SIR-Spheres® Microspheres in Neuroendocrine Tumour Liver Metastases

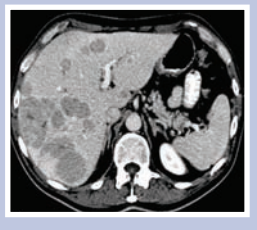
The following summarises some of the key data supporting the use of SIR-Spheres microspheres and selective internal radiation therapy (SIRT) in the treatment of liver metastases from Neuroendocrine Tumours (mNET):

Retrospective review of SIRT in mNET across US centres

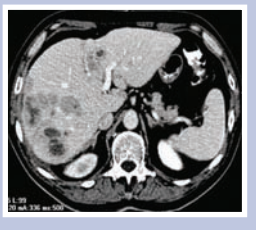
A retrospective analysis of 84 patients with unresectable bilobar liver metastases from neuroendocrine tumours that had progressed under chemotherapy and/or TACE, and were subsequently treated with SIRT in seven US centres reported that:

- a response by PET scans in 67% of patients with disease stabilisation in the remaining 33% – PET-positive tumours became normal (or complete response) in 24% of patients, with a partial response in 43%;[1]
- 80% of patients who had symptomatic disease received relief[1] – a subsequent analysis of 36 patients whose full health records were available revealed that 25 (69%) responded on the basis of symptoms, PET or Octreotide scans, and of these, 18 (72%) reduced their somatostatin usage by at least 50%, and 4 (16%) were taken off somatostatin completely for in excess of 6 months;[2]
- there were no significant complications but there were 14 cases of grade 3 GI toxicity which all resolved with medical therapy;[1]
- the authors concluded that SIRT is a viable and effective treatment for unresectable metastatic neuroendocrine tumours.[1]

SIR-Spheres in mNET: CT Response in Neuroendocrine [1]



Baseline CT scan pre-SIRT
2.5 GBq in right, 1.5 GBq in left lobe



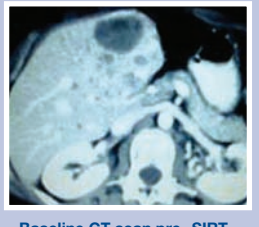
CT scan 26 months post-SIRT
Outcome: patient lived 30 months
Died from pulmonary disease

Interim results of a phase IV (II) study of SIR-Spheres microspheres in mNET

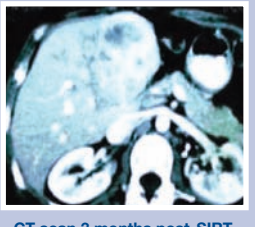
The interim results of an on-going phase IV (II) study on SIR-Spheres microspheres in combination with 5FU used to treat 34 patients with unresectable mNET, including those failing prior liver treatment as well as those with extrahepatic disease, demonstrated:

- 24% of patients treated having a partial response of target lesions by RECIST criteria at 1 month together with 68% experiencing stable disease and 9% progressive disease, and 83% of evaluable patients having stable disease at 18 months;[3]
- the disease control rate was 91% at 1 month, 83% at 3 months, 80% at 12 months and 83% at 18 months;[3]
- response by tumour marker CgA from baseline was seen in 53% of patients at 1 month, 60% at 3 months, 50% at 6 months, 66% at 12 months and 80% at 18 months;[3]
- 4 patients (12%) died from progressive liver disease at 1, 4, 7 and 15 months, with a median follow-up of 9.8 months;[3]
- 3 patients developed duodenal ulcers and 1 developed self-resolving pancreatitis due to inappropriate perfusion of SIRT to extra-hepatic arteries. 2 patients developed self-limiting jaundice, and all patients reported abdominal pain, nausea and lethargy from 1 to 4 weeks post-SIRT;[3]
- the authors concluded that SIRT appears to have efficacy in treating unresectable neuroendocrine tumours liver metastases.[3]

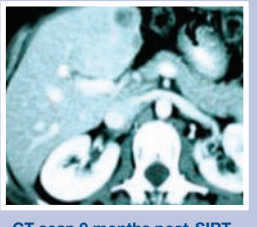
SIR-Spheres in mNET Phase II Study: CT Response [3]



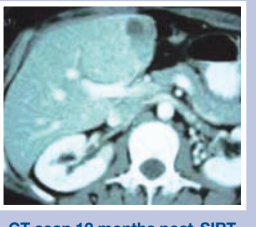
Baseline CT scan pre -SIRT



CT scan 3 months post-SIRT



CT scan 9 months post-SIRT



CT scan 12 months post-SIRT

Phase IV (II) clinical trial of SIR-Spheres microspheres in first-line treatment of patients with mNET

A prospective pilot study of SIR-Spheres microspheres in 10 patients with unresectable progressive or symptomatic mNET liver metastases treated mainly (90%) in the first-line setting demonstrated:

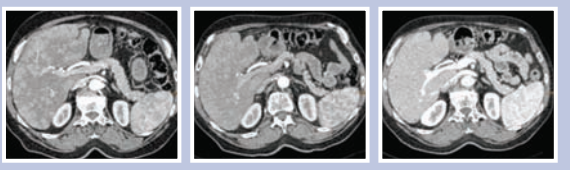
- a partial response rate of 30% by CT using RECIST criteria at 3 months, with stable disease in the remaining 70%;[4]
- survival was 70% at a follow up of 8–35 months, with three patients having died at 8, 11 and 15 months due to progressive extrahepatic disease;[4]
- there was no evidence of hepatic toxicity or acute carcinoid crisis following therapy;[4]
- symptomatic improvement was reported in 2 of 3 patients with moderate to severe symptoms at baseline;[4]
- the authors concluded that use of SIR-Spheres microspheres in mNET resulted in stable disease or partial response over 3 to 12 months with little toxicity or short-term morbidity. The authors also noted that SIR-Spheres microspheres appeared to be tolerated as well if not better than TACE, and that it compares favourably with other loco-regional therapies.[4]

Interim results of a phase IV (I) pilot study of SIR-Spheres microspheres in mNET salvage therapy

The interim results of a phase IV (I) pilot study on SIR-Spheres microspheres in unresectable advanced progressive mNET of the first 6 of 10 planned patients with diffuse bilobar disease, >50 metastases and progression under treatment, showed:[5]

- an objective response by CT using RECIST criteria in 10 lesions in the 2 patients evaluable through ≥9 months, with a reduction of 63–89% in the mean tumour size, including 40% of lesions showing a complete response with disappearance of the tumour, 50% showed a partial response of >50% reduction in area, and 10% showed a minor response;[5]
- the authors concluded that SIRT seems to be very effective and safe, with less negative impact on the quality of life of patients than standard therapies for mNET;[5]
- the authors also noted that their results to date raised questions about the role of SIRT as standard therapy, whether it could be a better option than TACE, and on the potential patients who could benefit.[5]

SIR-Spheres in mNET Pilot Study: CT Response [5]



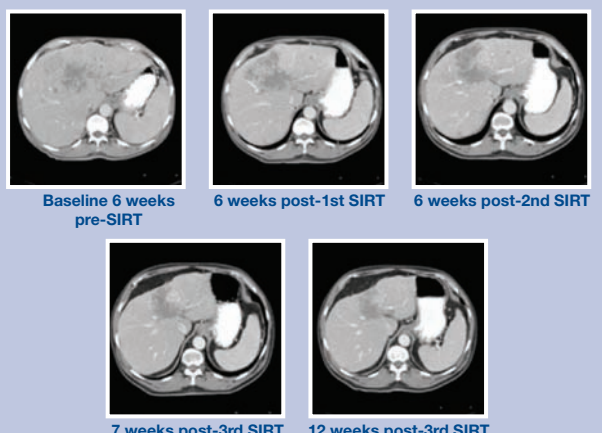
Baseline CT scan pre-SIRT | 6 months post-SIRT | 9 months post-SIRT

Review of sequential, fractionated whole-liver treatment of mNET using SIR-Spheres microspheres

A retrospective review of 18 consecutive patients with mNET, including 13 with carcinoid symptoms, who were treated second-line with a total of 24 fractions of SIR-Spheres microspheres revealed:

- an objective response rate of 89% by imaging and CgA;[6]
- 16 of the 18 patients (89%) were alive at a median follow-up of 27 months (4–44 months), thus median survival had not yet been reached;[6]
- there were no treatment-related deaths, radiation-induced liver disease or veno-occlusive disease;[6]
- the authors concluded that whole liver and multiple fraction SIRT are safe, feasible and produce a high response rate, even with extensive tumour replacement of the liver – nearly all patients experienced a significant objective response;[6]
- the authors noted that acute and delayed toxicity was low, without any treatment-related grade 4 events or radiation-induced liver disease.[6]

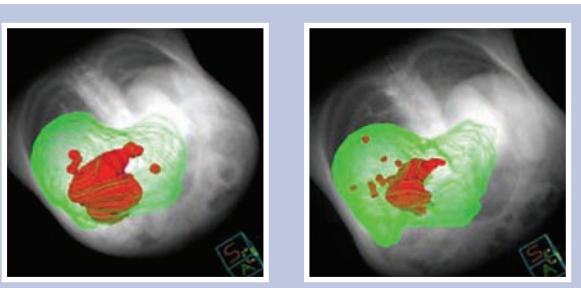
SIR-Spheres in mNET: CT Imaging of Sequential Treatment [6]



Baseline 6 weeks pre-SIRT | 6 weeks post-1st SIRT | 6 weeks post-2nd SIRT | 7 weeks post-3rd SIRT | 12 weeks post-3rd SIRT

SIR-Spheres in mNET: Liver & Tumour Volume Change [6]

Treatment Number	Liver Volume (mL)	Tumor Volume (mL)	% change from prior Tx
Pre-1st	4000	669	n/a
Pre-2nd	2986	454	-9
Pre-3rd	2306	139	-61
Total Pre-1st to Post-3rd	-1694	-530	-81



References

1. Coldwell D, Nutting C, Kennedy A. Use of Yttrium-90 SIR-Spheres to treat unresectable metastatic neuroendocrine tumors in the liver. *World Congress of Gastrointestinal Cancer* 2005; Abstract O-002.
2. Coldwell D . Personal communication.
3. King J, Morris D, Glenn D *et al*. SIR-Spheres for liver metastases from neuroendocrine cancer. *European Neuroendocrine Society (ENETS) meeting* 2006; Abstract C28.
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5. El-Sheik M, Wagner H -J. Selective intraarterial radiation therapy with Y90-microspheres (SIR-Spheres®) of advanced hepatic metastases in neuroendocrine tumors: Preliminary results of a pilot study and proposed design of a prospective randomized multi-center study. *Liver-Directed Radiotherapy with Microspheres: A Clinical Symposium* 11–12 February 2006; Barcelona, Spain.
6. Kennedy A, Dezarn W, McNeillie P *et al*. Fractionation, dose selection, and response of hepatic metastases of neuroendocrine tumors after ^{90}Y-microsphere brachytherapy. *Brachytherapy* 2006 Annual American Brachytherapy Society Meeting; **5** (2): 103 Abstract P -75.

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