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ABSTRACT

Introduction

For patients with perihilar cholangiocarcinoma (CCA), surgery is the only treatment modality that can result in cure. Unfortunately, in the majority of these patients the tumours are found to be unresectable at presentation due to either local invasive tumour growth or the presence of distant metastases. For patients with unresectable CCA palliative chemotherapy is the standard treatment yielding an estimated median overall survival (OS) of 12-15.2 months. There is no evidence from randomized trials to support the use of stereotactic body radiation therapy (SBRT) for CCA. However, small and most often retrospective studies combining chemotherapy with SBRT have shown promising results with OS reaching up to 33-35 months.

Methods and analysis

This study has been designed as a single center phase I feasibility trial and will investigate the addition of SBRT after standard chemotherapy in patients with unresectable perihilar CCA (T1-4 N0-1 M0). A total of six patients will be included. SBRT will be delivered in 15 fractions of 3-4.5Gy (risk adapted). The primary objective of this study is to determine feasibility and toxicity. Secondary outcomes include local tumour control, progression free survival (PFS), OS and quality of life. Length of follow-up will be 2 years. As an ancillary study, the personalized effects of radiotherapy will be measured in vitro, in patient derived tumour and bile duct organoid cultures.

Ethics and dissemination

Ethics approval for the STRONG trial has been granted by the Medical Ethics Committee of Erasmus MC Rotterdam, the Netherlands. It is estimated that all patients will be included between October 2017 and October 2018. The results of this study will be published in a peer-reviewed journal, and presented at national and international conferences.

Trial registration number NCT03307538

Strengths and limitations of this study	
Strengths	• A promising local treatment option will be studied for patients with unresectable perihilar cholangiocarcinoma. • The fractionation scheme used in this trial makes it possible to deliver a relative high radiation dose to the tumour and protect surrounding organs. • Toxicity will be closely observed. • Inter- and intrafraction motion will be assessed using multiple CT-scans during treatment.
Limitations	• The study population is small, therefore no robust analysis other than feasibility and toxicity can be done.

INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common primary liver tumour worldwide[1]. CCA accounts for 3% of all gastro-intestinal tumours[2]. Of all CCA approximately 50-70% arise at the hilar plate of the biliary tree, and these tumours are being referred to as either perihilar CCA or Klatskin tumours[3]. Resection is the only potential curative treatment for patients with perihilar CCA. Median overall survival (OS) ranges from 27-58 months among operated patients with negative resection margins[4]. Unfortunately, the majority of patients presents with unresectable disease at diagnosis[4 5]. Selected patients are eligible for liver transplantation. Five year survival rates for both margin-negative resection and neoadjuvant therapy combined with liver transplantation are similar[4].

The standard treatment for patients with unresectable or metastatic perihilar CCA is chemotherapy that consists of 8 courses of Gemcitabine and Cisplatin. The survival rates for inoperable patients who receive this chemotherapy regimen are poor: Valle et al. reported in a prospective study (ABC-02 trial) a median OS of 11.7 months, and a PFS of 8.0 months[6]. In a retrospective study Eckmann et al. showed a median OS of 15.2 months in these patients treated with Gemcitabine and Cisplatin. Partial response or stable disease rates of 72% were found, with a median duration of response of 8.1 months[7].

Local ablative therapies

Because of these poor OS rates for patients treated with chemotherapy, some local therapies have been investigated. One of these treatment options is ablation with irreversible electroporation (IRE), which is currently under investigation in the ALPACA trial[8]. Until now there is little evidence to support the routine use of IRE for perihilar CCA patients. One case report describes a technically successful procedure, but data on toxicity and disease outcome are lacking[9]. Another local therapy option is radiofrequency ablation (RFA). Wu et al. published a retrospective study that showed prolongation of stent patency and better functional status and quality of life in a group of patients treated with intraductal RFA before stent placement, compared to stent placement alone. There are no data on disease outcome after RFA. A third ablative therapy option is photodynamic therapy using temoporfin (T-PDT). Wagner et al. report a local response after one treatment of 55%, with a median time to local tumour progression of 6.5 months, but also a high percentage of cutaneous photo toxicity (41%)[10]. Finally, brachytherapy has been studied mostly as a palliative treatment in combination with external beam radiotherapy or in a neoadjuvant setting. In combination with external beam radiotherapy survival rates are poor, with a median OS of 12 months[11].

Stereotactic body radiation therapy (SBRT)

Also, the role for radiotherapy in the treatment of CCA is currently not well defined. Various groups have tried to use SBRT to deliver high radiation doses to control the disease locally. Most of the published studies have been retrospective (table 1).

Table 1. Treatment outcomes of SBRT for CCA

AUTHOR	DESIGN	LOCATION	LESION NUMBER	FRACTION NUMBER	TOTAL DOSE (Gy)	1year LOCAL CONTROL	MEDIAN SURVIVAL (months)	TOXICITY[a]
Kopek[12]	R	PH-CCA IH-CCA	26 1	3	45	84%	10.6	6 ulceration 3 stenosis
Tse[13]	P	IH-CCA	10	6	28-48	65%	15	2 liver enzymes 1 bowel obstruction
Polistina[14]	R	PH-CCA	10	3	30	80%[b]	35.5	1 ulceration 2 stenosis
Barney[15]	R	IH-CCA PH-CCA EH-CCA	6 3 1	3-5	45-60	100%	15.5	1 biliary stenosis 1 liver failure
Momm[16]	R	PH-CCA	13	8-16	32-56	N.R.	33.5	1 nausea 5 cholangitis
Jung[17]	R	IH-CCA EH-CCA	33 25	1-5	15-60	85%	10	2 ulceration 2 cholangitis 1 biliary stenosis 1 gastric perforation
Mahadevan[18]	R	IH-CCA PH-CCA	31 11	1-5	10-45	88%	17	2 duodenal ulceration 1 cholangitis 1 liver abscess
Tao[19]	R	IH-CCA	79	15-30	50.4-75	81%	30	3 cholangitis 2 gastric bleeding 7 biliary stenosis
Sandler[20]	R	IH-CCA EH-CCA	6 25	5	40	78%	15.7	2 duodenal obstruction 3 duodenal ulceration

P: Prospective. R: Retrospective. OS: Overall survival. IH-CCA: Intrahepatic cholangiocarcinoma. PH-CCA: Perihilar cholangiocarcinoma. EH-CCA: Extrahepatic cholangiocarcinoma. N.R.: not reported

[a] Early and late toxicity, grade 3 or more. [b] At 6 months

SBRT has been explored as single-modality treatment in patients who are unsuitable for resection, although it has also been administered as adjuvant treatment after surgery with positive margins[18]. The patient groups were almost invariably small and/or heterogeneous, which makes it hard to draw firm conclusions[12-20]. Most studies did not limit number or size of lesions, with the exception of one study (maximum diameter of ≥6cm was an exclusion criterium)[14].

High rates of 2-year local control (LC) after SBRT have been reported. In most studies, this was achieved in ≥72% of the patients. Median OS ranged between 10 and 35.5 months, with five studies reporting OS ≥15 months, and three reporting OS ≥24 months[12-20]. Tao et al. found a significant improvement in LC when high radiation doses were delivered. When biologically effective doses (BED) were >80.5Gy, three-year LC was achieved in 78% vs. 45% with lower doses[19].

One of the difficulties for a SBRT treatment in the perihilar region is the proximity of organs at risk like the common bile duct and duodenum. The hepatobiliary toxicity reported by other groups varied widely but was generally limited in most of the series. A slightly higher number of gastrointestinal toxicity has been reported, mainly duodenal obstruction and stenosis (table 1)[12-20]. This toxicity could potentially be limited by the application of strict dose-volume constraints.

METHODS AND ANALYSIS

Design

This study has been designed as a single center phase I feasibility trial. Six patients with unresectable perihilar CCA, who already received the standard treatment with systemic chemotherapy (cisplatin and gemcitabine), will be included.

The reason to design a feasibility study is that no data have been published about the delivery of SBRT in 15 fractions of 3-4.5Gy in patients with perihilar CCA after chemotherapy. Data have been reported on patients with intrahepatic CCA treated with 15 fractions of radiotherapy, although the chemotherapy regimen and the timing of administration before or after the local treatment varied largely[19]. The possibility of delivering the standard treatment without interferences due to potential toxicity caused by SBRT, was the main reason to choose for an adjuvant approach instead of neo-adjuvant or concomitant.

The trial follows the conventional `3+3'-design. First 3 patients will be included, after which the trial will temporarily be put on hold for 3 months. When 2 or 3 patients develop limiting toxicity (LT), the conclusion will be that the proposed risk adapted radiotherapy protocol is not feasible and the trial will be ended. When 0 or 1 of 3 patients develops LT, 3 additional patients will be included. LT will be defined as grade 4 or more hepatobiliary toxicity related to study procedures, or grade 3 or more gastrointestinal toxicity related to study procedures, occurring in the period up to 3 months after the last SBRT administration. When 0 or 1 of these 6 patients develops LT, then the conclusion will be that the current risk adapted radiotherapy protocol is feasible, and should be considered for further research in this patient population (i.e. in a phase II trial). Otherwise, if 2 or more patients have limiting toxicity, the conclusion will be that the current risk adapted radiotherapy protocol is not feasible.

Study objectives

Primary study outcome

The primary objective of this study will be to determine feasibility and toxicity (according to the Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 grading system) of adding SBRT to standard chemotherapy, in patients with perihilar CCA ineligible for surgery.

Secondary study outcomes

- Local control, defined as time from inclusion to local radiological progression. Definition of progression is based on RECIST 1.1[21].
- Progression free survival, defined as time from inclusion until radiological progression. Definition of progression is based on RECIST.
- Overall survival, defined as time from inclusion until death from any cause.
- Quality of life, assessed by means of the EuroQol EQ-5D-5L (measure of health outcome in general population), and the EORTC QLQ-C30 (quality of life specific for cancer patients) with the supplementary module EORTC QLQ- BIL21 (specific for CCA and gallbladder cancer).

- Cellular radiosensitivity, as a side track of this study. The effects of radiotherapy will be measured in normal bile duct organoids[22] and CCA cancer-derived organoids (Broutier et al. Tumour-derived organoid cultures model primary human liver cancer in vitro, article in press) obtained from cells of brush cytology obtained during ERCP. The goal is to set up assays to measure genomic mutations, cell death/apoptosis, cellular senescence and proliferative capacity after ionizing radiation treatment ex vivo. In the future, these effects will be measured in organoids and will be correlated with tumour response on imaging (CT/MRI) in a large phase II trial. Prediction of response and toxicity before treatment will be the ultimately goal of this approach in the future.

Study population

Six patients with unresectable perihilar CCA after completion of standard chemotherapy with cisplatin and gemcitabine will be enrolled in this study. In order to be eligible, a subject must be discussed in a multidisciplinary liver tumour board and should meet all of the in- and exclusion criteria as listed in table 2. All types of biliary stents are accepted. The expected time to include the required patients for this trial will be one year.

Table 2. In- and exclusion criteria

Inclusion criteria	Exclusion criteria

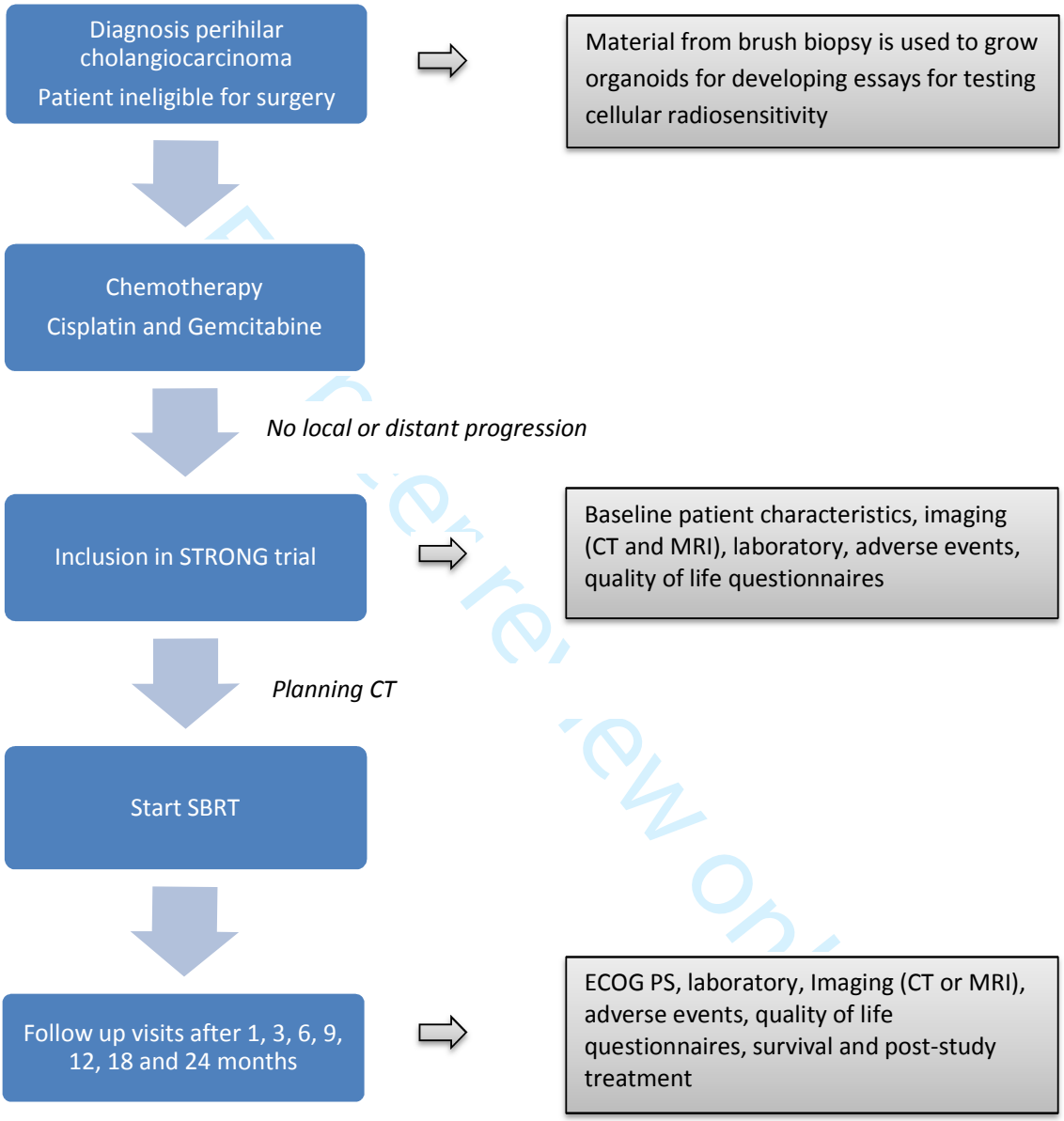
• Patients diagnosed with perihilar CCA according to the criteria of the Mayo Clinic, Rochester[23]:
  ○ Positive or strongly suspicious intraluminal brush or biopsy, or
  ○ A radiographic malignant appearing stricture plus either:
  ▪ CA 19-9>100 U/ml in the absence of acute bacterial cholangitis, or
  ▪ Polysomy on FISH, or
  ▪ A well-defined mass on cross sectional imaging
• One tumour mass
• Unresectable tumour
• Finished chemotherapy treatment with Gemcitabine and Cisplatin, preferably 8 cycles.[a] T1-T4 (AJCC staging 7th edition)[b] before chemotherapy
• N0-N1 (AJCC staging 7th edition), radiologically or pathologically suspect
• Measurable disease to be selected as a target on CT/MRI-scan, according to RECIST criteria[c,d]
• Tumour visibility on CT
• If liver cirrhosis is present, it should be well compensated, with Child-Pugh grade A
• Age ≥ 18 years
• ECOG performance status 0-1
• Bilirubin ≤1.5 times normal value, AST/ALT ≤5 times ULN[d]
• Platelets ≥ $50x10^9$/l, Leukocytes > $1.5x10^9$/l, Hb > 6 mmol/l[d]
• Written informed consent[c]
• Willing and able to comply to the follow-up schedule
• Able to start SBRT within 12 weeks after completion of chemotherapy.
	• Eligibility for resection
	• Prior surgery or transplantation
	• Multifocal tumour
	• Tumour extension in stomach, colon, duodenum, pancreas or abdominal wall
	• N2, (AJCC staging 7th edition), radiologically or pathologically suspect[b]
	• Distant metastases
	• Progression (local or distant) during or after chemotherapy
	• Ascites
	• Previous radiotherapy to the liver
	• Current pregnancy

[a] If less cycles have been given, patients are still eligible for this study. [b] Before chemotherapy. [c] After chemotherapy. [d] Within 6 weeks prior to inclusion

Study outline

The general outline of the study procedures is presented in figure 1.

Figure 1. Study outline



Pre-SBRT

Chemotherapy is considered the standard treatment for unresectable perihilar CCA, and therefore will not be considered as study treatment in this trial. Cisplatin plus gemcitabine will be administered according to standard practice of the Erasmus MC Cancer Institute. Chemotherapy will be discontinued at 24 weeks (8 cycles) or earlier in case of disease progression, patient or clinician decision, or unacceptable toxic effects. Biliary obstruction per se is not considered to be disease progression in the absence of radiologically confirmed tumour progression, and treatment can be recommenced after further biliary stenting and normalization of liver function[6]. In case of unacceptable toxic effects and in absence of disease progression, the patient can proceed to SBRT without completing 8 cycles of chemotherapy. In that case, no signs of progressive disease should have been observed on a chest/abdomen CT scan performed within 6 weeks before patient inclusion.

SBRT

Treatment with SBRT will start preferably within 6 weeks after the last chemotherapy course. However, if due to toxicity or other medical or personal reasons the start of the treatment has to be postponed, the time to start can be expanded till a maximum of 12 weeks after the last course of chemotherapy.

We will use a risk-adapted dose prescription for delivering the highest possible dose to the tumour, using 15 fractions of 3-4,5Gy, while not exceeding widely accepted dose constraints in the surrounding organs at risk (table 3 and 4). This approach has already been tested with favorable outcome and limited biliary toxicity in a multicenter retrospective study for intrahepatic CCA[19]. The same radiotherapy protocol (dose and fractionation) is currently being tested in a prospective phase III trial between chemotherapy and chemotherapy combined with radiotherapy in patients with unresectable intrahepatic CCA (NRG-GI001). To the best of our knowledge, this approach for perihilar CCA has not been published yet.

Table 3. Organs at risk constraints

Organ at risk	**Hard constraints**
Healthy liver	≥700ml liver-GTV, dose <25.5Gy[24] If cirrhosis is present: NTCP liver-GTV ≤5%[25] and >800ml liver-GTV, dose <31.5Gy[26]
Stomach	Max point dose <57Gy[27] Volume receiving ≥41Gy should be ≤5cc
Duodenum Small and large bowel (when needed combined in one structure)	Max point dose <57Gy[27] Volume receiving ≥41Gy should be ≤5cc
Esophagus	Max point dose ≤50.25Gy[28]
Spinal cord	Max point dose ≤33.8Gy[24]
Kidney	2/3 right kidney <25.5Gy[24]

Table 4: Organ at risk objectives

Organ at risk	Objectives
Central biliary tract	Less than 0.5cc ≥70Gy (NRG-GI001 - http://www.cancer.gov/clinicaltrials) V_{BED10} 40 <37cc and V_{BED10}30 < 45cc[29]
Heart	Max dose <57Gy (RTOG 1112 - http://www.cancer.gov/clinicaltrials)
Gallbladder	Max dose <86.7Gy (RTOG 1112- http://www.cancer.gov/clinicaltrials)
Skin (external contour)	Less than 0.5cc ≥50.25Gy (RTOG 1112 - http://www.cancer.gov/clinicaltrials)

Marker implantation

A tumour tracking technique (Synchrony-Cyberknife, Accuray, Sunnyvale, CA, USA) will be applied for daily positioning and during dose delivery. Therefore, implantation of fiducials is compulsory. For perihilar CCA, fiducials should be implanted in the liver and not in the tumour to avoid the risk of tumour seeding. A distance of around 2.0 cm from the tumour edge is recommended. The procedure will be performed by an experienced interventional radiologist. INR should be <2.0, and platelets should be ≥50×10^9/l. We will plan around one week (minimum of 5 and maximum of 10 days) between the implantation of the fiducials and the treatment preparation (planning CT). Patients should remain hospitalized during at least 2-3 hours after the implantation in order to detect and treat unexpected complications as soon as possible. In case of lymph node involvement, no fiducials will be implanted in the affected nodes.

Tumour delineation

The gross target volume (GTV) is defined in a contrast-enhanced CT acquired in expiration and in a hepatic venous phase. An arterial phase CT with bolus tracking technique is also performed since valuable complementary information from this phase could be valuable to better depict the tumour. The use of MRI to support the tumour delineation is recommended. In case that enlarged lymph nodes (N1) have to be considered as a target for SBRT, the venous phase of the planning CT in expiration will also be used for the delineation. No additional margin will be added around the GTV to generate the clinical target volume (CTV) for both tumour and lymph nodes.

Margins

The information acquired from a 4DCT scan and from the inspiration/expiration CT will be used to establish the margin around the GTV to generate the planning target volume (PTV). This margin should ensure that despite geometrical uncertainties (i.e. imaging artifacts in the planning CT-scan due to respiratory tumour motion, inter-fraction motion of the tumour, uncertainty in the set-up, etc.), the full GTV is irradiated with an adequate dose with a very high probability.

Planning protocol

Efforts should be made to deliver a BED>80.5Gy to the tumour, since a multicenter retrospective study of intrahepatic CCA demonstrated a significant improvement in LC depending on the BED (3y

45% for BED<80.5Gy vs. 78% for BED>80.5Gy)[19]. In case the tumour is located very close/adjacent to organs at risk as the duodenum, stomach, esophagus or bowel, it may be impossible to deliver such high doses to the periphery of most of the tumour, and therefore lower doses at the periphery are allowed in these cases.

Any plan delivered to a patient should adhere to the imposed organs at risk (OAR) hard constraints (table 3). Within these constraints, ideally the full PTV is irradiated with a dose of ≥67.5Gy (15×4.5Gy). Due to the hard constraints and the objectives for the OARs, this ideal PTV dose may not always be achievable. In that case, compromises in PTV dose delivery can be made. First of all, the PTV coverage may be reduced, i.e. only 95% of the PTV may receive ≥67.5Gy. Second, instead of delivering 67.5Gy (15×4.5Gy), a dose of 60Gy (15×4Gy), 52.5Gy (15×3.5Gy) or even 45Gy (15×3Gy) can be chosen. An effort should be made to deliver at least 60Gy (BED>80.5Gy) to a large portion of the PTV without violating OAR constraints.

Fractionation and daily imaging

The total dose is delivered in 15 fractions. Time between fractions should be 24h (in case of a weekend in between it will be 72h). Effort should be made to deliver the treatment without gaps.

In order to evaluate the relationship between tumour and organs at risk in this perihilar location, a CT scan before and after treatment in expiration phase will be performed in treatment position the first day and on days 3, 6, 9, 12 and 15 during treatment. No intravenous contrast will be used.

Post SBRT follow up

Follow up visits will be scheduled at 1, 3, 6, 9, 12, 18 and 24 months after treatment. At every visit a MRI or CT scan will be made to detect local or distant disease progression. Also toxicity and performance score will be scored every visit. Patients will be asked to fill out quality of life (QoL) questionnaires (EuroQol EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ- BIL21) at most visits. For further detailed information see table 5. If a patient is still alive after 2 years, follow up will be continued by the medical oncologist according current clinical practice.

Ancillary study: evaluating cellular radio-sensitivity in patient-derived organoid models

We will grow organoids from tumour and bile duct cells collected by brush biopsies[22](Broutier et al. Tumour-derived organoid cultures model primary human liver cancer in vitro, article in press). For this purpose a second brush will be obtained during the same procedure while the first brush is taken (just directly after the first one) and only for patients where a brush biopsy is considered needed as part of the diagnostic work up. We will set up assays to measure cell survival (clonogenic assays, HE staining of organoids), apoptosis (TUNEL staining), accumulation of DNA repair proteins on DNA double strand breaks (gamma-H2AX, 53BP1 and RAD51 foci) and repair of the DNA damage at various time points after irradiation (loss of these foci after 24-48 hours of incubation). In addition to the functional assays, organoid cultures are also ideal sources of tumour material, such as DNA for mutation analysis and RNA for gene expression studies[30].

Table 5: Schedule of events

	Eligibility check	Written informed consent	Medical history	Co-morbidity	ECOG PS	Laboratory[a]	CT/MRI[b]	Adverse events[c]	QOL	Survival and post-study treatment
Standard treatment (Chemotherapy) 1-8 courses. No progressive disease										
≤6 weeks	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Experimental add on treatment (SBRT)										
+1 month					**X**	**X**	**X**	**X**	**X**	**X**
+3 months					**X**	**X**	**X**	**X**	**X**	**X**
+6 months					**X**	**X**	**X**	**X**	**X**	**X**
+9 months					**X**	**X**	**X**	**X**	**X**	**X**
+12 months					**X**	**X**	**X**	**X**	**X**	**X**
+18 months					**X**	**X**	**X**	**X**		**X**
+24 months					**X**	**X**	**X**	**X**	**X**	**X**

[a] Lab assessments should include albumin, bilirubin, alkaline phosphatase, AST, ALT, GGT, Hb, leukocytes, platelets, and CA-19.9. Notice that CA-19.9 should only be assessed during follow-up if indicated, i.e. if elevated at baseline. [b] Radiology report should include tumour measurement, tumour measurements should be performed according to RECIST criteria. [c] CTCAE v 4.03 should be applied for grading toxicity

Data analysis

This trial will be performed as a feasibility study and will focus on toxicity until 3 months after SBRT treatment. The number of patients with LT as defined before will be determined. If two or more patients have LT, the conclusion will be that the regimen is not feasible. Otherwise the conclusion will be that the regimen warrants further research in this population.

In addition, the analysis of toxicity will be done by tabulation of the incidence of adverse events CTCAE grade 3 and 4. Adverse events will be summarized by worst CTCAE grade. Demographics of the patients at study entry will be recorded, and presented as percentages in case of discrete variables, or by median and range in case of continuous variables. All patients with the baseline and at least one follow-up QoL questionnaire, separately for QLQ-C30, QLQ-BIL21 and EuroQoL-5D, will be included in the analysis. The repeated measures will be analyzed using ANOVA models. The

Kaplan-Meier method will be used to estimate local control, progression free survival and overall survival.

ETHICS AND DISSEMINATION

Prior to any study procedure written informed consent will be obtained from every participating patient. Ethics approval for the study was granted 31 August 2017 by the Medical Ethics Committee of Erasmus MC Rotterdam, the Netherlands (ID: NL 60588.078.17). The STRONG trial is registered on clincaltrials.gov (ID: NCT03307538). The results of this study will be published in an academic journal, and presented at national and international conferences.

DISCUSSION

The STRONG trial is designed to assess feasibility and toxicity of adding SBRT to standard chemotherapy in patients with inoperable perihilar CCA. Currently, only a few prospective studies are available on the use of SBRT for treating patients with CCA in the perihilar region. These studies report promising results for LC (≥72% at 2 years) and median OS (up to 35 months), with low toxicity rates. However, the exact treatment approach (combination with chemotherapy, chemotherapy scheme, timing, SBRT fractionation) varied widely[12-20]. The scarce available results suggest that the combination of chemotherapy and SBRT may improve disease control above SBRT alone.

We chose a more fractionated scheme than the other studies on SBRT for perihilar tumours because of the proximity of organs at risk like duodenum and bile duct to the tumour. By using 15 fractions, instead of fewer, we hope to reach an acceptable coverage of the PTV with a biologically effective dose of more than 80.5Gy, and at the same time respect the dose constraints for the OAR's. Acceptable results have been published with this fractionating scheme for intrahepatic CCA[19].

In this study we will encounter some technical challenges and uncertainties. First of all is the assessment of the breathing motion of tumours located in the perihilar region. Since we use the Synchrony-Cyberknife system for tumour tracking, fiducial markers will have to be implanted close to the tumour. These markers will be placed in the liver in the proximity of the tumour and not in the tumour itself to avoid tumour seeding. Second, there is little known about the inter- and intrafraction motion of organs at risk located in the vicinity of the perihilar region and the correlation with the tumour motion. If present, involved lymph nodes may be situated at a certain distance of the tumour. Again, motion assessment and correlation with tumour motion will be another point that should be addressed within this study. In order to measure variations in inter- and intrafraction motion, a CT scan in expiration phase before and after treatment will be performed in treatment position the first day and on days 3, 6, 9, 12 and 15 during treatment.

Because of these technical uncertainties in combination with the experimental fractionation scheme for tumours located in the perihilar region, the first step is to complete this feasibility trial with just 6 patients. Since this small number results in limitations for interpreting results on disease control and QoL, our aim is to proceed to a large phase II trial if the treatment turns out to be feasible.

AUTHOR CONTRIBUTIONS All authors contributed to the design of the study protocol and approved the final manuscript. AMR and MSK principal investigators, initiators of the trial. BJMH medical physics aspects. BvdH statistical design and data analysis. DCvG and LJWvdL molecular genetics side study. FEJAW radiological support. BGK surgical aspects. FE systemic therapy advise. DS and JWP for endoscopic and gastroenterological procedures.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	clinicaltrials.gov NCT03305538
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	9
	5b	Name and contact information for the trial sponsor	n.a.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n.a.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9 + 11+37

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	22

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n.a.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n.a.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n.a.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n.a.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	32+33
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21, 33, 39
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix I
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	41
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n.a.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	41, 42
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	40
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	42, 43
	31b	Authorship eligibility guidelines and any intended use of professional writers	42, 43
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	see PIF
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for the STRONG trial: stereotactic body radiation therapy following chemotherapy for unresectable perihilar cholangiocarcinoma, a phase I feasibility study

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Protocol for the STRONG trial: stereotactic body radiation therapy following chemotherapy for unresectable perihilar cholangiocarcinoma, a phase I feasibility study

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ABSTRACT

Introduction

For patients with perihilar cholangiocarcinoma (CCA), surgery is the only treatment modality that can result in cure. Unfortunately, in the majority of these patients the tumours are found to be unresectable at presentation due to either local invasive tumour growth or the presence of distant metastases. For patients with unresectable CCA palliative chemotherapy is the standard treatment yielding an estimated median overall survival (OS) of 12-15.2 months. There is no evidence from randomized trials to support the use of stereotactic body radiation therapy (SBRT) for CCA. However, small and most often retrospective studies combining chemotherapy with SBRT have shown promising results with OS reaching up to 33-35 months.

Methods and analysis

This study has been designed as a single center phase I feasibility trial and will investigate the addition of SBRT after standard chemotherapy in patients with unresectable perihilar CCA (T1-4 N0-1 M0). A total of six patients will be included. SBRT will be delivered in 15 fractions of 3-4.5Gy (risk adapted). The primary objective of this study is to determine feasibility and toxicity. Secondary outcomes include local tumour control, progression free survival (PFS), OS and quality of life. Length of follow-up will be 2 years. As an ancillary study, the personalized effects of radiotherapy will be measured in vitro, in patient derived tumour and bile duct organoid cultures.

Ethics and dissemination

Ethics approval for the STRONG trial has been granted by the Medical Ethics Committee of Erasmus MC Rotterdam, the Netherlands. It is estimated that all patients will be included between October 2017 and October 2018. The results of this study will be published in a peer-reviewed journal, and presented at national and international conferences.

Trial registration number NCT03307538

Strengths and limitations of this study	
Strengths	• A promising local treatment option will be studied for patients with unresectable perihilar cholangiocarcinoma. • The fractionation scheme used in this trial makes it possible to deliver a relative high radiation dose to the tumour and protect surrounding organs. • Toxicity will be closely observed. • Inter- and intrafraction motion will be assessed using multiple CT-scans during treatment.
Limitations	• The study population is small, therefore no robust analysis other than feasibility and toxicity can be done.

INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common primary liver tumour worldwide[1]. CCA accounts for 3% of all gastro-intestinal tumours[2]. Of all CCA approximately 50-70% arise at the hilar plate of the biliary tree, and these tumours are being referred to as either perihilar CCA or Klatskin tumours[3]. Resection is the only potential curative treatment for patients with perihilar CCA. Median overall survival (OS) ranges from 27-58 months among operated patients with negative resection margins[4]. Unfortunately, the majority of patients presents with unresectable disease at diagnosis[4 5]. Selected patients are eligible for liver transplantation. Five year survival rates for both margin-negative resection and neoadjuvant therapy combined with liver transplantation are similar[4].

The standard treatment for patients with unresectable or metastatic perihilar CCA is chemotherapy that consists of 8 courses of Gemcitabine and Cisplatin. The survival rates for inoperable patients who receive this chemotherapy regimen are poor: Valle et al. reported in a prospective study (ABC-02 trial) a median OS of 11.7 months, and a PFS of 8.0 months[6]. In a retrospective study Eckmann et al. showed a median OS of 15.2 months in these patients treated with Gemcitabine and Cisplatin. Partial response or stable disease rates of 72% were found, with a median duration of response of 8.1 months[7].

Local ablative therapies

Because of these poor OS rates for patients treated with chemotherapy, some local therapies have been investigated. One of these treatment options is ablation with irreversible electroporation (IRE), which is currently under investigation in the ALPACA trial[8]. Until now there is little evidence to support the routine use of IRE for perihilar CCA patients. One case report describes a technically successful procedure, but data on toxicity and disease outcome are lacking[9]. Another local therapy option is radiofrequency ablation (RFA). Wu et al. published a retrospective study that showed prolongation of stent patency and better functional status and quality of life in a group of patients treated with intraductal RFA before stent placement, compared to stent placement alone. There are no data on disease outcome after RFA. A third ablative therapy option is photodynamic therapy using temoporfin (T-PDT). Wagner et al. report a local response after one treatment of 55%, with a median time to local tumour progression of 6.5 months, but also a high percentage of cutaneous photo toxicity (41%)[10]. Finally, brachytherapy has been studied mostly as a palliative treatment in combination with external beam radiotherapy or in a neoadjuvant setting. In combination with external beam radiotherapy survival rates are poor, with a median OS of 12 months[11].

Stereotactic body radiation therapy (SBRT)

Also, the role for radiotherapy in the treatment of CCA is currently not well defined. Various groups have tried to use SBRT to deliver high radiation doses to control the disease locally. Most of the published studies have been retrospective (table 1).

Table 1. Treatment outcomes of SBRT for CCA

AUTHOR	DESIGN	LOCATION	LESION NUMBER	FRACTION NUMBER	TOTAL DOSE (Gy)	1year LOCAL CONTROL	MEDIAN SURVIVAL (months)	TOXICITY[a]
Kopek[12]	R	PH-CCA IH-CCA	26 1	3	45	84%	10.6	6 ulceration 3 stenosis
Tse[13]	P	IH-CCA	10	6	28-48	65%	15	2 liver enzymes 1 bowel obstruction
Polistina[14]	R	PH-CCA	10	3	30	80%[b]	35.5	1 ulceration 2 stenosis
Barney[15]	R	IH-CCA PH-CCA EH-CCA	6 3 1	3-5	45-60	100%	15.5	1 biliary stenosis 1 liver failure
Momm[16]	R	PH-CCA	13	8-16	32-56	N.R.	33.5	1 nausea 5 cholangitis
Jung[17]	R	IH-CCA EH-CCA	33 25	1-5	15-60	85%	10	2 ulceration 2 cholangitis 1 biliary stenosis 1 gastric perforation
Mahadevan[18]	R	IH-CCA PH-CCA	31 11	1-5	10-45	88%	17	2 duodenal ulceration 1 cholangitis 1 liver abscess
Tao[19]	R	IH-CCA	79	15-30	50.4-75	81%	30	3 cholangitis 2 gastric bleeding 7 biliary stenosis
Sandler[20]	R	IH-CCA EH-CCA	6 25	5	40	78%	15.7	2 duodenal obstruction 3 duodenal ulceration

P: Prospective. R: Retrospective. OS: Overall survival. IH-CCA: Intrahepatic cholangiocarcinoma. PH-CCA: Perihilar cholangiocarcinoma. EH-CCA: Extrahepatic cholangiocarcinoma. N.R.: not reported

[a] Early and late toxicity, grade 3 or more. [b] At 6 months

SBRT has been explored as single-modality treatment in patients who are unsuitable for resection, although it has also been administered as adjuvant treatment after surgery with positive margins[18]. The patient groups were almost invariably small and/or heterogeneous, which makes it hard to draw firm conclusions[12-20]. Most studies did not limit number or size of lesions, with the exception of one study (maximum diameter of ≥6cm was an exclusion criterium)[14].

High rates of 2-year local control (LC) after SBRT have been reported. In most studies, this was achieved in ≥72% of the patients. Median OS ranged between 10 and 35.5 months, with five studies reporting OS ≥15 months, and three reporting OS ≥24 months[12-20]. Tao et al. found a significant improvement in LC when high radiation doses were delivered. When biologically effective doses (BED) were >80.5Gy, three-year LC was achieved in 78% vs. 45% with lower doses[19].

One of the difficulties for a SBRT treatment in the perihilar region is the proximity of organs at risk like the common bile duct and duodenum. The hepatobiliary toxicity reported by other groups varied widely but was generally limited in most of the series. A slightly higher number of gastrointestinal toxicity has been reported, mainly duodenal obstruction and stenosis (table 1)[12-20]. This toxicity could potentially be limited by the application of strict dose-volume constraints.

METHODS AND ANALYSIS

Design

This study has been designed as a single center phase I feasibility trial. Six patients with unresectable perihilar CCA, who already received the standard treatment with systemic chemotherapy (cisplatin and gemcitabine), will be included.

The reason to design a feasibility study is that no data have been published about the delivery of SBRT in 15 fractions of 3-4.5Gy in patients with perihilar CCA after chemotherapy. Data have been reported on patients with intrahepatic CCA treated with 15 fractions of radiotherapy, although the chemotherapy regimen and the timing of administration before or after the local treatment varied largely[19]. The possibility of delivering the standard treatment without interferences due to potential toxicity caused by SBRT, was the main reason to choose for an adjuvant approach instead of neo-adjuvant or concomitant.

The trial follows the conventional `3+3'-design. First 3 patients will be included, after which the trial will temporarily be put on hold for 3 months. When 2 or 3 patients develop limiting toxicity (LT), the conclusion will be that the proposed risk adapted radiotherapy protocol is not feasible and the trial will be ended. When 0 or 1 of 3 patients develops LT, 3 additional patients will be included. LT will be defined as grade 4 or more hepatobiliary toxicity related to study procedures, or grade 3 or more gastrointestinal toxicity related to study procedures, occurring in the period up to 3 months after the last SBRT administration. When 0 or 1 of these 6 patients develops LT, then the conclusion will be that the current risk adapted radiotherapy protocol is feasible, and should be considered for further research in this patient population (i.e. in a phase II trial). Otherwise, if 2 or more patients have limiting toxicity, the conclusion will be that the current risk adapted radiotherapy protocol is not feasible. The most important toxicities are listed in table 2.

Table 2. Toxicity

Gastrointestinal disorders:
Duodenal or gastric obstruction/stenosis
Duodenal or gastric perforation
Duodenal or gastric ulcer
Hepatobiliary disorders:
Bile duct stenosis
Perforation bile duct
Infections and infestations:
Biliary tract infection

Study objectives

Primary study outcome

The primary objective of this study will be to determine feasibility and toxicity (according to the Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 grading system) of adding SBRT to standard chemotherapy, in patients with perihilar CCA ineligible for surgery.

Secondary study outcomes

- Local control, defined as time from inclusion to local radiological progression. Definition of progression is based on RECIST 1.1[21].
- Progression free survival, defined as time from inclusion until radiological progression. Definition of progression is based on RECIST.
- Overall survival, defined as time from inclusion until death from any cause.
- Quality of life, assessed by means of the EuroQol EQ-5D-5L (measure of health outcome in general population), and the EORTC QLQ-C30 (quality of life specific for cancer patients) with the supplementary module EORTC QLQ- BIL21 (specific for CCA and gallbladder cancer).

- Cellular radiosensitivity, as a side track of this study. The effects of radiotherapy will be measured in normal bile duct organoids[22] and CCA cancer-derived organoids (Broutier et al. Tumour-derived organoid cultures model primary human liver cancer in vitro, article in press) obtained from cells of brush cytology obtained during ERCP. The goal is to set up assays to measure genomic mutations, cell death/apoptosis, cellular senescence and proliferative capacity after ionizing radiation treatment ex vivo. In the future, these effects will be measured in organoids and will be correlated with tumour response on imaging (CT/MRI) in a large phase II trial. Prediction of response and toxicity before treatment will be the ultimately goal of this approach in the future.

Study population

Six patients with unresectable perihilar CCA after completion of standard chemotherapy with cisplatin and gemcitabine will be enrolled in this study. In order to be eligible, a subject must be discussed in a multidisciplinary liver tumour board and should meet all of the in- and exclusion

criteria as listed in table 3. All types of biliary stents are accepted. The expected time to include the required patients for this trial will be one year.

Table 3. In- and exclusion criteria

Inclusion criteria	Exclusion criteria

• Patients diagnosed with perihilar CCA according to the criteria of the Mayo Clinic, Rochester[23]:
  ○ Positive or strongly suspicious intraluminal brush or biopsy, or
  ○ A radiographic malignant appearing stricture plus either:
  ▪ CA 19-9>100 U/ml in the absence of acute bacterial cholangitis, or
  ▪ Polysomy on FISH, or
  ▪ A well-defined mass on cross sectional imaging
• One tumour mass
• Unresectable tumour
• Finished chemotherapy treatment with Gemcitabine and Cisplatin, preferably 8 cycles.[a] T1-T4 (AJCC staging 7th edition)[b] before chemotherapy
• N0-N1 (AJCC staging 7th edition), radiologically or pathologically suspect
• Measurable disease to be selected as a target on CT/MRI-scan, according to RECIST criteria[c,d]
• Tumour visibility on CT
• If liver cirrhosis is present, it should be well compensated, with Child-Pugh grade A
• Age ≥ 18 years
• ECOG performance status 0-1
• Bilirubin ≤1.5 times normal value, AST/ALT ≤5 times ULN[d]
• Platelets ≥ $50x10^9$/l, Leukocytes > $1.5x10^9$/l, Hb > 6 mmol/l[d]
• Written informed consent[c]
• Willing and able to comply to the follow-up schedule
• Able to start SBRT within 12 weeks after completion of chemotherapy.
	• Eligibility for resection
	• Prior surgery or transplantation
	• Multifocal tumour
	• Tumour extension in stomach, colon, duodenum, pancreas or abdominal wall
	• N2, (AJCC staging 7th edition), radiologically or pathologically suspect[b]
	• Distant metastases
	• Progression (local or distant) during or after chemotherapy
	• Ascites
	• Previous radiotherapy to the liver
	• Current pregnancy

[a] If less cycles have been given, patients are still eligible for this study. [b] Before chemotherapy. [c] After chemotherapy. [d] Within 6 weeks prior to inclusion

Study outline

The general outline of the study procedures is presented in figure 1.

Pre-SBRT

Chemotherapy is considered the standard treatment for unresectable perihilar CCA, and therefore will not be considered as study treatment in this trial. Cisplatin plus gemcitabine will be administered according to standard practice of the Erasmus MC Cancer Institute. Chemotherapy will be discontinued at 24 weeks (8 cycles) or earlier in case of disease progression, patient or clinician decision, or unacceptable toxic effects. Biliary obstruction per se is not considered to be disease progression in the absence of radiologically confirmed tumour progression, and treatment can be recommenced after further biliary stenting and normalization of liver function[6]. In case of unacceptable toxic effects and in absence of disease progression, the patient can proceed to SBRT without completing 8 cycles of chemotherapy. In that case, no signs of progressive disease should have been observed on a chest/abdomen CT scan performed within 6 weeks before patient inclusion.

SBRT

Treatment with SBRT will start preferably within 6 weeks after the last chemotherapy course. However, if due to toxicity or other medical or personal reasons the start of the treatment has to be postponed, the time to start can be expanded till a maximum of 12 weeks after the last course of chemotherapy.

We will use a risk-adapted dose prescription for delivering the highest possible dose to the tumour, using 15 fractions of 3-4,5Gy, while not exceeding widely accepted dose constraints in the surrounding organs at risk (table 4 and 5). This approach has already been tested with favorable outcome and limited biliary toxicity in a multicenter retrospective study for intrahepatic CCA[19]. The same radiotherapy protocol (dose and fractionation) is currently being tested in a prospective phase III trial between chemotherapy and chemotherapy combined with radiotherapy in patients with unresectable intrahepatic CCA (NRG-GI001). To the best of our knowledge, this approach for perihilar CCA has not been published yet.

Table 4. Organs at risk constraints

Organ at risk	**Hard constraints**
Healthy liver	≥700ml liver-GTV, dose <25.5Gy[24] If cirrhosis is present: NTCP liver-GTV ≤5%[25] and >800ml liver-GTV, dose <31.5Gy[26]
Stomach	Max point dose <57Gy[27] Volume receiving ≥41Gy should be ≤5cc
Duodenum Small and large bowel (when needed combined in one structure)	Max point dose <57Gy[27] Volume receiving ≥41Gy should be ≤5cc
Esophagus	Max point dose ≤50.25Gy[28]
Spinal cord	Max point dose ≤33.8Gy[24]
Kidney	2/3 right kidney <25.5Gy[24]

Table 5: Organ at risk objectives

Organ at risk	Objectives
Central biliary tract	Less than 0.5cc ≥70Gy (NRG-GI001 - http://www.cancer.gov/clinicaltrials) V_{BED10} 40 <37cc and V_{BED10}30 < 45cc[29]
Heart	Max dose <57Gy (RTOG 1112 - http://www.cancer.gov/clinicaltrials)
Gallbladder	Max dose <86.7Gy (RTOG 1112- http://www.cancer.gov/clinicaltrials)
Skin (external contour)	Less than 0.5cc ≥50.25Gy (RTOG 1112 - http://www.cancer.gov/clinicaltrials)

Marker implantation

A tumour tracking technique (Synchrony-Cyberknife, Accuray, Sunnyvale, CA, USA) will be applied for daily positioning and during dose delivery. Therefore, implantation of fiducials is compulsory. For perihilar CCA, fiducials should be implanted in the liver and not in the tumour to avoid the risk of tumour seeding. A distance of around 2.0 cm from the tumour edge is recommended. The procedure will be performed by an experienced interventional radiologist. INR should be <2.0, and platelets should be ≥50×10^9/l. We will plan around one week (minimum of 5 and maximum of 10 days) between the implantation of the fiducials and the treatment preparation (planning CT). Patients should remain hospitalized during at least 2-3 hours after the implantation in order to detect and treat unexpected complications as soon as possible. In case of lymph node involvement, no fiducials will be implanted in the affected nodes.

Tumour delineation

The gross target volume (GTV) is defined in a contrast-enhanced CT acquired in expiration and in a hepatic venous phase. An arterial phase CT with bolus tracking technique is also performed since valuable complementary information from this phase could be valuable to better depict the tumour. The use of MRI to support the tumour delineation is recommended. In case that enlarged lymph nodes (N1) have to be considered as a target for SBRT, the venous phase of the planning CT in expiration will also be used for the delineation. No additional margin will be added around the GTV to generate the clinical target volume (CTV) for both tumour and lymph nodes.

Margins

The information acquired from a 4DCT scan and from the inspiration/expiration CT will be used to establish the margin around the GTV to generate the planning target volume (PTV). This margin should ensure that despite geometrical uncertainties (i.e. imaging artifacts in the planning CT-scan due to respiratory tumour motion, inter-fraction motion of the tumour, uncertainty in the set-up, etc.), the full GTV is irradiated with an adequate dose with a very high probability.

Planning protocol

Efforts should be made to deliver a BED>80.5Gy to the tumour, since a multicenter retrospective study of intrahepatic CCA demonstrated a significant improvement in LC depending on the BED (3y

45% for BED<80.5Gy vs. 78% for BED>80.5Gy)[19]. In case the tumour is located very close/adjacent to organs at risk as the duodenum, stomach, esophagus or bowel, it may be impossible to deliver such high doses to the periphery of most of the tumour, and therefore lower doses at the periphery are allowed in these cases.

Any plan delivered to a patient should adhere to the imposed organs at risk (OAR) hard constraints (table 4). Within these constraints, ideally the full PTV is irradiated with a dose of ≥67.5Gy (15×4.5Gy). Due to the hard constraints and the objectives for the OARs, this ideal PTV dose may not always be achievable. In that case, compromises in PTV dose delivery can be made. First of all, the PTV coverage may be reduced, i.e. only 95% of the PTV may receive ≥67.5Gy. Second, instead of delivering 67.5Gy (15×4.5Gy), a dose of 60Gy (15×4Gy), 52.5Gy (15×3.5Gy) or even 45Gy (15×3Gy) can be chosen. An effort should be made to deliver at least 60Gy (BED>80.5Gy) to a large portion of the PTV without violating OAR constraints.

Fractionation and daily imaging

The total dose is delivered in 15 fractions. Time between fractions should be 24h (in case of a weekend in between it will be 72h). Effort should be made to deliver the treatment without gaps.

In order to evaluate the relationship between tumour and organs at risk in this perihilar location, a CT scan before and after treatment in expiration phase will be performed in treatment position the first day and on days 3, 6, 9, 12 and 15 during treatment. No intravenous contrast will be used.

Post SBRT follow up

Follow up visits will be scheduled at 1, 3, 6, 9, 12, 18 and 24 months after treatment. At every visit a MRI or CT scan will be made to detect local or distant disease progression. Also toxicity and performance score will be scored every visit. Patients will be asked to fill out quality of life (QoL) questionnaires (EuroQol EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ- BIL21) at most visits. For further detailed information see table 6. If a patient is still alive after 2 years, follow up will be continued by the medical oncologist according current clinical practice.

Ancillary study: evaluating cellular radio-sensitivity in patient-derived organoid models

We will grow organoids from tumour and bile duct cells collected by brush biopsies[22](Broutier et al. Tumour-derived organoid cultures model primary human liver cancer in vitro, article in press). For this purpose a second brush will be obtained during the same procedure while the first brush is taken (just directly after the first one) and only for patients where a brush biopsy is considered needed as part of the diagnostic work up. We will set up assays to measure cell survival (clonogenic assays, HE staining of organoids), apoptosis (TUNEL staining), accumulation of DNA repair proteins on DNA double strand breaks (gamma-H2AX, 53BP1 and RAD51 foci) and repair of the DNA damage at various time points after irradiation (loss of these foci after 24-48 hours of incubation). In addition to the functional assays, organoid cultures are also ideal sources of tumour material, such as DNA for mutation analysis and RNA for gene expression studies[30].

Table 6: Schedule of events

	Eligibility check	Written informed consent	Medical history	Co-morbidity	ECOG PS	Laboratory[a]	CT/MRI[b]	Adverse events[c]	QOL	Survival and post-study treatment
Standard treatment (Chemotherapy) 1-8 courses. No progressive disease										
≤6 weeks	X	X	X	X	X	X	X	X	X	
Experimental add on treatment (SBRT)										
+1 month					X	X	X	X	X	X
+3 months					X	X	X	X	X	X
+6 months					X	X	X	X	X	X
+9 months					X	X	X	X	X	X
+12 months					X	X	X	X	X	X
+18 months					X	X	X	X		X
+24 months					X	X	X	X	X	X

[a] Lab assessments should include albumin, bilirubin, alkaline phosphatase, AST, ALT, GGT, Hb, leukocytes, platelets, and CA-19.9. Notice that CA-19.9 should only be assessed during follow-up if indicated, i.e. if elevated at baseline. [b] Radiology report should include tumour measurement, tumour measurements should be performed according to RECIST criteria. [c] CTCAE v 4.03 should be applied for grading toxicity

Data analysis

This trial will be performed as a feasibility study and will focus on toxicity until 3 months after SBRT treatment. The number of patients with LT as defined before will be determined. If two or more patients have LT, the conclusion will be that the regimen is not feasible. Otherwise the conclusion will be that the regimen warrants further research in this population.

In addition, the analysis of toxicity will be done by tabulation of the incidence of adverse events CTCAE grade 3 and 4. Adverse events will be summarized by worst CTCAE grade. Demographics of the patients at study entry will be recorded, and presented as percentages in case of discrete variables, or by median and range in case of continuous variables. All patients with the baseline and at least one follow-up QoL questionnaire, separately for QLQ-C30, QLQ-BIL21 and EuroQoL-5D, will be included in the analysis. The repeated measures will be analyzed using ANOVA models. The

Kaplan-Meier method will be used to estimate local control, progression free survival and overall survival.

Patient and Public Involvement

While designing the study, our first priority was the patients´ well-being. Although we did not involve patients in the design of the trial, all information about the study is available on the website of the Dutch Hepato & Cholangio Carcinoma Group (www.dhcg.org). During the development phase, the study was discussed several times within this multidisciplinary group. A final report of the trial will also be placed at the website for patient information. At any time, participants can be informed about study outcomes through the principal investigator.

ETHICS AND DISSEMINATION

Prior to any study procedure written informed consent will be obtained from every participating patient. Ethics approval for the study was granted 31 August 2017 by the Medical Ethics Committee of Erasmus MC Rotterdam, the Netherlands (ID: NL 60588.078.17). The STRONG trial is registered on clincaltrials.gov (ID: NCT03307538). The results of this study will be published in an academic journal, and presented at national and international conferences.

DISCUSSION

The STRONG trial is designed to assess feasibility and toxicity of adding SBRT to standard chemotherapy in patients with inoperable perihilar CCA. Currently, only a few prospective studies are available on the use of SBRT for treating patients with CCA in the perihilar region. These studies report promising results for LC (≥72% at 2 years) and median OS (up to 35 months), with low toxicity rates. However, the exact treatment approach (combination with chemotherapy, chemotherapy scheme, timing, SBRT fractionation) varied widely[12-20]. The scarce available results suggest that the combination of chemotherapy and SBRT may improve disease control above SBRT alone.

We chose a more fractionated scheme than the other studies on SBRT for perihilar tumours because of the proximity of organs at risk like duodenum and bile duct to the tumour. By using 15 fractions, instead of fewer, we hope to reach an acceptable coverage of the PTV with a biologically effective dose of more than 80.5Gy, and at the same time respect the dose constraints for the OAR's. Acceptable results have been published with this fractionating scheme for intrahepatic CCA[19].

In this study we will encounter some technical challenges and uncertainties. First of all is the assessment of the breathing motion of tumours located in the perihilar region. Since we use the Synchrony-Cyberknife system for tumour tracking, fiducial markers will have to be implanted close to the tumour. These markers will be placed in the liver in the proximity of the tumour and not in the tumour itself to avoid tumour seeding. Second, there is little known about the inter- and intrafraction motion of organs at risk located in the vicinity of the perihilar region and the correlation with the tumour motion. If present, involved lymph nodes may be situated at a certain distance of the tumour. Again, motion assessment and correlation with tumour motion will be another point that should be addressed within this study. In order to measure variations in inter- and intrafraction motion, a CT scan in expiration phase before and after treatment will be performed in treatment position the first day and on days 3, 6, 9, 12 and 15 during treatment.

Because of these technical uncertainties in combination with the experimental fractionation scheme for tumours located in the perihilar region, the first step is to complete this feasibility trial with just 6 patients. Since this small number results in limitations for interpreting results on disease control and QoL, our aim is to proceed to a large phase II trial if the treatment turns out to be feasible.

AUTHOR CONTRIBUTIONS All authors contributed to the design of the study protocol and approved the final manuscript. AMR and MSK principal investigators, initiators of the trial. BJMH medical physics aspects. BvdH statistical design and data analysis. DCvG and LJWvdL molecular genetics side study. FEJAW radiological support. BGK surgical aspects. FE systemic therapy advise. DS and JWP for endoscopic and gastroenterological procedures.

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Figure legends:

- Figure 1. Study outline

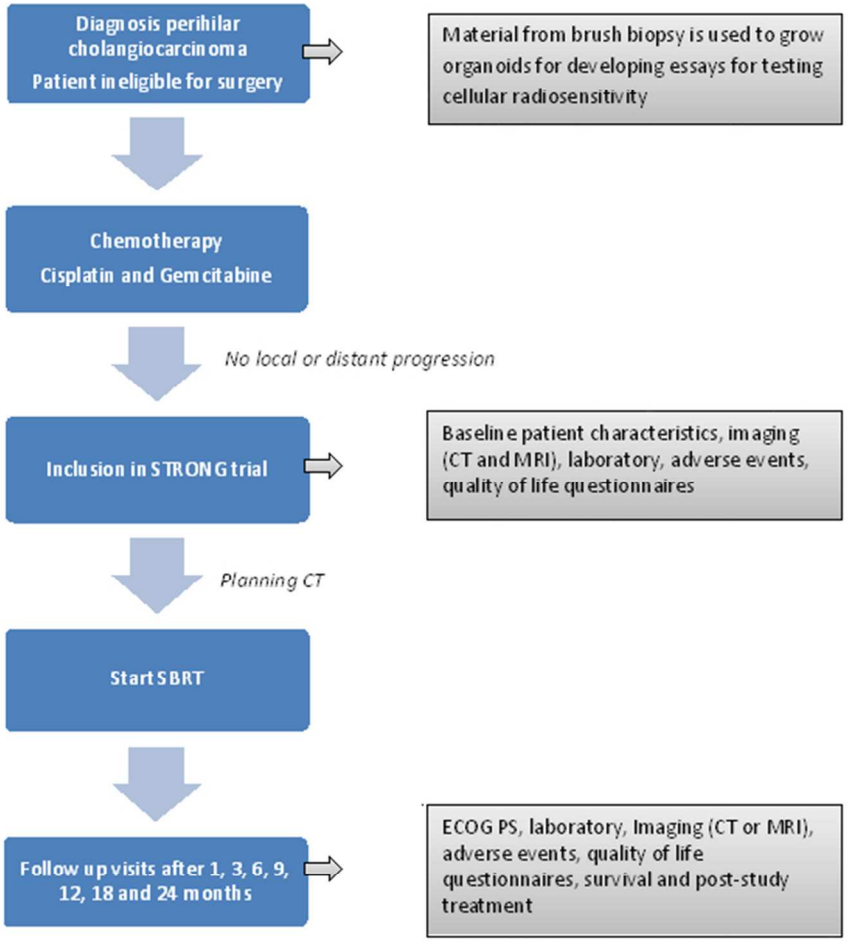

Figure 1. Study outline

54x53mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	clinicaltrials.gov NCT03305538
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	9
	5b	Name and contact information for the trial sponsor	n.a.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n.a.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9 + 11+37

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	22

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n.a.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n.a.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n.a.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n.a.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	32+33
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21, 33, 39
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix I
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	41
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n.a.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	41, 42
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	40
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	42, 43
	31b	Authorship eligibility guidelines and any intended use of professional writers	42, 43
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	see PIF
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for the STRONG trial: stereotactic body radiation therapy following chemotherapy for unresectable perihilar cholangiocarcinoma, a phase I feasibility study

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Protocol for the STRONG trial: stereotactic body radiation therapy following chemotherapy for unresectable perihilar cholangiocarcinoma, a phase I feasibility study

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ABSTRACT

Introduction

For patients with perihilar cholangiocarcinoma (CCA), surgery is the only treatment modality that can result in cure. Unfortunately, in the majority of these patients the tumours are found to be unresectable at presentation due to either local invasive tumour growth or the presence of distant metastases. For patients with unresectable CCA palliative chemotherapy is the standard treatment yielding an estimated median overall survival (OS) of 12-15.2 months. There is no evidence from randomized trials to support the use of stereotactic body radiation therapy (SBRT) for CCA. However, small and most often retrospective studies combining chemotherapy with SBRT have shown promising results with OS reaching up to 33-35 months.

Methods and analysis

This study has been designed as a single center phase I feasibility trial and will investigate the addition of SBRT after standard chemotherapy in patients with unresectable perihilar CCA (T1-4 N0-1 M0). A total of six patients will be included. SBRT will be delivered in 15 fractions of 3-4.5Gy (risk adapted). The primary objective of this study is to determine feasibility and toxicity. Secondary outcomes include local tumour control, progression free survival (PFS), OS and quality of life. Length of follow-up will be 2 years. As an ancillary study, the personalized effects of radiotherapy will be measured in vitro, in patient derived tumour and bile duct organoid cultures.

Ethics and dissemination

Ethics approval for the STRONG trial has been granted by the Medical Ethics Committee of Erasmus MC Rotterdam, the Netherlands. It is estimated that all patients will be included between October 2017 and October 2018. The results of this study will be published in a peer-reviewed journal, and presented at national and international conferences.

Trial registration number NCT03307538

Strengths and limitations of this study	
Strengths	• A promising local treatment option will be studied for patients with unresectable perihilar cholangiocarcinoma. • The fractionation scheme used in this trial makes it possible to deliver a relative high radiation dose to the tumour and protect surrounding organs. • Toxicity will be closely observed. • Inter- and intrafraction motion will be assessed using multiple CT-scans during treatment.
Limitations	• The study population is small, therefore no robust analysis other than feasibility and toxicity can be done.

INTRODUCTION

Cholangiocarcinoma (CCA) is the second most common primary liver tumour worldwide[1]. CCA accounts for 3% of all gastro-intestinal tumours[2]. Of all CCA approximately 50-70% arise at the hilar plate of the biliary tree, and these tumours are being referred to as either perihilar CCA or Klatskin tumours[3]. Resection is the only potential curative treatment for patients with perihilar CCA. Median overall survival (OS) ranges from 27-58 months among operated patients with negative resection margins[4]. Unfortunately, the majority of patients presents with unresectable disease at diagnosis[4 5]. Selected patients are eligible for liver transplantation. Five year survival rates for both margin-negative resection and neoadjuvant therapy combined with liver transplantation are similar[4].

The standard treatment for patients with unresectable or metastatic perihilar CCA is chemotherapy that consists of 8 courses of Gemcitabine and Cisplatin. The survival rates for inoperable patients who receive this chemotherapy regimen are poor: Valle et al. reported in a prospective study (ABC-02 trial) a median OS of 11.7 months, and a PFS of 8.0 months[6]. In a retrospective study Eckmann et al. showed a median OS of 15.2 months in these patients treated with Gemcitabine and Cisplatin. Partial response or stable disease rates of 72% were found, with a median duration of response of 8.1 months[7].

Local ablative therapies

Because of these poor OS rates for patients treated with chemotherapy, some local therapies have been investigated. One of these treatment options is ablation with irreversible electroporation (IRE), which is currently under investigation in the ALPACA trial[8]. Until now there is little evidence to support the routine use of IRE for perihilar CCA patients. One case report describes a technically successful procedure, but data on toxicity and disease outcome are lacking[9]. Another local therapy option is radiofrequency ablation (RFA). Wu et al. published a retrospective study that showed prolongation of stent patency and better functional status and quality of life in a group of patients treated with intraductal RFA before stent placement, compared to stent placement alone. There are no data on disease outcome after RFA. A third ablative therapy option is photodynamic therapy using temoporfin (T-PDT). Wagner et al. report a local response after one treatment of 55%, with a median time to local tumour progression of 6.5 months, but also a high percentage of cutaneous photo toxicity (41%)[10]. Finally, brachytherapy has been studied mostly as a palliative treatment in combination with external beam radiotherapy or in a neoadjuvant setting. In combination with external beam radiotherapy survival rates are poor, with a median OS of 12 months[11].

Stereotactic body radiation therapy (SBRT)

Also, the role for radiotherapy in the treatment of CCA is currently not well defined. Various groups have tried to use SBRT to deliver high radiation doses to control the disease locally. Most of the published studies have been retrospective (table 1).

Table 1. Treatment outcomes of SBRT for CCA

AUTHOR	DESIGN	LOCATION	LESION NUMBER	FRACTION NUMBER	TOTAL DOSE (Gy)	1year LOCAL CONTROL	MEDIAN SURVIVAL (months)	TOXICITY[a]
Kopek[12]	R	PH-CCA IH-CCA	26 1	3	45	84%	10.6	6 ulceration 3 stenosis
Tse[13]	P	IH-CCA	10	6	28-48	65%	15	2 liver enzymes 1 bowel obstruction
Polistina[14]	R	PH-CCA	10	3	30	80%[b]	35.5	1 ulceration 2 stenosis
Barney[15]	R	IH-CCA PH-CCA EH-CCA	6 3 1	3-5	45-60	100%	15.5	1 biliary stenosis 1 liver failure
Momm[16]	R	PH-CCA	13	8-16	32-56	N.R.	33.5	1 nausea 5 cholangitis
Jung[17]	R	IH-CCA EH-CCA	33 25	1-5	15-60	85%	10	2 ulceration 2 cholangitis 1 biliary stenosis 1 gastric perforation
Mahadevan[18]	R	IH-CCA PH-CCA	31 11	1-5	10-45	88%	17	2 duodenal ulceration 1 cholangitis 1 liver abscess
Tao[19]	R	IH-CCA	79	15-30	50.4-75	81%	30	3 cholangitis 2 gastric bleeding 7 biliary stenosis
Sandler[20]	R	IH-CCA EH-CCA	6 25	5	40	78%	15.7	2 duodenal obstruction 3 duodenal ulceration

P: Prospective. R: Retrospective. OS: Overall survival. IH-CCA: Intrahepatic cholangiocarcinoma. PH-CCA: Perihilar cholangiocarcinoma. EH-CCA: Extrahepatic cholangiocarcinoma. N.R.: not reported

[a] Early and late toxicity, grade 3 or more. [b] At 6 months

SBRT has been explored as single-modality treatment in patients who are unsuitable for resection, although it has also been administered as adjuvant treatment after surgery with positive margins[18]. The patient groups were almost invariably small and/or heterogeneous, which makes it hard to draw firm conclusions[12-20]. Most studies did not limit number or size of lesions, with the exception of one study (maximum diameter of ≥6cm was an exclusion criterium)[14].

High rates of 2-year local control (LC) after SBRT have been reported. In most studies, this was achieved in ≥72% of the patients. Median OS ranged between 10 and 35.5 months, with five studies reporting OS ≥15 months, and three reporting OS ≥24 months[12-20]. Tao et al. found a significant improvement in LC when high radiation doses were delivered. When biologically effective doses (BED) were >80.5Gy, three-year LC was achieved in 78% vs. 45% with lower doses[19].

One of the difficulties for a SBRT treatment in the perihilar region is the proximity of organs at risk like the common bile duct and duodenum. The hepatobiliary toxicity reported by other groups varied widely but was generally limited in most of the series. A slightly higher number of gastrointestinal toxicity has been reported, mainly duodenal obstruction and stenosis (table 1)[12-20]. This toxicity could potentially be limited by the application of strict dose-volume constraints.

METHODS AND ANALYSIS

Design

This study has been designed as a single center phase I feasibility trial. Six patients with unresectable perihilar CCA, who already received the standard treatment with systemic chemotherapy (cisplatin and gemcitabine), will be included.

The reason to design a feasibility study is that no data have been published about the delivery of SBRT in 15 fractions of 3-4.5Gy in patients with perihilar CCA after chemotherapy. Data have been reported on patients with intrahepatic CCA treated with 15 fractions of radiotherapy, although the chemotherapy regimen and the timing of administration before or after the local treatment varied largely[19]. The possibility of delivering the standard treatment without interferences due to potential toxicity caused by SBRT, was the main reason to choose for an adjuvant approach instead of neo-adjuvant or concomitant.

The trial follows the conventional `3+3'-design. First 3 patients will be included, after which the trial will temporarily be put on hold for 3 months. When 2 or 3 patients develop limiting toxicity (LT), the conclusion will be that the proposed risk adapted radiotherapy protocol is not feasible and the trial will be ended. When 0 or 1 of 3 patients develops LT, 3 additional patients will be included. LT will be defined as grade 4 or more hepatobiliary toxicity related to study procedures, or grade 3 or more gastrointestinal toxicity related to study procedures, occurring in the period up to 3 months after the last SBRT administration. When 0 or 1 of these 6 patients develops LT, then the conclusion will be that the current risk adapted radiotherapy protocol is feasible, and should be considered for further research in this patient population (i.e. in a phase II trial). Otherwise, if 2 or more patients have limiting toxicity, the conclusion will be that the current risk adapted radiotherapy protocol is not feasible. The most important toxicities are listed in table 2.

Table 2. Toxicity

Gastrointestinal disorders:
Duodenal or gastric obstruction/stenosis
Duodenal or gastric perforation
Duodenal or gastric ulcer
Hepatobiliary disorders:
Bile duct stenosis
Perforation bile duct
Infections and infestations:
Biliary tract infection

Toxicity will be determined based on symptoms, laboratory, imaging and endoscopic examinations. Limiting toxicity is defined as grade 4 or more hepatobiliary toxicity related to study procedures, or grade 3 or more gastrointestinal toxicity related to study procedures.

Study objectives

Primary study outcome

The primary objective of this study will be to determine feasibility and toxicity (according to the Common Toxicity Criteria for Adverse Events (CTCAE) v4.03 grading system) of adding SBRT to standard chemotherapy, in patients with perihilar CCA ineligible for surgery.

Secondary study outcomes

- Local control, defined as time from inclusion to local radiological progression. Definition of progression is based on RECIST 1.1[21].
- Progression free survival, defined as time from inclusion until radiological progression. Definition of progression is based on RECIST.
- Overall survival, defined as time from inclusion until death from any cause.
- Quality of life, assessed by means of the EuroQol EQ-5D-5L (measure of health outcome in general population), and the EORTC QLQ-C30 (quality of life specific for cancer patients) with the supplementary module EORTC QLQ- BIL21 (specific for CCA and gallbladder cancer).

- Cellular radiosensitivity, as a side track of this study. The effects of radiotherapy will be measured in normal bile duct organoids[22] and CCA cancer-derived organoids (Broutier et al. Tumour-derived organoid cultures model primary human liver cancer in vitro, article in press) obtained from cells of brush cytology obtained during ERCP. The goal is to set up assays to measure genomic mutations, cell death/apoptosis, cellular senescence and proliferative capacity after ionizing radiation treatment ex vivo. In the future, these effects will be measured in organoids and will be correlated with tumour response on imaging (CT/MRI) in a large phase II trial. Prediction of response and toxicity before treatment will be the ultimately goal of this approach in the future.

Study population

Six patients with unresectable perihilar CCA after completion of standard chemotherapy with cisplatin and gemcitabine will be enrolled in this study. In order to be eligible, a subject must be

discussed in a multidisciplinary liver tumour board and should meet all of the in- and exclusion criteria as listed in table 3. All types of biliary stents are accepted. The expected time to include the required patients for this trial will be one year.

Table 3. In- and exclusion criteria

Inclusion criteria	Exclusion criteria

• Patients diagnosed with perihilar CCA according to the criteria of the Mayo Clinic, Rochester[23]:
  ○ Positive or strongly suspicious intraluminal brush or biopsy, or
  ○ A radiographic malignant appearing stricture plus either:
  ▪ CA 19-9>100 U/ml in the absence of acute bacterial cholangitis, or
  ▪ Polysomy on FISH, or
  ▪ A well-defined mass on cross sectional imaging
• One tumour mass
• Unresectable tumour
• Finished chemotherapy treatment with Gemcitabine and Cisplatin, preferably 8 cycles.[a] T1-T4 (AJCC staging 7th edition)[b] before chemotherapy
• N0-N1 (AJCC staging 7th edition), radiologically or pathologically suspect
• Measurable disease to be selected as a target on CT/MRI-scan, according to RECIST criteria[c,d]
• Tumour visibility on CT
• If liver cirrhosis is present, it should be well compensated, with Child-Pugh grade A
• Age ≥ 18 years
• ECOG performance status 0-1
• Bilirubin ≤1.5 times normal value, AST/ALT ≤5 times ULN[d]
• Platelets ≥ $50x10^9$/l, Leukocytes > $1.5x10^9$/l, Hb > 6 mmol/l[d]
• Written informed consent[c]
• Willing and able to comply to the follow-up schedule
• Able to start SBRT within 12 weeks after completion of chemotherapy.
	• Eligibility for resection
	• Prior surgery or transplantation
	• Multifocal tumour
	• Tumour extension in stomach, colon, duodenum, pancreas or abdominal wall
	• N2, (AJCC staging 7th edition), radiologically or pathologically suspect[b]
	• Distant metastases
	• Progression (local or distant) during or after chemotherapy
	• Ascites
	• Previous radiotherapy to the liver
	• Current pregnancy

[a] If less cycles have been given, patients are still eligible for this study. [b] Before chemotherapy. [c] After chemotherapy. [d] Within 6 weeks prior to inclusion

Study outline

The general outline of the study procedures is presented in figure 1.

Pre-SBRT

Chemotherapy is considered the standard treatment for unresectable perihilar CCA, and therefore will not be considered as study treatment in this trial. Cisplatin plus gemcitabine will be administered according to standard practice of the Erasmus MC Cancer Institute. Chemotherapy will be discontinued at 24 weeks (8 cycles) or earlier in case of disease progression, patient or clinician decision, or unacceptable toxic effects. Biliary obstruction per se is not considered to be disease progression in the absence of radiologically confirmed tumour progression, and treatment can be recommenced after further biliary stenting and normalization of liver function[6]. In case of unacceptable toxic effects and in absence of disease progression, the patient can proceed to SBRT without completing 8 cycles of chemotherapy. In that case, no signs of progressive disease should have been observed on a chest/abdomen CT scan performed within 6 weeks before patient inclusion.

SBRT

Treatment with SBRT will start preferably within 6 weeks after the last chemotherapy course. However, if due to toxicity or other medical or personal reasons the start of the treatment has to be postponed, the time to start can be expanded till a maximum of 12 weeks after the last course of chemotherapy.

We will use a risk-adapted dose prescription for delivering the highest possible dose to the tumour, using 15 fractions of 3-4,5Gy, while not exceeding widely accepted dose constraints in the surrounding organs at risk (table 4 and 5). This approach has already been tested with favorable outcome and limited biliary toxicity in a multicenter retrospective study for intrahepatic CCA[19]. The same radiotherapy protocol (dose and fractionation) is currently being tested in a prospective phase III trial between chemotherapy and chemotherapy combined with radiotherapy in patients with unresectable intrahepatic CCA (NRG-GI001). To the best of our knowledge, this approach for perihilar CCA has not been published yet.

Table 4. Organs at risk constraints

Organ at risk	**Hard constraints**
Healthy liver	≥700ml liver-GTV, dose <25.5Gy[24] If cirrhosis is present: NTCP liver-GTV ≤5%[25] and >800ml liver-GTV, dose <31.5Gy[26]
Stomach	Max point dose <57Gy[27] Volume receiving ≥41Gy should be ≤5cc
Duodenum Small and large bowel (when needed combined in one structure)	Max point dose <57Gy[27] Volume receiving ≥41Gy should be ≤5cc
Esophagus	Max point dose ≤50.25Gy[28]
Spinal cord	Max point dose ≤33.8Gy[24]
Kidney	2/3 right kidney <25.5Gy[24]

Table 5: Organ at risk objectives

Organ at risk	Objectives
Central biliary tract	Less than 0.5cc ≥70Gy (NRG-GI001 - http://www.cancer.gov/clinicaltrials) V_{BED10} 40 <37cc and V_{BED10}30 < 45cc[29]
Heart	Max dose <57Gy (RTOG 1112 - http://www.cancer.gov/clinicaltrials)
Gallbladder	Max dose <86.7Gy (RTOG 1112- http://www.cancer.gov/clinicaltrials)
Skin (external contour)	Less than 0.5cc ≥50.25Gy (RTOG 1112 - http://www.cancer.gov/clinicaltrials)

Marker implantation

A tumour tracking technique (Synchrony-Cyberknife, Accuray, Sunnyvale, CA, USA) will be applied for daily positioning and during dose delivery. Therefore, implantation of fiducials is compulsory. For perihilar CCA, fiducials should be implanted in the liver and not in the tumour to avoid the risk of tumour seeding. A distance of around 2.0 cm from the tumour edge is recommended. The procedure will be performed by an experienced interventional radiologist. INR should be <2.0, and platelets should be ≥50×10^9/l. We will plan around one week (minimum of 5 and maximum of 10 days) between the implantation of the fiducials and the treatment preparation (planning CT). Patients should remain hospitalized during at least 2-3 hours after the implantation in order to detect and treat unexpected complications as soon as possible. In case of lymph node involvement, no fiducials will be implanted in the affected nodes.

Tumour delineation

The gross target volume (GTV) is defined in a contrast-enhanced CT acquired in expiration and in a hepatic venous phase. An arterial phase CT with bolus tracking technique is also performed since valuable complementary information from this phase could be valuable to better depict the tumour. The use of MRI to support the tumour delineation is recommended. In case that enlarged lymph nodes (N1) have to be considered as a target for SBRT, the venous phase of the planning CT in expiration will also be used for the delineation. No additional margin will be added around the GTV to generate the clinical target volume (CTV) for both tumour and lymph nodes.

Margins

The information acquired from a 4DCT scan and from the inspiration/expiration CT will be used to establish the margin around the GTV to generate the planning target volume (PTV). This margin should ensure that despite geometrical uncertainties (i.e. imaging artifacts in the planning CT-scan due to respiratory tumour motion, inter-fraction motion of the tumour, uncertainty in the set-up, etc.), the full GTV is irradiated with an adequate dose with a very high probability.

Planning protocol

Efforts should be made to deliver a BED>80.5Gy to the tumour, since a multicenter retrospective study of intrahepatic CCA demonstrated a significant improvement in LC depending on the BED (3y

45% for BED<80.5Gy vs. 78% for BED>80.5Gy)[19]. In case the tumour is located very close/adjacent to organs at risk as the duodenum, stomach, esophagus or bowel, it may be impossible to deliver such high doses to the periphery of most of the tumour, and therefore lower doses at the periphery are allowed in these cases.

Any plan delivered to a patient should adhere to the imposed organs at risk (OAR) hard constraints (table 4). Within these constraints, ideally the full PTV is irradiated with a dose of ≥67.5Gy (15×4.5Gy). Due to the hard constraints and the objectives for the OARs, this ideal PTV dose may not always be achievable. In that case, compromises in PTV dose delivery can be made. First of all, the PTV coverage may be reduced, i.e. only 95% of the PTV may receive ≥67.5Gy. Second, instead of delivering 67.5Gy (15×4.5Gy), a dose of 60Gy (15×4Gy), 52.5Gy (15×3.5Gy) or even 45Gy (15×3Gy) can be chosen. An effort should be made to deliver at least 60Gy (BED>80.5Gy) to a large portion of the PTV without violating OAR constraints.

Fractionation and daily imaging

The total dose is delivered in 15 fractions. Time between fractions should be 24h (in case of a weekend in between it will be 72h). Effort should be made to deliver the treatment without gaps.

In order to evaluate the relationship between tumour and organs at risk in this perihilar location, a CT scan before and after treatment in expiration phase will be performed in treatment position the first day and on days 3, 6, 9, 12 and 15 during treatment. No intravenous contrast will be used.

Post SBRT follow up

Follow up visits will be scheduled at 1, 3, 6, 9, 12, 18 and 24 months after treatment. At every visit a MRI or CT scan will be made to detect local or distant disease progression. Also toxicity and performance score will be scored every visit. Patients will be asked to fill out quality of life (QoL) questionnaires (EuroQol EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ- BIL21) at most visits. For further detailed information see table 6. If a patient is still alive after 2 years, follow up will be continued by the medical oncologist according current clinical practice.

Ancillary study: evaluating cellular radio-sensitivity in patient-derived organoid models

We will grow organoids from tumour and bile duct cells collected by brush biopsies[22](Broutier et al. Tumour-derived organoid cultures model primary human liver cancer in vitro, article in press). For this purpose a second brush will be obtained during the same procedure while the first brush is taken (just directly after the first one) and only for patients where a brush biopsy is considered needed as part of the diagnostic work up. We will set up assays to measure cell survival (clonogenic assays, HE staining of organoids), apoptosis (TUNEL staining), accumulation of DNA repair proteins on DNA double strand breaks (gamma-H2AX, 53BP1 and RAD51 foci) and repair of the DNA damage at various time points after irradiation (loss of these foci after 24-48 hours of incubation). In addition to the functional assays, organoid cultures are also ideal sources of tumour material, such as DNA for mutation analysis and RNA for gene expression studies[30].

Table 6: Schedule of events

	Eligibility check	Written informed consent	Medical history	Co-morbidity	ECOG PS	Laboratory[a]	CT/MRI[b]	Adverse events[c]	QOL	Survival and post-study treatment
Standard treatment (Chemotherapy) 1-8 courses. No progressive disease										
≤6 weeks	X	X	X	X	X	X	X	X	X	
Experimental add on treatment (SBRT)										
+1 month					X	X	X	X	X	X
+3 months					X	X	X	X	X	X
+6 months					X	X	X	X	X	X
+9 months					X	X	X	X	X	X
+12 months					X	X	X	X	X	X
+18 months					X	X	X	X		X
+24 months					X	X	X	X	X	X

[a] Lab assessments should include albumin, bilirubin, alkaline phosphatase, AST, ALT, GGT, Hb, leukocytes, platelets, and CA-19.9. Notice that CA-19.9 should only be assessed during follow-up if indicated, i.e. if elevated at baseline. [b] Radiology report should include tumour measurement, tumour measurements should be performed according to RECIST criteria. [c] CTCAE v 4.03 should be applied for grading toxicity

Data analysis

This trial will be performed as a feasibility study and will focus on toxicity until 3 months after SBRT treatment. The number of patients with LT as defined before will be determined. If two or more patients have LT, the conclusion will be that the regimen is not feasible. Otherwise the conclusion will be that the regimen warrants further research in this population.

In addition, the analysis of toxicity will be done by tabulation of the incidence of adverse events CTCAE grade 3 and 4. Adverse events will be summarized by worst CTCAE grade. Demographics of the patients at study entry will be recorded, and presented as percentages in case of discrete variables, or by median and range in case of continuous variables. All patients with the baseline and at least one follow-up QoL questionnaire, separately for QLQ-C30, QLQ-BIL21 and EuroQoL-5D, will be included in the analysis. The repeated measures will be analyzed using ANOVA models. The

Kaplan-Meier method will be used to estimate local control, progression free survival and overall survival.

Patient and Public Involvement

While designing the study, our first priority was the patients´ well-being. Although we did not involve patients in the design of the trial, all information about the study is available on the website of the Dutch Hepato & Cholangio Carcinoma Group (www.dhcg.org). During the development phase, the study was discussed several times within this multidisciplinary group. A final report of the trial will also be placed at the website for patient information. At any time, participants can be informed about study outcomes through the principal investigator.

ETHICS AND DISSEMINATION

Prior to any study procedure written informed consent will be obtained from every participating patient. Ethics approval for the study was granted 31 August 2017 by the Medical Ethics Committee of Erasmus MC Rotterdam, the Netherlands (ID: NL 60588.078.17). The STRONG trial is registered on clincaltrials.gov (ID: NCT03307538). The results of this study will be published in an academic journal, and presented at national and international conferences.

DISCUSSION

The STRONG trial is designed to assess feasibility and toxicity of adding SBRT to standard chemotherapy in patients with inoperable perihilar CCA. Currently, only a few prospective studies are available on the use of SBRT for treating patients with CCA in the perihilar region. These studies report promising results for LC (≥72% at 2 years) and median OS (up to 35 months), with low toxicity rates. However, the exact treatment approach (combination with chemotherapy, chemotherapy scheme, timing, SBRT fractionation) varied widely[12-20]. The scarce available results suggest that the combination of chemotherapy and SBRT may improve disease control above SBRT alone.

We chose a more fractionated scheme than the other studies on SBRT for perihilar tumours because of the proximity of organs at risk like duodenum and bile duct to the tumour. By using 15 fractions, instead of fewer, we hope to reach an acceptable coverage of the PTV with a biologically effective dose of more than 80.5Gy, and at the same time respect the dose constraints for the OAR's. Acceptable results have been published with this fractionating scheme for intrahepatic CCA[19].

In this study we will encounter some technical challenges and uncertainties. First of all is the assessment of the breathing motion of tumours located in the perihilar region. Since we use the Synchrony-Cyberknife system for tumour tracking, fiducial markers will have to be implanted close to the tumour. These markers will be placed in the liver in the proximity of the tumour and not in the tumour itself to avoid tumour seeding. Second, there is little known about the inter- and intrafraction motion of organs at risk located in the vicinity of the perihilar region and the correlation with the tumour motion. If present, involved lymph nodes may be situated at a certain distance of the tumour. Again, motion assessment and correlation with tumour motion will be another point that should be addressed within this study. In order to measure variations in inter- and intrafraction motion, a CT scan in expiration phase before and after treatment will be performed in treatment position the first day and on days 3, 6, 9, 12 and 15 during treatment.

Because of these technical uncertainties in combination with the experimental fractionation scheme for tumours located in the perihilar region, the first step is to complete this feasibility trial with just 6 patients. Since this small number results in limitations for interpreting results on disease control and QoL, our aim is to proceed to a large phase II trial if the treatment turns out to be feasible.

AUTHOR CONTRIBUTIONS All authors contributed to the design of the study protocol and approved the final manuscript. AMR and MSK principal investigators, initiators of the trial. BJMH medical physics aspects. BvdH statistical design and data analysis. DCvG and LJWvdL molecular genetics side study. FEJAW radiological support. BGK surgical aspects. FE systemic therapy advise. DS and JWP for endoscopic and gastroenterological procedures.

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Figure legends:

- Figure 1. Study outline

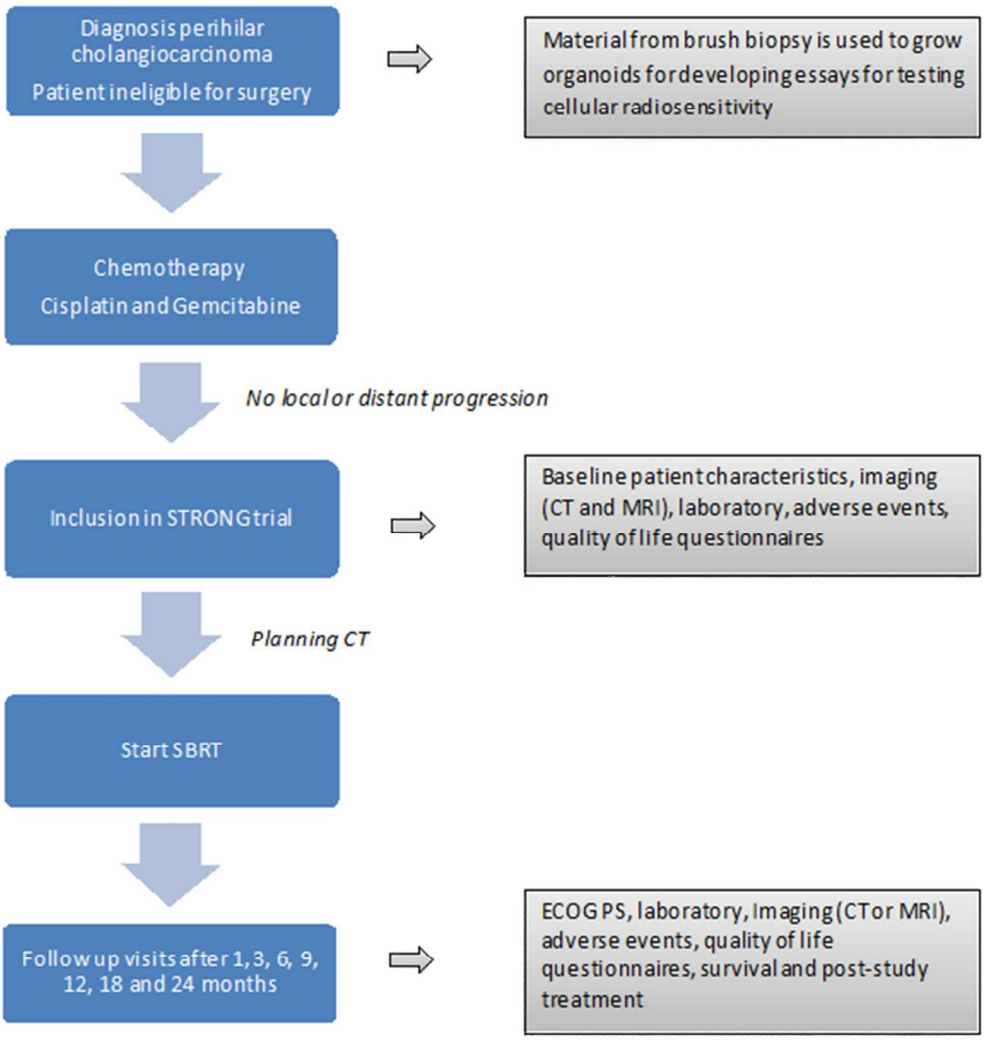

Figure 1. Study outline

99x105mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	clinicaltrials.gov NCT03305538
	2b	All items from the World Health Organization Trial Registration Data Set	-
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	9
	5b	Name and contact information for the trial sponsor	n.a.
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n.a.
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9 + 11+37

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	22
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	22

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n.a.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n.a.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n.a.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n.a.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	32+33
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	-

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21, 33, 39
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Appendix I
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	41
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n.a.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	41, 42
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	40
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	42, 43
	31b	Authorship eligibility guidelines and any intended use of professional writers	42, 43
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n.a.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	see PIF
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.