# A prospective, multicentre, randomised, controlled study evaluating SIR-Spheres® Y-90 resin microspheres preceding standard cisplatin-gemcitabine (CIS-GEM) chemotherapy versus CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic CholangioCArcinoma.

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Hepatobiliary neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON47572

**Source**
ToetsingOnline

**Brief title**
SIRCCA

### Condition

- Hepatobiliary neoplasms malignant and unspecified

**Synonym**
billiary tract cancer, intrahepatic cholangiocarcinoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Sirtex Technology Pty Ltd
**Source(s) of monetary or material Support:** de opdrachtgever Sirtex Technology Pty Ltd

## Intervention

**Keyword:** CIS-GEM chemotherapy, intrahepatic cholangiocarcinoma, SIR-Spheres® Y-90, Sirtex

## Outcome measures

### Primary outcome

Primary endpoint:

Survival at 18 months

### Secondary outcome

Secondary endpoints:

- Liver-specific PFS

- PFS at any site

- Objective response rate by RECIST 1.1 and refined RECIST* - liver

- Objective response rate by RECIST 1.1 and refined RECIST* - at any site

- Overall Survival

- Liver surgical resection

- Liver ablation rate

- Safety (CTCAE v4.03) and tolerability

- Quality of Life

# Study description

### Background summary

Despite the advances in different modalities for cholangiocarcinoma the 3 and 5 year survival in non-surgically resected selected patients remains below 50% and 10% respectively.
This approach to integrating potentially curative tumoricidal therapies (ablation, locoregional SIRT and external beam radiotherapy) in patients with unresectable intrahepatic cholangiocarcinoma has to be compared to the current standard of care therapy * cisplatin and gemcitabine (CIS-GEM) systemic chemotherapy (Valle 2009 (65), Valle 2010 (66)) * in order to judge potential benefits.
SIR-Spheres Y-90 resin microspheres have been studied for the treatment of patients with inoperable intrahepatic cholangiocarcinoma. Although no randomised controlled study has been performed to date, the results of SIRT in patients with ICC, in either prospective or retrospective cohort studies, look very promising and provide preliminary evidence that SIRT is a safe and effective treatment option for unresectable ICC.

### Study objective

This study will assess the benefit of adding SIRT to a standard regimen of cisplatin and gemcitabine (CIS-GEM) systemic chemotherapy in unresectable liver-only or liver predominant intrahepatic cholangiocarcinoma.
Patients will be offered the accepted treatment in conventional practice and the active arm of the trial will combine the standard of care with radioembolization. Such a trial design guarantees that patients do not lose the benefits of conventional therapy and allows the determination of survival benefits of the combined approach.

### Study design

This clinical study is a prospective, multicentre, randomised, controlled study evaluating SIR-Spheres Y-90 resin microspheres preceding standard cisplatin-gemcitabine (CIS-GEM) chemotherapy vs. CIS-GEM chemotherapy alone as first-line treatment of patients with unresectable intrahepatic cholangiocarcinoma.
The target recruitment is about 180 randomised patients who started treatment. However, it is expected that about 160 of the patients in both arms will satisfy the compliance criteria i.e. (Arm A: completed at least one cycle; Arm B completed SIRT treatment and complete at least one cycle).
Patients will be randomised 1:1 (about 90 patients in each arm) to receive either:
1. Treatment Arm A: Standard of care systemic chemotherapy with an intention to

treat with 8 cycles of cisplatin + gemcitabine, or until progression, toxicity or patient choice. Treatment may be continued beyond 8 cycles in the absence of significant disease progression, at the treating clinicians* discretion.
2. Treatment Arm B: A single treatment of hepatic arterial injection of SIR-Spheres Y-90 resin microspheres followed 14-16 days later by standard of care systemic chemotherapy (ABC-02 CIS-GEM protocol) with an intention to treat with 8 cycles of cisplatin + gemcitabine, or until progression, toxicity or patient choice. Treatment may be continued beyond 8 cycles in the absence of significant disease progression, at the treating clinicians* discretion.
Patients will be stratified by: presence of extra-hepatic disease, presence of cirrhosis, intention for whole liver versus non-whole liver Y-90 treatment, baseline albumin levels (< 35g/L vs * 35g/L) and ECOG status (0 versus 1).

**Intervention**

Patients will be randomised 1:1 (about 90 patients in each arm) to receive either:
1. Treatment Arm A: Standard of care systemic chemotherapy with an intention to treat with 8 cycles of cisplatin + gemcitabine, or until progression, toxicity or patient choice. Treatment may be continued beyond 8 cycles in the absence of significant disease progression, at the treating clinicians* discretion.
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**Study burden and risks**

With more than 50,000 doses (as of June 2015) supplied, SIRT has been shown to be generally well tolerated.

Minor side effects of SIRT include the following
1. Most frequently, patients develop a fever that begins within 24 hours of treatment. This will usually go away without treatment. This fever is a result of the action of the SIRT in the liver.
2. Up to half of patients develop pain in the upper abdomen after SIRT. This may start during the procedure and usually lasts only for a few hours. .
3. Nausea is common in approximately half of patients but this subsides with time and medication.
4. Some patients complain of feeling *off colour* or tired with loss of appetite for several days after treatment. This goes away with time, and it is due to the fact that, although the SIRT is only administered once, the effects of treatment last for several weeks.

More serious side effects include:
1. It is possible that the SIR-Spheres Y-90 resin microspheres can be incorrectly delivered and they do not all remain in the liver. This can be due to technical problems while inserting the catheter into the artery in the liver. If this happens, the spheres may be inadvertently supplied to other organs in the body, including the stomach, intestine, pancreas and lungs. If this were to happen then it may cause pancreatitis or gastritis. If too many SIR-Spheres Y-90 resin microspheres go to the lung, then this may cause pneumonitis.
2. There is a very small risk that the treatment with SIRT could result in a fatal complication, however from past experience the chance of this is less than 1%.
3. The dose of radiation that you receive is individually calculated. However, if the normal liver receives too high a dose, some patients may develop long-term damage to the liver. In a recent study using SIR-Spheres Y-90 resin microspheres, in a very small number of cases, there was evidence of damage to the normal healthy part of the liver, but this will be minimised by carefully assessing the individual dose.

The use of chemotherapy and radiation using SIR-Spheres Y-90 resin microspheres together may increase the effect of the treatment, but may also increase the possibility of side effects. It is presumed that any side effects would be the same sort as are known to occur with each treatment alone, but they may be more common or more severe.

Risks associated with the insertion of SIR-Spheres Y-90 resin microspheres, the hepatic angiogram and the MAA breakthrough scan:
There is a risk of pain, bruising, infection and minor blood loss from the groin artery where the catheter is inserted. Allergic reactions to the contrast dye used may occur. Rarely, the arteries may be damaged from the insertion of the catheter but this risk is minimised because only experienced doctors will perform these procedures.

Advice radiation committee:
In this multi-center study a maximum of 180 patients with Cholangiocarcinoma (20 patients in AMC) will be treated with SIR-spheres. We estimate the target dose due to the treatment around 120 Gy. For the study also some extra diagnostic tests will be done. The organ doses due to these diagnostic tests are expected to be more than 100 times lower than the therapeutic doses and therefore are considered negligible compared to the target dose. A calculation of the extra risk due to the diagnostic scans is therefore not meaningful. On top of this comes the fact that the targeted patients are not considered *normal average adults*, due to their limited life expectancy of on average ca. 1 year. This makes the risk much less than in other cases.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

a) Willing, able and mentally competent to provide written informed consent
b) Aged 18 years or older
c) Histologically or cytologically confirmed unresectable and/or non ablatable intrahepatic cholangiocarcinoma
d) Liver-only or liver predominant intrahepatic cholangiocarcinoma. Patients are permitted to have loco-regional lymph node involvement defined as: portal LN * 2 cm and/or para aortic LN * 1.5 cm in longest diameter, and/or up to 2 indeterminate lung lesions < 1 cm if these lung lesions are PET negative.
e) Chemotherapy naïve. Adjuvant chemotherapy is not permitted
f) ECOG performance status 0 or 1,
g) Adequate haematological function defined as:
Haemoglobin * 10g/dL

WBC * 3.0 x 109/L
Absolute neutrophil count (ANC) * 1.5 x 109/L
Platelet count * 100,000/mm3,
h) Adequate liver function defined as:
Total bilirubin * 30 *mol/L (1.75 mg/dL)
Albumin * 30 g/L
i) Adequate renal function defined as:
Serum urea and serum creatinine < 1.5 times upper limit of normal (ULN)
Creatinine clearance * 45 ml/min (calculated with Cockcroft-Gault Equation)
All blood test results must be within 14 days prior to randomisation.
j) Life expectancy of at least 3 months without any active treatment
k) Female patients must either be postmenopausal, sterile (surgically or radiation- or chemically-induced), or if sexually active use an acceptable method of contraception during the study.
l) Male patients must be surgically sterile or if sexually active must use an acceptable method of contraception during the study.
m) Considered suitable to receive either treatment regimen in the clinical judgement of the treating investigator.

## Exclusion criteria

a) Patients with only non-measurable lesions in the liver according to RECIST criteria
b) Incomplete recovery from previous liver surgery, e.g. unresolved biliary tree obstruction or biliary sepsis or inadequate liver function
c) Biliary stenting in situ
d) Main trunk Portal Vein Thrombosis (PVT)
e) Ascites, even if controlled with diuretics. (A minor peri-hepatic rim of ascites detected at imaging is acceptable.)
f) Mixed HCC-ICC disease.
g) History of prior malignancy. Exceptions include in-situ carcinoma of the cervix treated by cone-biopsy/resection, non-metastatic basal and/or squamous cell carcinomas of the skin, recurrent intra-hepatic cholangiocarcinoma post local treatment, or any early stage (stage I) malignancy adequately resected with curative intent at least 5 years prior to study entry
h) Suspicion of any bone metastasis/metastases or central nervous system metastasis/metastases on clinical or imaging examination.
i) Prior internal or external radiation delivered to the liver.
j) Pregnancy; breast feeding,
k) Participation within 28 days prior to randomisation, in an active part of another clinical study that would compromise any of the endpoints of this study.
l) Evidence of ongoing active infection that may affect treatment feasibility or outcome
m) Prior Whipple*s procedure

# Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 15-05-2017 |
| Enrollment: | 20 |
| Type: | Actual |

# Ethics review

| | |
|---|---|
| Approved WMO Date: | 18-01-2017 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 06-08-2019 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| ClinicalTrials.gov | NCT02807181 |
| CCMO | NL56423.018.16 |