Stereotactic body radiation therapy after chemotherapy for unresectable perihilar cholangiocarcinoma: a multicenter phase II trial (The STRONG 2 trial)

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To evaluate the efficacy of SBRT as additional treatment after standard care chemotherapy regarding tumor local control, toxicity, progression-free survival, overall survival and quality of life. In addition, to explore the value of immunodynamics...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bile duct disorders
Study type	Interventional

Summary

ID

NL-OMON56809

Source
ToetsingOnline

Brief title
The STRONG II trial

Condition

- Bile duct disorders
- Hepatobiliary neoplasms malignant and unspecified

Synonym
Cholangiocarcinoma, perihilar

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: KWF (Alpe d'HuZes/KWF-fonds)

Intervention

Keyword: Cholangiocarcinoma, Efficacy, Immunodynamics, perihilar, Stereotactic body radiation therapy

Outcome measures

Primary outcome

The main endpoint with regards to the radiotherapy is local tumor control. With regards to the translational part of the study the aim is to explore the value of immunodynamics in peripheral blood for predicting progression-free survival in patients undergoing chemotherapy.

Secondary outcome

Toxicity, biliary stent-related events (SRE) (*), progression-free survival, overall survival, quality of life.

(*) The definition of SRE in this study is based on the definition used in the study by Lamarca et al. [1], and includes the following:

*A SRE is defined as any one or more of the following: (1) any episode of jaundice which is considered significant enough for new stenting or medical treatment and is confirmed by radiological imaging to be associated with biliary dilatation; (2) any episode of infection which is clinically in keeping with cholangitis (bile duct infection) requiring antibiotic therapy; (3) bacteraemia with isolation in blood cultures of bacteria suspected to have

originated in the biliary tract; and (4) any episode of cholecystitis or gallbladder perforation. The following will not be considered SREs: (1) jaundice related to high tumour burden liver disease with no significant change in biliary dilatation compared with previous imaging; (2) episodes of neutropenic or non-neutropenic fever with no identified biliary focus; and (3) patients with non-clinically significant biliary occlusion or biliary dilatation (i.e., radiological evidence only with no jaundice, increasing bilirubin, increasing liver function tests (LFTs), fever or evidence of infection) who require no action (no new stenting or no new antibiotic therapy).*

Reference:

[1]: https://doi.org/10.3748/wjg.v22.i26.6065

Study description

Background summary

For patients with perihilar cholangiocarcinoma, surgery is the only treatment modality that can result in cure. Unfortunately, in the majority of these patients the tumors are found to be unresectable at presentation due to local invasive tumor growth or the presence of distal metastases. For patients with unresectable cholangiocarcinoma palliative chemotherapy is the standard treatment yielding an estimated median overall survival of 12-15.2 months. There is no evidence from randomized trials that support the routine use of stereotactic body radiation therapy (SBRT) for cholangiocarcinoma. However, the STRONG phase 1 feasibility study, showed favorable outcomes regarding safety, and that the therapy was generally well tolerated.

Based upon these observations, we propose a phase 2 multi-center study with SBRT after chemotherapy in patients with unresectable perihilar cholangiocarcinoma in order to further research the efficacy of adding SBRT to

standard care chemotherapy.

We will add an explorative translational research component to the study in which peripheral immunodynamics (NF-kB and IFN/ISG) may help to predict survival after chemotherapy and may also help to predict the value of additional treatment with radiotherapy.

Study objective

To evaluate the efficacy of SBRT as additional treatment after standard care chemotherapy regarding tumor local control, toxicity, progression-free survival, overall survival and quality of life. In addition, to explore the value of immunodynamics in peripheral blood for predicting PFS in patients undergoing chemotherapy.

Study design

Phase II multicenter study. 30 patients will be included.

Intervention

SBRT will be delivered in 15 fractions of 4 to 4.5Gy after 8 cycles of chemotherapy. In case of toxicity causing premature termination of systemic treatment, the patient can still proceed to SBRT.

Study burden and risks

The phase 1 STRONG study evaluating toxicity of SBRT delivered in 15 fractions in perihilar cholangiocarcinoma provided evidence that SBRT is a relatively safe treatment with acceptable complication risks.

Expected associated gastrointestinal grade >=3 toxicity such as stomach or bowel perforation, is expected to be low (<5%). The risk of biliary grade >=4 toxicity with the SBRT protocol used in this trial is also expected to be low (<5%). However, biliary toxicity grade 3 (cholangitis) was observed in 5 of 6 patients (83%) in the STRONG 1 trial, and it was reversed by improving the biliary drainage (stent placement).
The burden associated with the participation in this study includes: 1-3 visits related to the preparation of the treatment with radiotherapy, 15 daily visits for the treatment itself, 8 times filling in QoL evaluation forms. The two blood samples required for the immunodynamics will be collected during scheduled appointments for blood collection regarding the standard of care treatment with chemotherapy. Regarding the radiotherapy, a standard follow-up protocol will be followed, with the 1st year after SBRT every 3 months a visit and from the 2nd year a minimum of 2 follow-up moments each year.

No DSMB will be installed in the present study. No interim analysis is planned for this study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

The initial translational part of the study will be performed in patients with unresectable pCCA eligible for gemcitabine-based chemotherapy (*). After chemotherapy, the patients will proceed to SBRT if they are still eligible based on the following inclusion and exclusion criteria (see below). It may happen that patients do not give consent for the translational part of the study, but they may wish to participate in the SBRT part of the trial and vice versa.

Inclusion criteria translational part of the study:
In order to be eligible to participate in the translational part of the study, a subject must be discussed in a liver tumor board, should be eligible for gemcitabine-based chemotherapy (and immunotherapy, if applicable), and should meet all of the following criteria pre-chemotherapy:
- pCCA according to the criteria of the Mayo Clinic, Rochester (22):
o Positive or strongly suspicious intraluminal brush cytology or biopsy or,
o A radiographic malignant appearing stricture plus either:
* CA 19-9>100 U/ml in the absence of acute bacterial cholangitis, or
* polysomy on fluorescence in situ hybridization (FISH), or
* a well-defined mass on cross sectional imaging
- One tumor mass
- Unresectable tumor or patient deemed unfit for surgery
- T1-T4 (AJCC staging 8th edition), N0-N2-M0 (AJCC staging 8th edition), radiologically or pathologically suspect
o N1 is defined as one to three affected lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes. N2 is defined as four or more affected lymph nodes from the sites described for N1.
o Endoscopic ultrasound (EUS) is leading in identifying pathological lymph nodes compared to CT.
- In case of (underlying) liver cirrhosis: Child-Pugh A
- Age >= 18 years
- ECOG performance status 0-1
- Written informed consent for the translational part of the study

Inclusion criteria SBRT part of the study:
Additionally, to the criteria mentioned above, patients should meet the following criteria to be eligible for the treatment with SBRT:
- Measurable disease to be selected as a target on a computed tomography (CT) or magnetic resonance imaging (MRI) scan, according to RECIST 1.1 criteria
- Finished gemcitabine-based chemotherapy treatment, preferably 8 cycles. If less cycles are given, patients are still eligible for this study
- Bilirubin <=3.0 times normal value (**), aspartate aminotransferase (AST)/alanine transami-nase (ALT) <=5 times ULN
- Platelets >= 50x10E9/ l, Leukocytes > 1.5x10E9/l, Hemoglobin (Hb) > 6 mmol/l
- Willing and able to comply to the follow-up schedule
- Able to start SBRT within 12 weeks after completion of chemotherapy and immuno-therapy (if applicable)
- Written informed consent for the SBRT part of the study

(*) Gemcitabine-based chemotherapy will most frequently include a combination of gemcitabine and cisplatin for this patient population. However, when deemed necessary by a medical oncologist, variations of this chemotherapy regimen regarding the cisplatin may be applied. Such variations in chemotherapy

regimens will be allowed in this study. Gemcitabine-based chemotherapy will be administered according to local practice.
(**) This corresponds to the threshold beyond which gemcitabine-based chemotherapy is no longer administered to patients in Erasmus MC, and also closely resembles the threshold beyond which gemcitabine and cisplatin combined with immunotherapy (durvalumab) is no longer administered to patients in a study by Oh et al. (bilirubin <=2.5 times normal value) [1].

[1]: https://doi.org/10.1056/EVIDoa2200015

Exclusion criteria

Exclusion criteria translational part of the study
- Prior surgery or transplantation of the liver
- Tumor extension in stomach, colon, duodenum, pancreas or abdominal wall
- Ascites
- Prior radiotherapy to the liver
- Current pregnancy
- Affected lymph nodes outside the regions described in the inclusion criteria (D4)

Exclusion criteria SBRT part of the study:
Progression (local or distant) during or after chemotherapy

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-06-2024
Enrollment:	23
Type:	Actual

Medical products/devices used

Generic name:	Abdominal corset
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	05-06-2024
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT06493734
CCMO	NL86210.078.24