patients there was substantial atrophy of more than 50 % of the lobe. Liver size differences in those patients in whom a difference was observed are shown in Table 4. Liver function tests did not detect any hepatic insufficiency in any of these patients. There was no correlation between the amount of activity delivered and the occurrence of liver size differences.

OR (CR+PR) according to the mRECIST criteria was seen in 54 % of treatments (29 of 54) at the early follow-up examination and in 34 % of treatments (15 of 44) at the late follow-up examination. DC (CR+PR+SD) was achieved in 94 % of treatments (51 of 54) at the early follow-up examination and in 57 % of treatments (25 of 44) at the late follow-up examination. Imaging response was significantly related to biochemical response at the early follow-up examination (correlation coefficient 0.65, $p=0.0001$), but there was no

Table 5 Tumour response according to mRECIST and to biochemical markers (CgA and 5HIAA) at the early and late follow-up examinations (per treatment)

	Early follow-up (mean 3 months)	Late follow-up (mean 20 months)
Imaging response		
No. of treatments	54	44
Complete remission, *n* (%)	0	1 (2 %)
Partial response, *n* (%)	29 (54 %)	14 (32 %)
Stable disease, *n* (%)	22 (41 %)	10 (23 %)
Progressive disease, *n* (%)	3 (5 %)	19 (43 %)
Biochemical response:		
No. of treatments	48	47
Complete remission, *n* (%)	0	0
Partial response, *n* (%)	10 (21 %)	4 (8 %)
Stable disease, *n* (%)	34 (71 %)	28 (60 %)
Progressive disease, *n* (%)	4 (8 %)	15 (32 %)

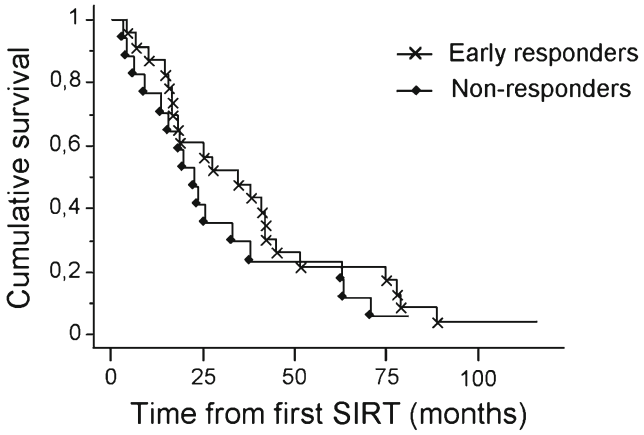

Fig. 1 CT images before and at different times after selective internal radiation therapy with 1.05 GBq to the right liver lobe showing decreasing contrast enhancement and size of the treated liver metastases over time. This was considered a partial response. The size of the treated lobe is slightly decreased after treatment

significant relation between them at the late follow-up examination (Table 5). CT images of a patient with a PR are shown in Fig. 1. There was no correlation between the ENETS tumour grade and the occurrence of OR or DC at the early or late follow-up examinations.

In the 16 patients with PD, the mean time to progression was 14.8 months (median 9.0 months, range 2.3 – 76.6 months) calculated per treated lobe (21 lobes).In the 18 patients who had received PRRT prior to SIRT the typical absorbed doses for a single cycle of ^{177}Lu-DOTA-octreotate were 1.2 – 2.5 Gy (maximum 3.8 Gy per cycle). Three patients received PRRT with ^{177}Lu-DOTA-octreotate after SIRT at 14, 16 and 80 months after which they were not included in further follow-up in the present study. The mean overall survival from the first SIRT treatment was 34.8 months (SD 27.3 months) and the median overall survival was 24.7 months (range 3 – 117 months). The survival rates at 1, 2, 3 and 5 years were 76 %, 59 %, 52 % and 35 %, respectively. The unadjusted hazard ratio (HR) for survival was 1.36 (95 % confidence interval 0.48 – 3.9; p=0.56) in patients with OR at the early follow-up examination (early responders). Kaplan-Meier curves are shown in Fig. 2. In patients with OR at the late follow-up examination (late responders) HR was 1.98 (95 % confidence interval 0.69 – 5.7; p=0.20).

Discussion

Liver metastases frequently occur in patients with NET, which substantially reduces their 5-year survival from 75 – 99 % (without metastases) [1] to 40 % (with metastases) [13]. Surgical debulking of the liver metastases has been reported to prolong median survival from 48 to 216 months [14] with 3-year and 5-year survival rates of 83 % [15] and 73 % [16], respectively. However, surgical debulking cannot be performed in the majority of NETLM patients [15, 16], which is why other liver-directed treatments are needed. Percutaneous or intraoperative RFA has proved to be successful in treating various types of liver metastases, but it is not effective in large tumours or in patients with an extensive tumour burden [17]. Thus, many NETLM are not suitable for surgical debulking or RFA, but can be treated effectively with different types of transarterial embolization.

Bland embolization with Embospheres™, particles or gelfoam has resulted in OR rates of 40 – 52 % [2, 3, 18, 19], chemoembolization with doxorubicin, mitomycin C or cisplatin has resulted in OR rates of 11 – 86 % [4, 18, 20–24], and radioembolization with ^{90}Y has resulted in OR rates of 21 – 63 % [9, 10, 25–31] (54 % in the present study). Radioembolization has advantages over the other embolization techniques as it causes fewer side effects and requires fewer treatments to achieve the same effect [32, 33]. The efficacy of SIRT depends on the distribution and distal penetration of the embolized microspheres [6]. Because of the difference in activity per microsphere [7], a larger number of resin microspheres than glass microspheres are needed to achieve the same amount of activity. The penetration depth of resin microspheres is higher than that of glass microspheres [6] but the distribution and the radiation effect are similar [7].

In the present study, all patients had PD despite extensive treatments when they were admitted for SIRT. Regarding this, a DC rate of 94 % at the early follow-up examination is excellent and even a DC rate of 57 % at the late follow-up

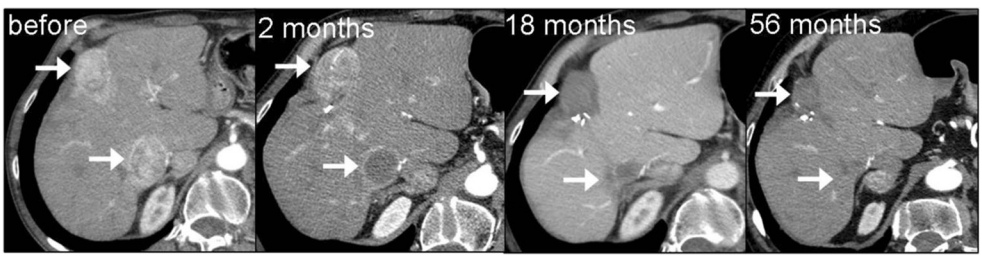

Fig. 2 Kaplan-Meier curves for overall survival in patients with an objective response to the first selective internal radiation therapy procedure (early responders) and patients with stable or progressive disease (nonresponders) according to mRECIST

examination could be considered good. In other NETLM cohorts, DC after SIRT has varied between 67 % and 97 % [9, 10, 25–31]. Median survival in the present cohort was 24.7 months and 1-year and 3-year survival rates were 76 % and 52 % respectively, which is consistent with the findings in other cohorts with 22 – 70 months median survival [9, 10, 25–27, 29] and 1-year and 3-year survival rates of 73 – 87 % and 42 – 47 %, respectively [26, 27, 29]. Thus, SIRT seems to improve short-term survival, but it might not improve long-term survival substantially in these patients. Furthermore, there was only a slight difference in survival between early responders (CR+PR) and nonresponders (SD+PD; HR 1.36; p=0.56) in the present cohort. These observations might be partly explained by the fact that SIRT only treats the liver metastases and has no effect on the primary tumour. Furthermore, SIRT was used as the last treatment option in late stage disease. It has been suggested that introducing SIRT at an earlier stage might provide a greater benefit for patients. The fact that an excellent DC was achieved in late stage disease in the present study might support this notion.

Adverse effects were generally mild and easily manageable in the present study. However, one patient died from REILD 3 months after the procedure. This patient had multiple small liver metastases and bilobar SIRT was performed. The activity delivered to the entire liver was 1.6 GBq, i.e. equal to the mean and the median dose delivered in bilobar treatment in the present study. The patient had no known underlying liver disease. Thus, it could not have been expected that this dose would induce liver failure. The patients were advised not to take alpha-interferon 2 weeks before and at least 3 months after SIRT. Unfortunately, this patient had started alpha-interferon treatment shortly after SIRT and the radiosensitizing effect of alpha-interferon may have contributed to the regrettable outcome.

In the present study, a decrease in size of the treated liver lobe and an increase in size of the contralateral lobe were observed in some patients. This effect of SIRT has been described by others who have suggested that SIRT could be used to provide simultaneous tumour control and future liver remnant hypertrophy before curative hemihepatectomy [34]. In the present study, the occurrence of liver size differences could not be predicted from the amount of activity delivered. An individual calculation of the absorbed doses to the liver parenchyma might reveal such a relationship. However, when prescribing the dose it may be difficult to predict the effect on liver size. Even though three of our patients had substantial atrophy of the treated lobe, liver function tests did not detect any hepatic insufficiency supporting the notion that the contralateral lobe may provide compensatory function. However, it is uncertain whether repeated treatment of the same lobe should be considered.

There is no consensus as to whether SIRT to the whole liver should be performed as one single bilobar treatment or whether each lobe should be treated on separate occasions. We preferred to treat the lobes on separate occasions unless there was rapid progression of the metastases in both liver lobes. One of our patients had a metastatic insulinoma with severe hypoglycaemic symptoms. SIRT was performed twice to the right lobe and once to the left lobe in an effort to decrease tumour burden, resulting in control of the hypoglycaemia. Extrahepatic disease is common in patients with NETLM [18, 27, 29], and 70 % (28) of our 40 patients had extrahepatic disease. Patients with PD or debilitating endocrine symptoms are often treated with PRRT, i.e. an intravenously administered radioactive somatostatin analogue that causes local radiation in somatostatin receptor-positive tumours throughout the body. The two most commonly used PRRT drugs are ^{177}Lu-DOTA-octreotate (which we have been using) and ^{90}Y-DOTA-octreotide. In patients with somatostatin receptor-negative tumours, SIRT is a tempting alternative especially if the major tumour burden is in the liver. SIRT may also be considered if the liver metastases progress and the extrahepatic metastases are virtually stable. In the present study 45 % (18) of the 40 patients had received PRRT prior to SIRT. No impairment of their liver function was seen after SIRT. Thus, SIRT may be considered safe in patients who have PD in the liver after initially having responded to PRRT. However, dose reduction may be required if the patient has impaired liver function or a large tumour burden.

In conclusion, SIRT with ^{90}Y-labelled resin microspheres is a safe and effective treatment for patients with progressive NETLM, and also for those who have received PRRT previously. Alpha-interferon treatment should be avoided for at least 3 months after radioembolization.

Compliance with ethical standards

Conflicts of Interest None.

Ethical approval 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 principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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