The following summarises the key data supporting the use of SIR-Spheres Y-90 resin microspheres in the treatment of intrahepatic cholangiocarcinoma:

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>ORR</th>
<th>SD</th>
<th>Median Survival Post-SIRT</th>
<th>Median Survival Post-Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxena</td>
<td>25</td>
<td>SIR-Spheres¹</td>
<td>24.0%</td>
<td>48.0%</td>
<td>9.3 months</td>
<td>20.4 months</td>
</tr>
<tr>
<td>Coldwell</td>
<td>23</td>
<td>SIR-Spheres¹</td>
<td>45.0%</td>
<td>nr</td>
<td>74.0% alive at 14 months</td>
<td>nr</td>
</tr>
<tr>
<td>Khanna</td>
<td>9</td>
<td>SIR-Spheres³</td>
<td>66.0%</td>
<td>13.5 months</td>
<td>20.0 months</td>
<td></td>
</tr>
<tr>
<td>Hoffmann</td>
<td>33</td>
<td>SIR-Spheres³</td>
<td>36.4%</td>
<td>51.5%</td>
<td>22.0 months</td>
<td>43.7 months</td>
</tr>
<tr>
<td>Camacho</td>
<td>21</td>
<td>SIR-Spheres³</td>
<td>6.2%</td>
<td>81.3%</td>
<td>16.3 months</td>
<td>nr</td>
</tr>
<tr>
<td>Rafi</td>
<td>19</td>
<td>SIR-Spheres³</td>
<td>11.0%</td>
<td>68.0%</td>
<td>11.3 months</td>
<td>25.1 months</td>
</tr>
<tr>
<td>Xing</td>
<td>24</td>
<td>SIR-Spheres³</td>
<td>nr</td>
<td>nr</td>
<td>11.5 months</td>
<td>20.8 months</td>
</tr>
<tr>
<td>Filippi</td>
<td>17</td>
<td>SIR-Spheres³ vs. BSC (non-randomised)</td>
<td>82.4%/PET</td>
<td>17.6%/PET</td>
<td>14.9 months</td>
<td>nr</td>
</tr>
<tr>
<td>Soydal</td>
<td>16</td>
<td>SIR-Spheres³</td>
<td>30.0%</td>
<td>nr</td>
<td>9.6 months</td>
<td>nr</td>
</tr>
</tbody>
</table>

Key: ORR: objective response rate (complete response + partial response) by RECIST; SD: stable disease; §SIR-Spheres Y-90 resin microspheres; †retrospective study; nr: not reported; BSC: best supportive care; PET: objective response rate by PERCIST

Prospective study of SIR-Spheres Y-90 resin microspheres in patients with cholangiocarcinoma

A prospective study of SIR-Spheres Y-90 resin microspheres in 25 patients with unresectable nodular intrahepatic cholangiocarcinoma (ICC) by Saxena et al. demonstrated:

- most patients had failed systemic chemotherapy (70%) and/or recurred following surgical resection (40%), with many having bilobar disease (80%), substantial tumour burden (60% having 26–50% liver involvement), extra-hepatic metastases (48%), infiltrative disease (40%) and/or ECOG performance status 1–2 (40%);
- a 24% objective response rate by RECIST with a further 48% having stable disease; one patient with a partial response was sufficiently down-staged to enable surgical resection;
- two patients with advanced symptoms (ECOG 2) died within four weeks of treatment; one at 11 days post-SIRT from hypercalcaemia and one at 28 days from hepatic and extra-hepatic progression;
- at a median follow-up of 8.1 months (range 0.4–56), the median overall survival was 9.3 months, with a 1-, 2- and 3-year survival rates of 40%, 27% and 13% respectively;
- by univariate analysis, there was a significant difference between the survival of ECOG performance status 0 and 1–2 (18.3 vs. 2.4 months; \( P < 0.001 \)) as well as peripheral compared to infiltrative type of disease (18.3 vs. 4.5 months; \( P < 0.004 \));
- however, there was no significant difference between the survival of patients with >11 or <11 months from diagnosis to treatment with SIRT (8.9 vs. 4 months; \( P = 0.097 \)), without or with extra-hepatic metastases (16.3 vs. 4.8 months; \( P = 0.140 \)), prior systemic chemotherapy or none (9.9 vs. 4.6 months; \( P = 0.265 \)), nor by tumour burden (0–25% vs. 26–50%), bilobar/lobar tumour distribution, sex or age;
- all grade clinical toxicities included fatigue (64%), self-limiting abdominal pain (40%), nausea (16%), anorexia (16%), vomiting (8%) and shortness of breath (8%). One patient (4%) had a self-limiting duodenal ulcer. Biochemical follow-up revealed that two patients (8%) had grade 3 bilirubin and albumin toxicities and one patient (4%) developed an alkaline phosphatase toxicity;
- the authors concluded that the study provided preliminary evidence that SIRT is a safe and effective treatment option for unresectable ICC.
Retrospective case series of SIR-Spheres Y-90 resin microspheres in patients with treatment-refractory cholangiocarcinoma

A retrospective study of 23 patients with unresectable nodular ICC who had all failed at least two regimens of chemotherapy and were subsequently treated with SIR-Spheres Y-90 resin microspheres by Coldwell et al. revealed:

- a response rate of 90% by PET and 45% by CT – three patients (13%) were without demonstrable disease on PET, MRI or CT at the time of submission;
- at a mean follow-up of 14 months (range 2–32 months), the median overall survival had not yet been reached with only six deaths in the group at the time of submission (74% survival);
- complications included five patients who had grade 3 GI toxicity which responded to medical therapy. No complications required surgery to correct and there were no treatment-related fatalities;
- in comparison, the author noted that cholangiocarcinoma is not very responsive to chemotherapy with response rates of 14–25% and that, given the hypervascularity of this tumour and its slow growth rate, it is an ideal candidate for loco-regional therapy;
- the author concluded that the tumour response to SIRT is similar to that of colorectal cancer and therefore allows the tumour to be treated effectively, with localised recurrences treated successfully with radiofrequency ablation;
- due to the mismatch in follow-up between CT and PET scanning, the author noted that the use of RECIST or WHO criteria on CT were not an adequate indicator of the effectiveness of SIRT, and that PET scanning should be the method of choice to follow this treatment.

Retrospective study of SIR-Spheres Y-90 resin microspheres in patients with chemotherapy-refractory cholangiocarcinoma

A retrospective study of SIR-Spheres Y-90 resin microspheres in nine patients with unresectable intrahepatic cholangiocarcinoma with an ECOG performance status of 1–2 that had progressed on or had adverse effects from systemic chemotherapy by Khanna et al. revealed:

- 66% of the patients experienced either a partial response or stable disease, with a mean progression-free duration of six months;
- the median survival was 13.5 months from first treatment with SIR-Spheres Y-90 resin microspheres and 20.0 months from diagnosis, with a trend to increased survival in the six patients with a partial response or stable disease on first imaging follow up (15.0 vs. 2.8 months; \( P = 0.081 \));
- there were non-significant differences in the survival of four patients (44%) who also received trans-arterial chemoembolisation [TACE] (13.5 vs. 3.2 months; \( P = 0.127 \), as well as in patients with an ECOG score of 1 or 2 (13.5 vs. 15.0 months; \( P = 0.97 \)) and in those without or with extra-hepatic metastases (15.0 vs. 13.5 months; \( P = 0.56 \));
- there were no early mortalities; two patients had a grade 3 bilirubin toxicity, but there were no other significant complications;
- the authors noted that treatment with SIR-Spheres Y-90 resin microspheres is feasible and may be a therapeutic option in patients with unresectable intrahepatic cholangiocarcinoma.

Retrospective study of SIR-Spheres Y-90 resin microspheres in patients with chemotherapy-refractory cholangiocarcinoma: Analysis of factors associated with prolonged survival

A retrospective study of SIR-Spheres Y-90 resin microspheres in 33 consecutive patients with unresectable or chemotherapy-refractory liver-dominant cholangiocarcinoma in a single institution by Hoffmann et al. showed:
- previous treatments included systemic chemotherapy (82%), surgery (36%) including surgical resection of the primary tumor and liver metastases, TACE (9%), RFA (6%) and external beam radiation (3%); 52% of patients were ECOG performance status 0, 21% were ECOG 1 and 27% were ECOG 2; 64% of patients had infiltrative-type disease and 24% had extra-hepatic disease;
- analysis of contrast-enhanced CT and MRI at three months in all patients by RECIST demonstrated 36.4% partial response and 51.5% stable disease;
- mean follow-up time was 13.5 months (range 3.1–44 months), with 15 of 33 patients still alive at the end of the study. The median decrease of CA19-9 was 28.3% three months after radioembolisation;
- median time to progression (TTP) was 9.8 months;
- median overall survival following SIR-Spheres Y-90 resin microspheres was 22 months and 43.7 months from the initial ICC diagnosis;
- Kaplan-Meier analysis of overall survival and TTP showed significant differences according to the baseline characteristics of the patients:
  - ECOG 0 compared with 1 or 2; median survival 29.4 vs. 10 vs. 5.1 months ($P < 0.001$) and median TTP 17.5 vs. 6.9 vs. 2.4 months ($P < 0.001$), respectively;
  - PR compared with SD or PD; median survival 35.3 vs. 17.7 vs. 5.7 months ($P < 0.001$) and median TTP 31.9 vs. 9.8 vs. 5.1 months ($P < 0.001$), respectively;
  - CA19-9 response compared with no response; median survival 12.5 vs. 6.4 months ($P = 0.02$) and median TTP 9.8 vs. 5.1 months ($P = 0.29$), respectively;
  - Tumour burden ≤25% compared with 26–50%, median survival 26.7 vs. 5.7 months ($P < 0.001$) and median TTP 17.5 vs. 2.3 months ($P < 0.001$), respectively;
- there were no differences in survival or TTP according to either previous chemotherapy or surgery;
- there were no clinically relevant acute or delayed toxicities during follow-up and no radiation-induced liver disease (RILD) was noted;
- Kaplan-Meier survival analysis for SIR-Spheres Y-90 resin microspheres stratified by pre-treatment characteristics:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 0</td>
<td>17</td>
<td>29.4 months (17.7–44)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>7</td>
<td>15.0 months (8.8–19.5)</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>9</td>
<td>5.1 months (3.5–7.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>12</td>
<td>35.3 months (9.8–44)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>17</td>
<td>17.7 months (7.3–26.7)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
<td>3.9 months (3.5–7.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤25% tumour burden</td>
<td>25</td>
<td>10.5 months (17.7–35.3)</td>
</tr>
<tr>
<td>26–50% tumour burden</td>
<td>8</td>
<td>6.0 months (3.5–9.8)</td>
</tr>
</tbody>
</table>

- a separate analysis at the same institution to evaluate the prognostic power of FDG PET/CT and pre-therapy scintigraphy with $^{99m}$Tc-labelled macroaggregated albumin ($^{99m}$Tc-MAA) was performed in 26 consecutive patients with unresectable ICC that received SIR-Spheres Y-90 resin microspheres. This study demonstrated that FDG PET/CT was able to predict patient outcome following SIR-Spheres Y-90 resin microspheres, with the change in metabolically active tumour volume at three months being the best independent predictor. A high uptake on $^{99m}$Tc-MAA scintigraphy did not predict overall survival and was not a pre-requisite for successful radioembolisation. 

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-radioembolisation</th>
<th>Post-radioembolisation (3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG score</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Tumour response</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Tumour burden</td>
<td>E</td>
<td>F</td>
</tr>
</tbody>
</table>

CA19-9

85.2 U/mL

49.2 U/mL

Patient with an intrahepatic cholangiocarcinoma of the left lobe demonstrating a marked decline in SUV$_{max}$ (-70%) and SUV$_{50}$ (-97%) at three months post-radioembolisation with a corresponding fall in CA19-9 tumour marker.

The patient was still alive 12 months post-radioembolisation with no evidence of progression within the liver.
Early imaging prognostic factors in patients with unresectable, chemo-refractory intrahepatic cholangiocarcinoma

A prospective study of 21 patients by Camacho et al. investigated different response criteria as prognostic factors after SIR-Spheres Y-90 resin microspheres:5

- all patients (100%) were chemotherapy refractory and had mass-forming tumour (non-infiltrative); half of the patients had >5 tumours (52%) or were ECOG PS >0 (52%);5
- for the 3-month follow-up imaging, a total of 16 patients were included (four died in the interval and one was lost of follow-up);6
- the objective response rate by RECIST was 6.2% at three months in target lesions, with a further 81.3% having stable disease (SD);6
- the objective response rate by mRECIST was 56.2% at three months in target lesions (12.5% CR; 43.7% PR), with a further 31.3% having SD;5
- the objective response rate by EASL was 50% at three months in target lesions (12.5% CR; 37.5% PR), with a further 37.5% having SD;5
- median overall survival was 16.3 months, no significant difference was observed between the responder and non-responder groups when the 3-month follow-up imaging was based on target RECIST criteria but was significantly longer when based on mRECIST criteria: 21.4 vs. 7.4 months (P = 0.005) or on EASL criteria: 24.3 vs. 6.2 months (P = 0.001);5
- the authors conclude that for intrahepatic cholangiocarcinoma, mRECIST and EASL criteria employing delayed-phase contrast enhancement at three months after radioembolisation predicted overall survival, whereas RECIST did not correlate with survival.5

Retrospective study of SIR-Spheres Y-90 resin microspheres for patients with unresectable, chemo-refractory intrahepatic cholangiocarcinoma

The overall survival, efficacy, and safety of SIR-Spheres Y-90 resin microspheres was assessed in 19 patients by Rafi et al.6

- all patients (mean age 63 ±15.1 years) received prior systemic chemotherapy and four patients (21%) underwent prior TACE with drug-eluting beads; the ECOG performance status was 0 in one patient (5%), one in 14 patients (74%), and two in four patients (21%); 11 patients (58%) had extra-hepatic disease; 16 patients (84%) had tumours >5 cm6
- follow-up imaging at three months based on RECIST criteria demonstrated a partial response in two patients (11%), stable disease in 13 patients (68%), and progressive disease in four patients (21%);6
- median overall survival after ICC diagnosis was 25.1 months, and following first SIR-Spheres Y-90 resin microspheres 11.5 months; the 1-year survival rate after first Y-90 therapy was 56%;6
- there was no significant difference in survival for patients with or without extra-hepatic disease, ECOG 1 or 2, tumour size, bilobar/lobar tumour distribution or single vs. multi-nodular tumours. However patients who received previous treatment with TACE had a better prognosis than the patients who did not (P = 0.047), of note all patients who received TACE had a ECOG PS of 1; this is therefore likely that the results reflect a better survival in patients with less severe cancer-related symptoms;6
- one patient developed grade 3 thrombocytopenia and one grade 3 bilirubin toxicity; no serious gastrointestinal complications, such as gastritis or ulceration of gastric mucosa, due to the presence of microspheres were observed;6
- the authors conclude that radioembolisation with SIR-Spheres Y-90 resin microspheres is effective for unresectable standard chemo-refractory ICC. It is important to note that the study population was of poor prognosis which may have an impact on the outcomes. As indicated in this study Y-90 resin radioembolisation is effective in large tumours (>5 cm) unlike radiofrequency ablation.6

References
2. Coldwell D. World Congress on Gastrointestinal Cancer, Ann Oncol 2006; 17 (Sup 6): v56 Abstract P-152.