Retrospective multi-centre study of SIR-Spheres microspheres in 148 patients with mNET

A retrospective 10-centre review was conducted of SIR-Spheres microspheres in 148 patients with unresectable liver metastases from neuroendocrine tumours that had all previously completed comprehensive evaluation and treatment of the primary tumour and metastatic disease. The majority of patients (82%) had carcinoid tumours, but the cohort also included patients with islet cell tumours (10%), insulinoma (2%), glucagonoma (2%) and atypical NET (2%). The results revealed that:

- a complete response by CT, MRI or OctreoScan scans in 2.7% of patients, with a partial response in 60.5%, stable disease in 22.7% and progressive disease in 4.9%;
- the median survival was 70 months;
- 67% of patients had no grade 3–4 side effects, with the most commonly reported being fatigue (6.5%), nausea (3.2%) and pain (2.7%);
- a subset 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;
- the authors concluded that treatment using SIR-Spheres microspheres can deliver high doses of radiation preferentially to NET liver metastases, resulting in an encouraging response rate and symptomatic improvement, with an improvement in debulking of tumour and survival, with a similar safety profile to other local treatments for mNETs.

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<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>ORR</th>
<th>SD</th>
<th>Symptomatic response</th>
<th>Median TTP</th>
<th>Median Survival</th>
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<td>Kennedy1</td>
<td>148</td>
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<td>63.2%</td>
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<tr>
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<td>14.7%</td>
<td>55%</td>
<td>nr</td>
<td>59% alive at 35.2 months</td>
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<td>60%</td>
<td>nr</td>
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<td>70% alive at 28 months</td>
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<td>89%*</td>
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<td>nr</td>
<td>89% alive at 27 months</td>
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<td>Cao5</td>
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<td>SIR-Spheres microspheres ± 5FU</td>
<td>39%</td>
<td>27%</td>
<td>nr</td>
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<td>36 months</td>
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<tr>
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<td>54%</td>
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<td>nr</td>
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<td>SIR-Spheres microspheres</td>
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<td>75%</td>
<td>94.7%</td>
<td>nr</td>
<td>95.2% alive at 16.2 months</td>
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</tbody>
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Key: ORR: objective response rate (complete response + partial response) by RECIST; SD: stable disease; TTP: time to progression; nr: not reported; *Imaging + CgA

The following summarises 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):
Results of a prospective study of SIR-Spheres microspheres + 5FU in mNET

The results of this phase IV (II) study on SIR-Spheres microspheres in combination with a 7-day systemic infusion of 5FU in 34 patients with progressive, unresectable NET liver metastases, demonstrated:

- the primary NETs were classified as 25 (74%) carcinoid tumours, 3 (9%) large cell, 2 (6%) glucagonoma, 2 (6%) unknown, 1 (3%) VIPoma and 1 (3%) somatostatinoma;
- patients included recurrent disease following resection (29%) or systemic chemotherapy (15%) and most (59%) had extra-hepatic disease;
- the mean interval from primary NET diagnosis to SIRT was 55.9 months and 36.6 months from diagnosis of liver metastases to SIRT;
- a radiological response was seen in 50% of patients, with 6 (18%) having a complete response and 11 (32%) a partial response of target lesions by RECIST criteria. A further 5 patients (15%) had stable disease;
- a fall in tumour marker CgA from baseline was seen in 41% at 3 months, 43% at 6 months, 42% at 12 months and 46% at 30 months;
- symptomatic improvement was reported in 55% of patients at 3 months and 50% at 6 months, with no de novo symptoms;
- the mean survival was 27.6 months (range 1–48+) at a mean follow-up of 35.2 months. The median survival had not been reached: 14 patients (41%) had died at a mean of 14.6 ± 2.2 months (standard error); 20 (59%) remained alive at a mean of 36.7 ± 1.8 months;
- complications included mild-to-severe abdominal pain, nausea and fever, and lethargy from one week to one month post-treatment. 3 patients developed radiation gastritis or ulcers and there was one early death from liver dysfunction and pneumonia;
- the authors concluded that SIR-Spheres microspheres can achieve relatively long-term responses in some patients with unresectable NET liver metastases – all 6 patients with a complete response remained alive at 26–48+ months. The authors noted that “it is questionable whether any other therapy previously has achieved such useful results in patients with inoperable disease”.

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 (80%) 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%;
- 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;
- there was no evidence of hepatic toxicity or acute carcinoid crisis following therapy;
- symptomatic improvement was reported in 2 of 3 patients with moderate to severe symptoms at baseline;
- 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.

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;
- 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;
- there were no treatment-related deaths, radiation-induced liver disease or veno-occlusive disease;
- 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;
- the authors noted that acute and delayed toxicity was low, without any treatment-related grade 4 events or radiation-induced liver disease.

Retrospective analysis of factors predicting survival following SIR-Spheres microspheres in unresectable mNET

A prospectively collected database of 58 patients (mean age 61 years) with mNET treated using SIR-Spheres microspheres either alone (41.4%) or in combination with concurrent 1-week infusion of 5FU chemotherapy (58.6%) was reviewed to evaluate response and prognostic factors affecting survival. This two-centre study demonstrated that:

- the primary tumour was classified as carcinoid (72%), large cell tumour (7%), glucagonoma (5%), medullary thyroid (3%), VIPoma (2%), somatostatinoma (2%) and unknown (9%);
- previous treatments included liver resection (33%), TAE/TACE (10%), ablation or percutaneous ethanol injection (17%) and previous chemotherapy (34%), in addition patients may have had concurrent chemotherap (59%) and post-radioembolisation chemotherapy (9%);
- median follow-up was 21 months (range 1–61), and no patient was lost to follow-up;
- of the 51 patients who could be categorized concerning their radiographic response, 6 (12%) had achieved a complete response, 14 (27%) a partial response, 14 (27%) stable disease and 17 (33%) had disease progression. Median follow-up for the 6 patients with a complete response and no radiographic evidence of metastatic liver disease was 55 months (range 39–61);
- the median survival in this prospective study was 36 months (range 1–61) with 1-, 2-, and 3-year survival of 86%, 58%, and 47%, respectively;
- the analysis of potential prognostic factors for survival showed that extent of tumor involvement (P = 0.003), radiographic response (P = 0.028), responder vs. non-responders (P = 0.005), presence of extrahepatic disease at the time of radioembolisation (P = 0.001) and histological grade of the tumor (P = 0.041) were significant prognostic factors;
- this study showed that concurrent systemic chemotherapy did not have a significant impact on overall survival. Other factors that had no significant impact on survival included age, sex, lung shunt, activity administered, ECOG performance status, prior chemotherapy, liver resection, TAE/TACE, ablation/PEI and post-SIRT chemotherapy;
- the authors concluded that in addition to the identified prognostic factors for survival, a significant proportion of patients, including some with extensive liver involvement of the liver, achieved a complete or partial response following therapy.
Analysis of factors predicting response and survival in a prospective study of SIR-Spheres microspheres in mNET

In a second report by the same investigators, the results of a phase II open-label study conducted in 48 patients (mean age 60 years) with unresectable mNET treated using SIR-Spheres microspheres either alone (25%) or in combination with concurrent 1-week infusion of 5FU chemotherapy (75%) were analysed to assess the factors affecting response and survival, as well as the effect of treatment on liver function:

- the primary tumour was classified as carcinoid (71%), large cell tumour (6%), glucagonoma (4%), somatostatinoma (4%), insulinoma (4%), medullary thyroid (4%), VIPoma (2%) and unknown (4%);8
- previous treatments included systemic chemotherapy (52%), TAE/TACE (15%) and ablative therapy (8%);6
- on imaging follow-up, 15% of patients had a complete response, 19% a partial response to treatment and 23% of patients had stable disease;6
- the median survival in this prospective study was 35 months (range 5–63) with 1-, 2-, 3-, 5-year survival of 87%, 62%, 46%, and 46% respectively;3
- univariate analysis identified 5 significant prognostic variables associated with an improved survival: good radiologic response to treatment ($P = 0.003$), low hepatic tumor burden ($P = 0.022$), well-differentiated tumor ($P = 0.001$), absence of extra-hepatic metastases ($P \leq 0.001$) and female gender ($P = 0.022$);8
- there was a significant increase in the level of alkaline phosphatase ($P = 0.001$), but no significant change in serum albumin, aspartate transaminase, alanine transaminase and total bilirubin over the 6-month period;6
- the authors concluded that radioembolisation using SIR-Spheres microspheres is a promising treatment option for unresectable mNET. Their study demonstrated the efficacy and safety of this treatment. The authors identified 4 factors associated with a good treatment response and/or prognosis: female gender, well-differentiated tumors, low hepatic burden and absence of extrahepatic disease.8

Prospective single-centre study of SIR-Spheres microspheres in mNET salvage therapy

The results of a prospective study on SIR-Spheres microspheres in 9 patients (mean age 58.8 years) with mNET who had failed to respond to other types of medical, surgical or local ablative treatment modalities revealed that:

- the primary tumour site was bronchus (11%), jejunum (22%), ileum (22%), stomach (11%) and insulinoma (22%);8
- prior treatments included surgical resection of the primary tumour (89%), chemoembolisation (56%), octreotide therapy (89%), interferon-α (22%), systemic chemotherapy (44%) and a radio-ligand therapy (11%);8
- contrast-enhanced CT images were available in all patients. Three months after SIRT therapy, partial response was seen in 6 patients (66%). Calculated reduction of liver volume was 49%. In 3 patients (33%), stable disease was seen with a calculated tumour reduction of 13%;8
- the estimated time to progression was 11.1 ± 4.9 months with survival rates of 100%, 57% and 57% for 1, 2 and 3 years, respectively;8
- no major complications occurred;8
- after 6 months, health-related quality of life (HRQoL) improved significantly in 6 of 7 evaluable patients ($P = 0.05$);8
- the authors concluded that their preliminary results show significant tumour response with low treatment-related toxicity. Biochemical response by tracking tumour markers (CgA) became evident earlier as compared to imaging response parameters. The HRQoL assessment performed in this trial showed that selective internal radiation therapy was well tolerated and improved or stabilized for up to 12 months after an initial post-procedural deterioration.8

![SIR-Spheres microspheres in refractory mNET Pilot Study](Baseline CT scan pre-SIRT 6 months post-SIRT 9 months post-SIRT)

Impact on CT Response12 Impact on Quality of Life6

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

Retrospective study of SIR-Spheres microspheres in unresectable refractory NET hepatic metastases

Forty-two patients with treatment-refractory neuroendocrine hepatic metastases who were treated consecutively with SIR-Spheres microspheres were analysed retrospectively:

- the most common primary tumour sites were small intestine (54.8%) and pancreas (21.4%), the primary tumour was classified as carcinoid (78.6%), islet cell (14.3%), insulinoma (4.8%) and atypical (2.4%). Previous treatments included surgery in 38 (90.5%) patients, chemoembolisation in 18 (42.9%) patients, systemic chemotherapy in 18 (42.9%) patients, interferon-therapy in 8 (19%) patients and octreotide therapy in 23 (54.8%) patients;6
- contrast-enhanced CT and/or MRI images were available in 40 patients, 2 patients were lost to imaging follow-up. Three months after SIRT therapy partial response and stable disease were seen in 22.5% and 75% of patients respectively;2
- the mean follow-up was 16.2 months [median 12.9 (range 2.8–50.1)] with 40 (95.2%) of the 42 patients alive at the time of analysis;9
- there were no acute or delayed toxicities greater than grade 2 according to CTCAE. No radiation-induced liver disease was noted;9
- the median decrease in tumour-marker levels, chromogranin A and serotonin, were 54.8% and 37.3% respectively;9
- 38 of 42 patients showed tumour-related clinical symptoms before treatment; in 36 (94.7%) of these patients a significant improvement or disappearance of clinical symptoms was observed 3 months after treatment;9
- the authors concluded that SIR-Spheres microspheres are a safe and effective treatment in patients with treatment-refractory mNET. Antitumoral effect is supported by good local tumour control, decreased tumour-marker levels and improved clinical symptoms.9
References
10. Coldwell D. Personal communication.

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