A retrospective 10-centre review was conducted of SIR-Spheres Y-90 resin 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:

- 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%;¹
- the median survival was 70.0 months;¹
- 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%);¹
- 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 four (16%) were taken off somatostatin completely for in excess of six months;¹

The following summarises the key data supporting the use of SIR-Spheres Y-90 resin microspheres and selective internal radiation therapy (SIRT) in the treatment of liver metastases from neuroendocrine tumours (mNET):

<table>
<thead>
<tr>
<th>Lead Author n, Treatment</th>
<th>ORR</th>
<th>SD</th>
<th>Symptomatic response</th>
<th>Median PFS</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Line to Treatment-Refractory Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kennedy⁷, 148 SIR-Spheres⁶</td>
<td>63.2%</td>
<td>22.7%</td>
<td>nr</td>
<td>nr</td>
<td>70.0 months</td>
</tr>
<tr>
<td>King², 34 SIR-Spheres³ + 5FU</td>
<td>50.0%</td>
<td>14.7%</td>
<td>55.0%</td>
<td>nr</td>
<td>59.0% alive at 35.2 months</td>
</tr>
<tr>
<td>McElmurray⁴, 10 SIR-Spheres³</td>
<td>30.0%</td>
<td>70.0%</td>
<td>nr</td>
<td>nr</td>
<td>60.0% alive at 36.0 months</td>
</tr>
<tr>
<td>Kennedy⁶, 56 SIR-Spheres³</td>
<td>49.0%</td>
<td>49.1%</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>Cao⁷, 58 SIR-Spheres³ ± 5FU</td>
<td>39.0%</td>
<td>27.0%</td>
<td>nr</td>
<td>nr</td>
<td>36.0 months</td>
</tr>
<tr>
<td>Saxena⁶, 48 SIR-Spheres³ ± 5FU</td>
<td>54.0%</td>
<td>23.0%</td>
<td>nr</td>
<td>nr</td>
<td>35.0 months</td>
</tr>
<tr>
<td>Ceelen⁷, 45 SIR-Spheres³</td>
<td>13.0%</td>
<td>82.0%</td>
<td>nr</td>
<td>24.2 months</td>
<td>nr</td>
</tr>
<tr>
<td>Oza-Choy⁷, 18 SIR-Spheres³</td>
<td>58.0%</td>
<td>32.0%</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
</tbody>
</table>

| **Salvage Therapy of Treatment-Refractory Disease** |
| Murthy⁶, 8 SIR-Spheres³ | 12.5% | 50.0% | nr | nr | 14.0 months |
| Kalinowski⁸, 9 SIR-Spheres³ | 66.0% | 33.0% | nr | 11.1 months | 57.0% alive at 36 months |
| Jahanpiriⁱ, 73 SIR-Spheres³ | nr | nr | nr | 10.6 months | 55.2 months |
| Paprottka¹², 42 SIR-Spheres³ | 22.5% | 75.0% | 94.7% | nr | 95.2% alive at 16.2 months |
| Ezziddin¹³, 23 SIR-Spheres³ | 30.4% | 60.9% | 80.0% | nr | 29.0 months |
| Kharton¹⁴, 26 SIR-Spheres³ | 42.0% | 50.0% | 69.0% | nr | nr |
| Peker⁵, 30 SIR-Spheres³ | 46.0% | 37.0% | nr | nr | 39.0 months |
| Barbier¹⁶, 40 SIR-Spheres³ | 54.0% | 41.0% | nr | nr | 24.7 months |
| Boni¹⁷, 11 SIR-Spheres³ | 33.0% | 66.0% | nr | nr | nr |
| Filippi¹⁸, 15 SIR-Spheres³ | 47.0% | 53.0% | nr | nr | 31.0 months |

**Key:** ORR: objective response rate (complete response + partial response) by RECIST; SD: stable disease; PFS: progression free survival; †: retrospective study; §: SIR-Spheres Y-90 resin microspheres; nr: not reported

SIR-Spheres Y-90 resin microspheres in mNET: CT Response

Baseline CT scan pre-SIRT

CT scan 26 months post-SIRT

Outcome: patient lived 30 months
Died from pulmonary disease

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the authors concluded that treatment using SIR-Spheres Y-90 resin 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.¹

Results of a prospective study of SIR-Spheres Y-90 resin microspheres + 5FU in mNET

The results of a prospective phase IV (II) study on SIR-Spheres Y-90 resin microspheres in combination with a 7-day systemic infusion of 5FU in 34 patients with progressive, unresectable NET liver metastases, demonstrated:²

- the primary NETs were classified as 25 (74%) carcinoid tumours, three (9%) large cell, two (6%) glucagonoma, two (6%) unknown, one (3%) VIPoma and one (3%) somatostatinoma;²
- patients included recurrent disease following resection (29%) or systemic chemotherapy (15%) and most (59%) had extra-hepatic disease;²
- the mean interval from primary NET diagnosis to SIRT was 55.9 months and 36.6 months from diagnosis of liver metastases to SIRT;²
- a radiological response was seen in 50% of patients, with six (18%) having a complete response and 11 (32%) a partial response of target lesions by RECIST criteria. A further five patients (15%) had stable disease;²
- a fall in tumour marker CgA from baseline was seen in 41% at three months, 43% at six months, 42% at 12 months and 46% at 30 months;²
- symptomatic improvement was reported in 55% of patients at three months and 50% at six months, with no de novo symptomatic improvement reported at 36 months;²
- 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;²
- complications included mild-to-severe abdominal pain, nausea and fever, and lethargy from one week to one month post-treatment. Three patients developed radiation gastritis or ulcers and there was one early death from liver dysfunction and pneumonia;²
- the authors concluded that SIR-Spheres Y-90 resin microspheres can achieve relatively long-term responses in some patients with unresectable NET liver metastases – all six 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”.²

Phase IV (II) clinical trial of SIR-Spheres Y-90 resin microspheres in first-line treatment of patients with mNET

A prospective pilot study of SIR-Spheres Y-90 resin microspheres in 10 patients with unresectable progressive or symptomatic mNET liver metastases (90%) in the first-line setting demonstrated:³

- a partial response rate of 27% by CT using RECIST criteria at three months, with stable disease in the remaining 73%;³
- patient survival averaged 45±9 (SEM) months (range 8–78) and was 100% at six months, 80% at 1 year, 70% at two years and 60% at three years;³
- there was no evidence of hepatic toxicity or acute carcinoid crisis following therapy;³
- physical and mental patient-reported health-related quality of life (HRQOL) was measured at baseline. Mental HRQOL improved over time (P = 0.044), while physical HRQOL did not change significantly after SIRT;³
- the authors concluded that use of SIR-Spheres Y-90 resin microspheres in mNET resulted in stable disease or partial response over three to 12 months with little toxicity or short-term morbidity and a stable or improved HRQOL through 24 months. The authors also noted that the survival rate with SIR-Spheres Y-90 resin microspheres appeared comparable to other loco-regional therapies with potentially fewer total treatments.³

Review of sequential, fractionated whole-liver treatment of mNET using SIR-Spheres Y-90 resin microspheres

A retrospective review of 56 consecutive patients with mNET, who were treated second-line with SIR-Spheres Y-90 resin microspheres revealed:⁴

- whole liver treatment was performed in 86% of the patients, right lobe only in 10% and left lobe only in 4%. Thirty-six patients (64.3%) received one treatment, 12 patients two treatments, seven patients three treatments, and one patient four treatments;⁴
• the estimated time to progression was 11.1 months (1–93.4 months);^4
• no grade 4 toxicities occurred, and only two grade 3 events were found (gastric ulcers);^4
• the authors concluded that these data confirm other published reports on the efficacy and low toxicity of SIRT and that multiple treatments to the whole liver were well tolerated.^4

Retrospective analysis of factors predicting survival following SIR-Spheres Y-90 resin microspheres in unresectable mNET

A prospectively collected database of 58 patients (mean age 61 years) with mNET treated using SIR-Spheres Y-90 resin 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:^5
• 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 chemotherapy (59%) and post-radioembolisation chemotherapy (9%);^5
• median follow-up was 21 months (range 1–61), and no patient was lost to follow-up;^5
• of the 51 patients who could be categorized concerning their radiographic response, six (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 six patients with a complete response and no radiographic evidence of metastatic liver disease was 55 months (range 39–61);^5
• the median survival in this prospective study was 36 months (range 1–61) with one, two, and three year survival of 86%, 58%, and 47%, respectively;^5
• the analysis of potential prognostic factors for survival showed that extent of tumour 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 tumour (P = 0.041) were significant prognostic factors;^5
• 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;^5
• the authors concluded that in addition to the identified prognosis factors for survival, a significant proportion of patients, including some with extensive 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 Y-90 resin 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 Y-90 resin microspheres either alone (25%) or in combination with concurrent one 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:^6
• 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%);^6
• 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 one, two, three, five-year survival of 87%, 62%, 46%, and 46% respectively.^6
• univariate analysis identified five significant prognostic variables associated with an improved survival: good radiologic response to treatment (P = 0.003), low hepatic tumour burden (P = 0.022), well-differentiated tumour (P = 0.001), absence of extra-hepatic metastases (P < 0.001) and female gender (P = 0.022);^6
• 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 sixmonth period;^6
• the authors concluded that radioembolisation using SIR-Spheres Y-90 resin microspheres is a promising treatment option for unresectable mNET. Their study demonstrated the efficacy and safety of this treatment. The authors identified four factors associated with a good treatment response and/or prognosis: female gender, well-differentiated tumours, low hepatic burden and absence of extrahepatic disease.}

Prospective single-centre study of SIR-Spheres Y-90 resin microspheres in mNET salvage therapy

The results of a prospective study on SIR-Spheres Y-90 resin microspheres in nine 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:^10
• the primary tumour site was bronchus (11%), jejunum (22%), ileum (22%), stomach (11%), pancreas (11%) and insulinoma (22%);^10
• 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%);^10
• contrast-enhanced CT images were available in all patients. Three months after SIRT therapy, partial response was seen in six patients (66%). Calculated reduction of liver volume was 49%. In three patients (33%), stable disease was seen with a calculated tumour reduction of 13%;^10
• the estimated time to progression was 11.1 ± 4.9 months with survival rates of 100%, 57% and 57% for one, two and three years, respectively;^10
no major complications occurred;¹⁰
after six months, health-related quality of life (HRQoL) improved significantly in six of seven evaluable patients \(P = 0.05\);¹⁰
the authors concluded that their preliminary results show significant tumour response with low treatment-related toxicity.

Biological 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.¹⁰

SIR-Spheres Y-90 resin microspheres in refractory mNET Pilot Study

Impact on CT Response²¹

Impact on Quality of Life¹²

P < 0.05

Retrospective study of SIR-Spheres Y-90 resin microspheres in unresectable refractory NET hepatic metastases

Forty-two patients with treatment-refractory neuroendocrine hepatic metastases who were treated consecutively with SIR-Spheres Y-90 resin microspheres were analysed retrospectively;¹²

• 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 eight (19%) patients and octreotide therapy in 23 (54.8%) patients;¹²

• contrast-enhanced CT and/or MRI images were available in 40 patients, two 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;¹²

• 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;¹²

• there were no acute or delayed toxicities greater than grade 2 according to CTCAE. No radiation-induced liver disease was noted;¹²

• the median decrease in tumour-marker levels, chromogranin A and serotonin, were 54.8% and 37.3% respectively;¹²

• thirty-eight 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 three months after treatment;¹²

• the authors concluded that SIR-Spheres Y-90 resin microspheres are a safe and effective treatment in patients with treatment-refractory mNET. Antitumoural effect is supported by good local tumour control, decreased tumour-marker levels and improved clinical symptoms.¹²

Salvage therapy of SIR-Spheres Y-90 resin microspheres in patients with NET hepatic metastases after radiation exposure from Peptide Receptor Radionucleotide Therapy (PRRT)

Twenty-three patients with treatment-refractory neuroendocrine hepatic metastases were treated as salvage therapy with SIR-Spheres Y-90 resin microspheres after failed PRRT:¹³

• all patients had unresectable gastroenteropancreatic NET with liver-dominant disease; all but one patient had a bilobar tumour spread; 19 patients were treated because of progression according to RECIST and four patients were treated because of persistent hormone hypersecretion; tumour-induced ascites was present in three patients;¹⁵

• radiologic imaging at three months after treatment yielded a partial response in seven patients (30.4%), stable disease in 14 patients (60.9%), and progressive disease in two patients (8.7%);¹³

• the overall response rates for biochemical and symptomatic responses were 52.8%, and 80% respectively;¹³

• the median overall survival after SIRT was 29 months (95% CI, 4–54 months);¹³

• only transient, mostly minor liver toxicity (no grade 4) was recorded; one patient developed a gastroduodenal ulcer (grade 2);¹³

• the authors conclude that radioembolisation using SIR-Spheres Y-90 resin microspheres is a safe and effective salvage treatment option in advanced NET patients with liver-dominant tumour burden who failed or progressed after PRRT; the authors noted that the preferable treatment sequence (PRRT followed by SIRT vs. SIRT followed by PRRT) remains a matter of discussion.¹³

Single-centre retrospective study of SIR-Spheres Y-90 resin microspheres as salvage therapy in patients with NET hepatic metastases

Thirty patients with unresectable mNET, not responding to alternative treatment modalities, underwent radioembolisation with SIR-Spheres Y-90 resin microspheres:¹⁵

• eleven women and 19 men were included; mean age was 55.2 ± 11.8 years (range, 27–75 years);¹⁵

• nine patients (30%) had extrahepatic metastatic disease; liver involvement was 1%–25% in 11 patients (37%), 26%–50% in eight patients (27%), 51%–75% in nine patients (30%), and 76%–100% in two patients (7%);¹⁵
• previous treatments included surgery, resection of the primary tumour and hepatic metastasis followed by systemic chemotherapy, chemoembolization, octreotide therapy, interferon-alpha treatment, ablation and radionuclide therapy (DOTA-TATE);15
• the median overall survival was 39.0 months (95% confidence interval, 12.6–65.4 months), with 71% one-year survival and 45% two-year survival;15
• imaging follow-up at three months using RECIST criteria demonstrated partial response in 43%, complete remission in 3%, stable disease in 37%, and progressive disease in 17% of patients;15
• patients with and without extrahepatic metastasis did not differ significantly in terms of mortality (44% vs. 42%, \( P = 0.936 \)) and radiologic response (33% vs. 52%, \( P = 0.338 \));15
• of the five clinical factors analysed for their prognostic value on overall survival, only the extent of tumour involvement, evaluated in four groups of 1%–25%, 26%–50%, 51%–75%, and 76%–100%, was found to have a statistically significant influence on overall survival (\( P = 0.033 \)); the existence of extrahepatic disease at the time of radioembolisation (\( P = 0.742 \)), radiographic response (\( P = 0.251 \)), age (\( P = 0.653 \)), and primary NET site (\( P = 0.335 \)) were not significant prognostic factors;15
• two patients had radiation-induced gastritis confirmed by endoscopy/biopsy at one, two, and six months after therapy. One of these patients died at six months with progressive liver disease. The other patient had persisting ulceration at 9-month follow-up;15
• the authors conclude that the current study demonstrates effectiveness and safety of radioembolisation for the treatment of unresectable mNET, and recommend to use imaging methods reflecting metabolic activity in the future, to evaluate response of liver metastases after radioembolisation.15

Retrospective study of patients with progressive NET hepatic metastases treated with SIR-Spheres Y-90 resin microspheres as salvage therapy

The study included 40 patients (22 women, 18 men, mean age 61.6 years) with mNET, treated with SIR-Spheres Y-90 resin microspheres:16

• 77% of the patients had small-intestinal NET, 10% had pancreatic NET (nonfunctioning), 7% had bronchial NET, 3% had Insulinoma, and 3% had Gastrinoma;16
• 97% of the patients had bilobar disease and 70% had extrahepatic metastases;16
• all patients had progressive disease, despite extensive treatments when they were admitted for SIRT;16
• previous treatments included resection of the primary tumour (73%), cholecystectomy (37%), somastatin analogues (90%), alpha interferon (75%), chemotherapy (27%), PRRT (45%), everolimus (10%), hepatic arterial embolisation with particles (15%), RFA (15%), SBRT to the liver (3%); 80% of the patients had ongoing treatment with somatostatin analogues;16
• 56 SIRT treatments were performed in 40 patients, of which 54 had imaging done and were evaluable for response;16
• of the 54 evaluable SIRT procedures, 33 were performed to the right liver lobe (mean activity 1.31 GBq), 13 to the left lobe (mean activity 0.85 GBq), and eight to both lobes (mean activity 1.61 GBq);16
• ORR (CR + PR) according to mRECIST was seen in 54% of the treatments at three months and in 34% of treatments at the late follow-up (mean 20 months);16
• DCR (CR + PR + SD) was 94% at the early follow-up and 57% at the late follow-up;16
• in the 16 patients with PD, the median TTP was 9.0 months, calculated per treated lobe;16
• median OS was 24.7 months (range 3–117 months); one, two, three and five year survival rates were 76%, 59%, 52% and 35%, respectively;16
• adverse effects were generally mild and easily manageable, except in one patient who died from radiation-induced liver failure three months after bilobar SIRT treatment. This patient had not discontinued interferon alpha medication as prescribed, which was revealed two months after the SIRT procedure. The radiosensitising effect of alpha-interferon may have contributed to the outcome;16
• the authors conclude that SIRT with \(^{90}\text{Y}\)-labelled resin microspheres is a safe and effective treatment for patients with progressive NETLM, and also for those who have received prior PRRT.16
References
19. Coldwell D. Personal communication.