Prospective study of SIR-Spheres microspheres in patients with cholangiocarcinoma

A prospective study of SIR-Spheres microspheres in 25 patients with unresectable nodular intrahepatic cholangiocarcinoma (ICC) 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;
- 2 patients with advanced symptoms (ECOG 2) died within 4 weeks of treatment; 1 at 11 days post-SIRT from hypercalcaemia and 1 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 (9.9 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 2 patients (8%) had grade 3 bilirubin and albumin toxicities and 1 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.

### Treatment of progressive disease or chemo-refractory disease

<table>
<thead>
<tr>
<th>Lead Author</th>
<th>n</th>
<th>Treatment</th>
<th>ORR (%)</th>
<th>SD (%)</th>
<th>Median Survival Post-SIRT (months)</th>
<th>Median Survival Post-Diagnosis (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxena¹</td>
<td>25</td>
<td>SIR-Spheres microspheres</td>
<td>24%</td>
<td>48%</td>
<td>9.3</td>
<td>20.4</td>
</tr>
<tr>
<td>Coldwell²</td>
<td>23</td>
<td>SIR-Spheres microspheres</td>
<td>45%</td>
<td>NR</td>
<td>74% alive at 14 months</td>
<td>NR</td>
</tr>
<tr>
<td>Khanna³</td>
<td>9</td>
<td>SIR-Spheres microspheres</td>
<td>66%</td>
<td></td>
<td>13.5</td>
<td>20.0</td>
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<tr>
<td>Rafi⁴</td>
<td>19</td>
<td>SIR-Spheres microspheres</td>
<td>79%</td>
<td></td>
<td>11.3</td>
<td>24.7</td>
</tr>
<tr>
<td>Hoffmann⁵</td>
<td>33</td>
<td>SIR-Spheres microspheres</td>
<td>36.4%</td>
<td>51.5%</td>
<td>22 months</td>
<td>43.7</td>
</tr>
<tr>
<td>Gaba⁶</td>
<td>1</td>
<td>SIR-Spheres microspheres</td>
<td>1 CR</td>
<td>NA</td>
<td>alive at 17 months</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Key:** ORR: objective response rate (complete response + partial response) by RECIST; SD: stable disease; † retrospective study; nr: not reported; CR: complete response; na: not applicable

### Kaplan-Meier survival analysis for SIR-Spheres microspheres stratified by pre-treatment characteristics

**Morphological tumour type**

- Parameter: Peripheral, Infiltrative
- Median Survival: 18.3 months
- P < 0.004

**ECOG performance status**

- Parameter: ECOG 0, ECOG 1–2
- Median Survival: 16.5 months
- P < 0.001

**Extra-hepatic disease (EHD)**

- Parameter: EHD
- Median Survival: 16.3 months
- P < 0.140

The following summarises the key data supporting the use of SIR-Spheres microspheres in the treatment of intrahepatic 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 microspheres revealed:2
- a response rate of 90% by PET and 45% by CT – 3 patients (13%) were without demonstrable disease on PET, MRI or CT at the time of submission;2
- at a mean follow-up of 14 months (range 2–32 months), the median overall survival had not yet been reached with only 6 deaths in the group at the time of submission (74% survival);2
- complications included 5 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;2
- 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;2
- 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;2
- 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.2

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

A retrospective study of SIR-Spheres microspheres in 9 patients with unresectable intrahepatic cholangiocarcinoma with an ECOG performance status of 1–2 that had progressed on or had adverse effects from systemic chemotherapy reported:3
- 66% of the patients experienced either a partial response or stable disease, with a mean progression-free duration of 6 months;3
- the median survival was 13.5 months from first treatment with SIR-Spheres microspheres and 20.0 months from diagnosis, with a trend to increased survival in the 6 patients with a partial response or stable disease on first imaging follow up (15.0 vs. 2.8 months; \( P = 0.081 \));3
- there were non-significant differences in the survival of 4 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; \( P = 0.56 \));3
- there were no early mortalities; 2 patients had a grade 3 bilirubin toxicity, but there were no other significant complications;3
- the authors noted that treatment with SIR-Spheres microspheres is feasible and may be a therapeutic option in patients with unresectable intrahepatic cholangiocarcinoma.3

Retrospective study of SIR-Spheres microspheres in patients with chemotherapy-refractory cholangiocarcinoma: analysis of factors associated with prolonged survival

A retrospective study of SIR-Spheres microspheres in 33 consecutive patients with unresectable or chemotherapy-refractory liver-dominant cholangiocarcinoma in a single institution showed:3
- previous treatments included systemic chemotherapy (82%), surgery (36%) including surgical resection of the primary tumour 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;3
- analysis of contrast-enhanced CT and MRI at 3 months in all patients by RECIST demonstrated 36.4% partial response and 51.5% stable disease;3
- 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%, 3 months after radioembolisation;3
- median time to progression (TTP) was 9.8 months;3
- median overall survival following SIR-Spheres microspheres was 22 months and 43.7 months from the initial ICC diagnosis;3
- Kaplan-Meier analysis of overall survival and TTP showed significant differences according to the baseline characteristics of the patients:3
  - ECOG 0 compared with 1 or 2; median survival 29.4 vs. 10 vs. 5.1 months \( (P \leq 0.001) \) and median TTP 17.5 vs. 6.9 vs. 2.4 months \( (P \leq 0.001) \), respectively;
  - PR compared with SD or PD; median survival 35.3 vs. 17.7 vs. 5.7 months \( (P \leq 0.001) \) and median TTP 31.9 vs. 9.8 vs. 2.5 months \( (P \leq 0.001) \), respectively;
  - CA19-9 response compared with no response; median survival 12.5 vs. 6.4 months \( (P \leq 0.02) \) and median TTP 9.8 vs. 5.1 months, \( (P \leq 0.29) \), respectively;
  - Tumour burden ≤25% compared with 26–50%, median survival 26.7 vs. 5.7 months \( (P \leq 0.001) \) and median TTP 17.5 vs. 2.3 months, \( (P \leq 0.001) \), respectively;3
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; 
the authors concluded that SIRT is an efficacious and safe treatment for unresectable ICC; 

a separate analysis at the same institution to evaluate the prognostic power of FDG PET/CT and pre-therapy scintigraphy with 99mTc-labelled macroaggregated albumin (99mTc-MAA) was performed in 26 consecutive patients with unresectable ICC that received SIR-Spheres microspheres. This study demonstrated that FDG PET/CT was able to predict patient outcome following SIR-Spheres microspheres, with the change in metabolically active tumour volume at 3 months being the best independent predictor. A high uptake on 99mTc-MAA scintigraphy did not predict overall survival and was not a pre-requisite for successful radioembolisation.

Tumour response following SIR-Spheres microspheres

Patient with an intrahepatic cholangiocarcinoma of the left lobe demonstrating a marked decline in SUVmax (-70%) and SUV2SD (-97%) at 3 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.

Radiation lobectomy following SIR-Spheres microspheres

The concept of ‘radiation lobectomy’ following SIR-Spheres microspheres was reported in a patient with biopsy-proven mixed cell type adenocarcinoma and cholangiocarcinoma, who had progressed on systemic chemotherapy comprising capecitabine and gemcitabine:

- a sequential treatment plan was adopted for the right hepatic lobe-dominant disease, delivering 1.58 GBq to the right lobe and 0.98 GBq to the left lobe 1 month later, with a subsequent 1.77 GBq re-treatment of the right lobe for recurrent disease – 10 months after the initial SIRT:
- CT imaging demonstrated marked temporal changes in hepatic lobar volumes, including right lobe atrophy (52% and 84% reduction at 3 and 17 months, respectively) with concomitant left lobe and caudate lobe hypertrophy (10% and 36% enlargement at 3 and 17 months, respectively), and accompanied by complete tumour response by size criteria, as well as loss of tumour and right lobar metabolic activity by PET imaging:
- laboratory analysis indicated that the enlarged left lobe functionally compensated for the atrophy of the right lobe:
- the patient remained alive with excellent performance status 17 months after treatment.
References


