Addition of stereotactic radiotherapy to the standard FOLFIRINOX treatment in locally advanced pancreatic cancer patients to determine efficacy and feasibility (LAPC-1)

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	adverse event
ALAT	alanine aminotransferase
AR	Adverse Reaction
ASAT	aspartate aminotransferase
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CI	confidence interval
CT	computed tomography
CTV	clinical target volume
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EBRT	external beam radiotherapy
eCRF	electronic case record form
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
EUS	endoscopic ultrasonography
FNA	fine needle aspiration
GCP	Good Clinical Practice
GI	gastrointestinal
GTV	gross tumor volume
IB	Investigator's Brochure
IC	Informed Consent
IGRT	image guided radiotherapy
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IQR	interquartile range
LAPC	locally advanced pancreatic cancer
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
miRNA	microRNA
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response
PTV	planning target volume
RNA	ribonucleic acid
RR	response rate
RTS	respiratory tracking system
SAE	(Serious) Adverse Event
SAE	serious adverse event
SBRT	stereotactic body radiation therapy

SD	standard deviation
SD	stable disease
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SRS	stereotactic radiosurgery
SST	serum separating tube
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	time to progression
VAS	visual analogue scale
WBC	white blood cells
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: FOLFIRINOX might be interesting in the setting of locally advanced pancreatic cancer (LAPC) as tumor shrinkage has been observed in metastatic pancreatic cancer and combination with radiotherapy appears to be feasible in a small uncontrolled study. Currently in the Erasmus MC Cancer Institute patients with LAPC are treated with up to 8 courses of FOLFIRINOX followed by standard radiotherapy consisting of a scheme of 30x2 Gray (Gy). Current studies with stereotactic radiotherapy in the treatment of locally advanced pancreatic cancer show an excellent local control but no gain in overall survival. Hence, combining FOLFIRINOX with stereotactic radiotherapy is an attractive approach as it could combine optimal systemic treatment and local control. In addition we want to determine if biological markers could be useful in deciding on the clinical course of the patient. This may possibly result in avoiding unnecessary invasive chemotherapy and radiotherapy in certain subgroups of patient with LAPC.

Objective: This is a prospective phase II non-randomized multi-center study in patients with LAPC. Patients are first treated with up to 8 cycles of FOLFIRINOX, followed by stereotactic radiotherapy for a total dose of 40 Gray in 5 fractions. Due to the known toxicity of FOLFIRINOX treatment and the expected late toxicity when combined with radiotherapy, we will explore sequential chemoradiotherapy. The objectives are to determine efficacy and feasibility of adding stereotactic radiotherapy to the FOLFIRINOX regime. The primary end-points are overall survival, time to progression and toxicity. Secondary endpoints will be radiological response, resectability at laparotomy in case of regression as well as local and distant progression.

Study design: prospective multi-center non-randomized phase II trial.

Study population: Patients with LAPC between 18 and 75 years of age.

Intervention: Up to 8 cycles of systemic chemotherapy with FOLFIRINOX followed by 5 days of stereotactic radiotherapy if patients responded to chemotherapy. After cycle 4 and 8 of chemotherapy a CT scan will be performed in order to rule out the development of metastatic disease. In the absence of disease progression during or after FOLFIRINOX, the patient can proceed with stereotactic radiotherapy. Before the first 3 radiation sessions patients will undergo a CT scan to determine if the dosage is correctly received. Six weeks after radiotherapy a CT scan will be performed to determine resectability of the tumor. In addition patients will undergo additional blood collection during every study and follow-up visit in order to determine the presence of certain biological markers.

Main study parameters/endpoints: The main endpoint is defined as overall survival (OS).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Before start of therapy, suitable patients will undergo a diagnostic workup which consists of triphase helical CT scan and endoscopic ultrasound in specific cases in which vascular involvement cannot adequately determined by CT scan. Endoscopic Ultrasonography with Fine Needle Aspiration (EUS/FNA) is also performed to obtain a pathological diagnosis. Furthermore the following will be done; medical history including duration of complaints associated with pancreatic cancer, pain score (visual analogue scale (VAS)), use and dosages of pain medication, weight loss and nutrient intake. Full physical examination, including actual height and weight. Contrast enhanced spiral CT scan of chest and abdomen if performed more than 1 month prior to therapy. Endoscopic ultrasound for obtaining pathological diagnosis or revision of pathology specimen from elsewhere. Laboratory investigation including Hemoglobin, WBC, platelets, ALAT, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium and tumormarker CA 19.9. All patients who meet the in- and exclusion criteria will receive 8 cycles of FOLFIRINOX for which they will be hospitalized for 2 days every 2 weeks. After cycle 4 and 8 a staging helical CT scan will be made. Patients who do not develop metastatic disease during this stage are eligible to continue with 5 days of stereotactic radiotherapy. During these 5 days, patients will receive daily stereotactic radiotherapy for a total dose of 40 Gray. Prior to the first three days of radiotherapy patients will undergo a CT scan to assess whether the radiation dose is correctly located. During every visit blood collection, pain scoring (VAS), physical examination, toxicity assessment and additional examinations (when indicated) will take place. After the treatment period patients will go into follow-up for 3 years. During every follow up visit the patients will undergo a CT scan, blood collection, pain scoring (VAS), physical examination, toxicity assessment and other examinations will be performed when indicated.

1. INTRODUCTION AND RATIONALE

1.1 Background

Approximately 80% of patients presenting with pancreatic cancer are not amenable to local surgical resection. These patients have metastatic pancreatic cancer or have localized unresectable disease because the tumor involves the celiac axis, superior mesenteric artery or vein, hepatic artery or portal vein; so called locally advanced pancreatic cancer (LAPC). For LAPC the standard of practice has been to give chemoradiotherapy with 5-FU. Over the years, gemcitabine has been studied to act as a substitute for 5-FU in the treatment of unresectable pancreatic cancer, either alone, in combination with radiotherapy or in combination with other drugs [1]. Currently, chemotherapy is frequently given as upfront modality, as the occurrence of metastases is the main problem in this patient population. Following successful upfront chemotherapy administrations, in several centers subsequent chemoradiotherapy or stereotactic radiotherapy is given after chemotherapy in an attempt to increase local control and potentially survival.

1.2 Systemic chemotherapy

Systemic chemotherapy is the first treatment of choice for patients with metastatic pancreatic carcinoma. Gemcitabine has been the standard of care for over a decade but the outcome has generally been disappointing with low response rates and short survival benefit in the range of only 6 months [2].

Interest in systemic chemotherapy was recently regained with the advent of the FOLFIRINOX combination [3]. In the randomized phase III ACCORD-11 trial, FOLFIRINOX was show to be superior to single-agent gemcitabine in response rate (RR), progression-free survival (PFS) and overall survival (OS). Post-hoc analysis added a significant reduction in Quality of Life after FOLFIRONOX treatment [4]. The RR in the FOLFIRINOX arm was 32% versus 9% in the gemcitabine arm, and this translated into an improvement in PFS to 6.4 months (versus 3.3. in the control arm, $p<0.0001$) and OS of 11.1 months (versus 6.8 months in the control arm, $p<0.0001$).

A retrospective study of 33 patients with LAPC (16 patients) and metastatic pancreatic cancer (17 patients) treated with FOLFIRINOX was performed to investigate toxicity and efficacy [5]. The response rate of FOLFIRINOX was 47% in metastatic disease and 50% in locally advanced disease, suggesting that the efficacy of FOLFIRINOX is comparable between LAPC and metastatic pancreatic cancer. Only two out of 16 patients were able to undergo resection after 4 and 6 cycles of FOLFIRINOX with one of them having complete response. Due to the limited disease extent both progression free survival and overall survival are better in patients with LAPC.

A retrospective analysis of 18 patients with borderline resectable and LAPC pre-operatively treated with FOLFIRINOX were evaluated [6]. One patient developed progression after 3 cycles and discontinued treatment. At maximum response or tolerability of FOLFIRINOX, 7 patients were converted to resectability by radiological criteria. After surgical resection 5 had R0 resections, 1 had an R1 resection and 1 had unresectable disease. The remaining 10 patients went on to receive chemoradiotherapy; 5 remained with unresectable disease; and 3 were radiologically assessed as being potentially resectable after chemoradiotherapy and went on to have R0 resections. The overall R0 resection rate was 8 out of 18 or 44% (95% CI 22-69%) using this sequential combined bimodality approach. The 1-year PFS was 93% (95% CI 59-96%) and the 1-year OS was 100% (95% CI 85-100%). The estimated 1-year PFS was not significantly different for the patients who achieved R0 resections (88%; 95% CI 47-100%) versus those who did not (80%; 95% CI 44094%, p=0.27). In summary, chemoradiation, including FOLFIRINOX, appears to be feasible in patients with LAPC.

1.3 Stereotactic radiotherapy

While the pancreas does not manifest any major clinical sequelae following radiation therapy, it is close to many other critical organs that are highly radiosensitive. The organs at risk needing consideration are the duodenum, liver, and stomach. The liver is not usually problematic, since the volume of liver tissue receiving a significant dose of radiation is likely to be small. The hardest organs at risk to avoid are the duodenum, and the stomach that directly abuts the pancreas. Delivery of moderate doses of radiation to small bowel is associated with a high risk of acute nausea, diarrhea, and vomiting and late complications as stenosis, ulceration, bleeding and perforation. With the use of stereotactic radiotherapy, a form of image guided radiotherapy (IGRT), the radiation dose to the organs at risk can be reduced.

A recent study with IGRT reported that the mean V50.4 Gray (volume covered by 50.4 Gray) for the duodenum was reduced from 43.4% for IGRT to 15.6% for the online Adaptive Radiotherapy scheme [7]. The first cases of stereotactic radiotherapy for pancreatic cancer were reported in 2000 from Stanford University and showed basic feasibility of single fraction with stereotactic radiotherapy in the treatment of pancreatic cancer [8].

This study was followed by an initial phase I dose escalation study with stereotactic radiotherapy for pancreatic cancer also from Stanford University [9]. A total of fifteen patients were enrolled and received doses of either 15, 20, or 25 Gray to the primary tumor. Twelve of the patients had not received any prior radiation or chemotherapy. Five patients had acute toxicity which consisted of grade 2 nausea, pain, or diarrhea. The 6 patients who received 25 Gray had local control of their primary pancreatic tumor, but all 6 died to distant metastases as the site of first progression. The median survival for the cohort was 11 months. There was no grade 3 toxicity or higher. This study established the feasibility and dose parameters of single fraction with stereotactic radiotherapy for the treatment of pancreatic cancer.

This same group then assessed efficacy of combining systemic 5-FU with conventionally fractionated external beam radiotherapy (EBRT) followed by a stereotactic boost in patients with locally advanced pancreatic cancer. This phase II trial looked at chemoradiation with 5-FU and 45 Gray delivered in 1.8 Gray per day fractions to both the tumor and regional lymph nodes, followed by a 25 Gray stereotactic radiosurgery (SRS) boost to the gross tumor volume (GTV) [10]. Fifteen out of 16 patients who completed treatment were free from local progression until death, but all patients developed distant disease, with a median survival of 8.25 months. Two patients experienced grade 3 acute toxicity. There was more gastrointestinal (GI) toxicity when combining a stereotactic boost with conventional fractionated radiotherapy and although there was excellent local control, there was no impact on overall survival because of rapid progression of systemic metastasis.

Another phase II trial from the Stanford group aimed to integrate standard gemcitabine chemotherapy with stereotactic radiotherapy to address the high propensity of distant metastasis with pancreatic carcinoma. This study on the combined use of chemotherapy and stereotactic radiotherapy studied gemcitabine (1,000 mg/m2 on days 1, 8, and 15) followed by a single dose of 25 Gray on day 29 for local control. Two weeks or more after the stereotactic radiotherapy, gemcitabine was restarted at 1,000 mg/m2 per week and continued until disease progression [11]. Sixteen patients were enrolled and all 16 completed treatment with a median survival of 11.4 months, and one-year survival was 50%. Thirteen of 16 patients were locally controlled, but these patients developed metastases. None of the patients had sufficient response to undergo resection. Acute toxicity was mild, but late toxicity was severe including five late grade 2 duodenal ulcers, one grade 3 duodenal stenosis requiring stenting, and one grade 4 duodenal perforation requiring surgery. Combining stereotactic radiotherapy, surgery and pre- and post-treatment gemcitabine is well tolerated and excellent local control was achieved, but late toxicities were more common.

Mahadevan *et al.* retrospectively analyzed a planned strategy of initial chemotherapy with restaging and then treatment for those patients with no evidence of metastatic progression with stereotactic body radiation therapy (SBRT) [12]. Patients without metastases after two cycles were treated with stereotactic radiotherapy (tolerance-based dose of 24-36 Gray in 3 fractions) between the third and fourth cycles without interrupting the chemotherapy cycles. Eight of the 47 patients (17%) were found to have metastatic disease after two cycles of gemcitabine; the remaining 39 patients received SBRT. The median overall survival for all patients who received SBRT was 20 months. The local control rate was 85% (33 of 39 patients); and 54% of patients (21 of 39) developed metastases. Late Grade III toxicities such as GI bleeding and obstruction were observed in 9% (3/39) of patients [12]. This median overall survival of 20 months is the highest reported median survival and shows that patients receiving stereotactic radiotherapy may benefit from this treatment with a longer overall survival, if they do not develop metastasis during the chemotherapy.

1.3.1 Management of interfractional and intrafractional anatomic variations during SRT

Liu *et al.* demonstrated that significant interfractional anatomical variations occur during pancreatic cancer radiotherapy [7]. These anatomical variations include organ deformation, rotation, and differential motion between different organs and the target. These variations cannot be accounted for by a translational correction of the treatment fields, which is currently common practice in image-guided radiotherapy. As a consequence the safety margins around the target (clinical-target-volume-to-planning-target-volume) are generous and the arrangement of the organs at risk on which the treatment plan is optimized is not fully representative for the actual treatment. In order to manage and reduce the interfractional anatomic variations, a 4D CT scan can be acquired just prior to the delivery of the treatment fraction. The CT scanning will be performed using a regular CT scanner of an in-room CT scanner with the patient in treatment position on a robotic couch. The robotic couch will move the patient automatically from the imaging position to the treatment position. Prior to the start of the treatment the planned dose distribution will be projected on the daily CT scan to verify sufficient target coverage and to verify that no dose constraints of the organs at risk are violated. If required the treatment plan will be adapted for the next treatment fraction.

1.4 Biological markers in pancreatic cancer

Predicting the results of FOLFIRINOX treatment based on biological markers could be useful in deciding on the further treatment course of the patient. This may possibly result in avoiding unnecessary invasive chemo- or radiotherapy in patients with LAPC.

Recently, microRNA (miRNA) has been investigated as a prognostic marker for chemo/radiation response [13]. miRNAs are short noncoding segments of RNA that can negatively regulate their mRNA targets. Only a small part of miRNA binds to its target, this imperfect match results in a variety of opportunities to bind its target. Thus it is possible for one miRNA to regulate the expression of numerous genes [14]. Each patient with pancreatic cancer has an unique pattern of upregulated (oncogenic) and downregulated (tumor suppressor) miRNAs [15]. These miRNAs play an important role in the development of pancreatic cancer and the response to chemotherapy and radiation therapy.

Development of cancer involves alterations in expression of multiple gene regulators. Therefore, using a single gene or protein as a biomarker may not reliably predict the behavior of a tumor. miRNA has the property to regulate multiple targets and hence may be a more reliable marker to study pancreatic cancer [16]. Detection of these alterations in miRNA of pancreatic cancer patients may result in a tool for personalized therapy.

1.5 Rationale study design

FOLFIRINOX might be interesting in the setting of LAPC as tumor shrinkage has been observed in metastatic pancreatic cancer and combination with radiotherapy appears to be feasible in a small uncontrolled study. Currently in the Erasmus MC Cancer Institute patients with LAPC are treated with up to 8 cycles of induction FOLFIRINOX followed by standard radiotherapy consisting of a scheme of 30x2 Gray.
Current studies with stereotactic radiotherapy in the treatment of locally advanced pancreatic cancer show an excellent local control but no gain in overall survival. Hence, combining FOLFIRINOX with stereotactic radiotherapy is an attractive approach as it could combine optimal systemic treatment and local control. Stereotactic radiotherapy is a standard procedure of care at the Erasmus MC Cancer Institute but currently no experience exists with this combination regimen in patients with LAPC. The treatment schedule is complex and involves a multidisciplinary approach from medical oncology, radiotherapy, gastroenterology and surgery. To assess its effectiveness and feasibility we intend to perform a prospective phase II non-randomized multi center study in the Erasmus MC Cancer Institute, Leids Universitair Medisch Centrum (LUMC) in Leiden, Maasstad ziekenhuis in Rotterdam and Reinier de Graaf Gasthuis in Delft.
In addition we will test a panel of miRNAs which may serve as a possible prognostic tool, and can help in further decision making during FOLFIRINOX therapy.

2. OBJECTIVES

Primary Objective:

- overall survival

Secondary Objective(s):

- toxicity of chemotherapy according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4)
- toxicity of radiotherapy according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4)
- radiological response rates after chemotherapy and radiotherapy (RECIST criteria)
- resection rate
- time to locoregional progression
- time to distant metastases
- determine prediction value of a set of biological markers

3. STUDY DESIGN

This study is designed as a non-randomized single arm multi-center phase II clinical trial.

In total 51 patients with LAPC will be included and will undergo systemic chemotherapy followed by stereotactic radiotherapy.

Total duration of the study for eligible patients will be a 16 week period of systemic chemotherapy, followed by single week of stereotactic radiotherapy The follow up period will be 2 years. In total the study period will have a duration of around 2,5 years. See Figure 1 for a schematic representation of the study design.

The total recruitment period will be around 2 years, based on an incidence of 25 eligible patients per year. This brings the total study duration to around 4,5 years.

Results of this study will be compared to current clinical practice. If at least half of the included patients are still alive 1 year after start of treatment, the studied treatment deserves further study in a randomized trial setting.

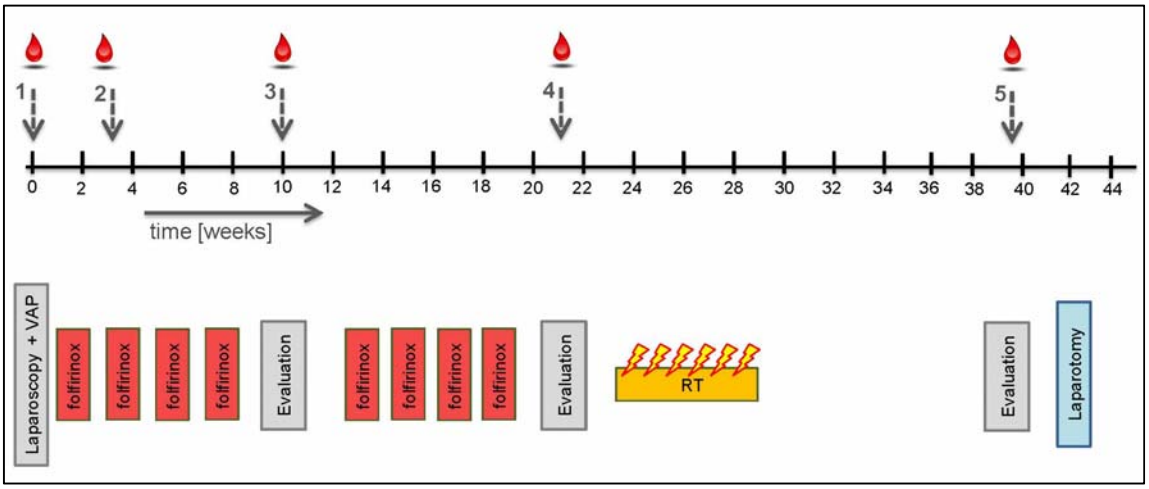

Figure 1: Study design including additional blood sampling time points for miRNA biomarker analysis.

Timelines for this study

Preparations:	01-01-2014
Start patient entry:	01-12-2014
End patient entry:	01-12-2016
End of follow up period:	01-05-2020
Final study analysis:	01-11-2020

4. STUDY POPULATION

4.1 Population

Patients will be selected from patients who come to the participating centers for treatment for suspected pancreatic cancer. Patients between 18 and 75 years of age with LAPC fulfilling the in- and exclusion criteria are eligible to enter the study.

4.2 Inclusion criteria

In order to be eligible for this study, subjects must meet all of the following criteria:

- Cytological or histologically confirmation of pancreatic cancer.
- WHO performance status of 0 or 1
- ASA classification I or II
- Tumor considered locally advanced after diagnostic work-up including CT-imaging and diagnostic laparoscopy.
- No evidence of metastatic disease
- Largest tumor diameter < 7 cm x 7 cm x 7 cm
- Normal renal function (Creatinine ≥ 30 ml/min).
- Normal liver tests (bilirubin < 1.5 times normal; ALAT/ASAT < 5 times normal)
- Normal bone marrow function (WBC > 3.0 x 10^e9/L, platelets > 100 x 10^e9/L and hemoglobin > 5.6 mmol/l)
- Age > 18 years and < 75 years
- Written informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Prior radiotherapy, chemotherapy or resection (bypass surgery allowed).
- Lymph node metastases from primary tumor outside the field of radiation.
- Second primary malignancy except in situ carcinoma of the cervix, adequately treated non-melanoma skin cancer, or other malignancy treated at least 3 years previously without evidence of recurrence.
- Pregnancy, breast feeding.
- Serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator.

4.4 Sample size calculation

Estimated number of potentially eligible patients per year is about 25. With a two-sided 5% significance test and a power of 80% a minimum of 51 patients need to be included in the study. If at least half of the included patients are alive 1 year after the start of treatment than this treatment deserves further study.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

In this study the investigational treatment is stereotactic radiotherapy following standard systemic chemotherapy.

5.2 Use of co-intervention

Participating female patients need to use adequate contraception and are not allowed to become pregnant during the study. If female patients are pregnant or breastfeeding before start of the study they are not allowed participate.

5.3 Escape medication

Not applicable.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

The investigational product is stereotactic radiation therapy using the Cyberknife (or equivalent). The Cyberknife is a frameless image guided radiotherapy system involving a 6 MV linear accelerator mounted on a computer-controlled robotic arm. Cyberknife differs from other stereotactic radiotherapy devices in its ability to chase tumors during the respiratory cycle. This allows a smaller margin for the planning target volume as a margin for movement of the tumor is no longer required. Tumor tracking is enabled by the Synchrony® Respiratory Tracking System (RTS) and requires the placement of radio-opaque markers in or near the tumor (fiducials). Fiducials are 3 mm gold objects frontloaded in a 19 Gauge FNA needle and pushed with the stylet through the entire length of the needle. Three fiducials are consecutively placed in the tumor or close to the tumor (within 3 cm distance of the tumor) under endoscopic ultrasound guidance [17].

6.2 Summary of findings from non-clinical studies

Not Applicable

6.3 Summary of findings from clinical studies

A recent study with IGRT reported that the mean V50.4 Gray (volume covered by 50.4 Gray) for the duodenum was reduced from 43.4% for IGRT to 15.6% for the online Adaptive Radiotherapy scheme [7]. The first cases of stereotactic radiotherapy for pancreatic cancer were reported in 2000 from Stanford University and showed basic feasibility of single fraction with stereotactic radiotherapy in the treatment of pancreatic cancer [8].

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6.4 Summary of known and potential risks and benefits

Side effects of endoscopic fiducial placement are low (6%) and are mainly grade 1 complications like bowel cramps and nausea [18].

In general, patients are fatigued throughout a radiotherapy treatment period. Further toxicity may concern the stomach, e.g. nausea, loss of appetite; weight loss and potentially a stress ulcer may develop. Furthermore, though not frequent, small bowel toxicities may occur resulting in frequent stools, or diarrhoea. Evaluation of the acute toxicity will be performed at the last fraction and at 2 weeks after the last radiation. Symptomatic medication as anti-emetics and anti-diarrhoea medication will be provided if required. A proton pump inhibitor is recommended during the first 6 months to diminish stomach secretion and to reduce pepsin production in order to prevent peptic ulcer. Late Grade III toxicities such as GI bleeding and obstruction can occur in 5-10% of the patients.

6.5 Description and justification of route of administration and dosage

Treatment planning should be done using the principles of stereotactic radiotherapy. The dose is prescripted to the 80% isodose line at the outerface of the planning target volume (PTV). At least 95% of the prescribed dose of 40 Gray in 5 fractions should cover 95% of the PTV. The PTV is allowed to be underdosed in order to meet the constraints of the organs at risk.

6.6 Dosages, dosage modifications and method of administration

Patients will be prepared for radiotherapy with a dedicated CT scanner in treatment position with an immobilisation device if used. Standard position is supine with the arms crossed over the chest, allowing optimal choice for possible beam angles. CT with 2 mm slices with intravenous contrast enhancement is warranted for a better definition of the tumour and neighbouring organs. A 4-dimensional CT with 10 phases must be used to determine the position variation of the pancreas and neighbouring organs due to breathing. Scans should be matched with pre-treatment diagnostic CT or MRI images if these provide better delineation of the tumour than the dedicated CT scan.

Volumes of interest are defined according to the ICRU Reports 50, 62 and 83. Gross tumour volume is defined as the macroscopically visible tumour at CT scan and/or MRI. The GTV must be delineated on the CT scan slice by slice using the 3D treatment planning software available on the department of radiation oncology. This may be performed in close co-operation between radiation oncologist and diagnostic radiologist, in order to define the tumour extensions optimally.

- Clinical target volume (CTV) includes the GTV plus possible tumour extension of 5 mm.
- Planning Target Volume (PTV) includes the CTV plus 2 mm margin.

The following criteria will be used to prevent side-effect of stereotactic radiotherapy to surrounding organs of the pancreas:

- The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) criteria will be used to define dose constraints for organs at risk.
- The dose to the spinal cord will at maximum be equivalent to 50 Gray in 2 Gray fractions (α/β = 3 Gray). The dose constraints for stomach and small bowel are 35 Gy in 5 fractions, are an equivalent of 70 Gray in 2 Gray/fraction.
- The mean kidney dose may not exceed 18 Gray (2 Gray fractions, α/β = 2.5 Gray). If the dose to one whole kidney exceeds 18 Gray one must avoid irradiation of the

contralateral kidney as much as possible. Liver: 700 cc of the liver should receive less than 20 Gray (total absolute dose).

During the first 3 fraction sessions the position of the target with respect to the implanted fiducials may change due to migration of the seeds, variations in filling in abutting organs (e.g. stomach and bowel), and tumor regression. These uncertainties in the alignment will be accounted for by a standard safety (CTV-to-PTV) margin of 2 mm. To verify the validity of this margin for each patient individually and thereby guaranteeing the highest treatment accuracy a 4D CT scan will be acquired just before the treatment fraction in treatment position. The CT scan will be matched to the planning CT scan by aligning the implanted fiducials and subsequently the planned dose distribution will be projected on the daily 4D CT scan. This procedure enables verifying the dose delivered to the target and healthy tissues. If the coverage of the CTV is insufficient a new treatment plan will be made with an increased safety margin. After the first 10 patients these data will be used to analyze the correctness of the applied margin of 2 mm. Depending on the results this margin will be adapted for the future patients. Moreover, the projected dose will be used to verify that no dose constraints of the organs at risk are violated. If required the treatment plan will be adapted for the next treatment fraction.

6.7 Preparation and labelling of Investigational Medicinal Product

Not Applicable

6.8 Drug accountability

Not Applicable

7. NON-INVESTIGATIONAL PRODUCT

7.1 Name and description of non-investigational product(s)

FOLFIRINOX, a combination of systemic chemotherapy agents. FOLFIRINOX consists of oxaliplatin at a dose of 85 mg/m^2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m^2 given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m^2, given as a 90-minute intravenous infusion through a Y-connector. This treatment is immediately followed by fluorouracil at a dose of 400 mg/m^2 administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg/m^2 over a 46-hour period every 2 weeks. Primary prophylaxis with G-CSF will be prescribed after every cycle of FOLFIRINOX.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

In the randomized phase III ACCORD-11 trial, FOLFIRINOX was show to be superior to single-agent gemcitabine in response rate, progression-free survival and overall survival. Post-hoc analysis added a significant reduction in Quality of Life after FOLFIRONOX treatment [4]. The RR in the FOLFIRINOX arm was 32% versus 9% in the gemcitabine arm, and this translated into an improvement in PFS to 6.4 months (versus 3.3. in the control arm, p<0.0001) and OS of 11.1 months (versus6.8 months in the control arm, p<0.0001).

A retrospective study of 33 patients with unresectable locally advanced (16 patients) and metastatic pancreatic cancer (17 patients) treated with FOLFIRINOX was performed to investigate toxicity and efficacy [5]. The response rate of FOLFIRINOX was 47% in metastatic disease and 50% in locally advanced disease, suggesting that the efficacy of FOLFIRINOX is comparable between LAPC and metastatic pancreatic cancer. Only two out of 16 patients were able to undergo resection after 4 and 6 cycles of FOLFIRINOX with one of them having complete response. Due to the limited disease extent both progression free survival and overall survival are better in patients with LAPC.

A retrospective analysis of 18 patients with borderline and locally advanced pancreatic cancer pre-operatively treated with FOLFIRINOX were evaluated [6]. One patient developed progression after 3 cycles and discontinued treatment. At maximum response or tolerability of FOLFIRINOX, 7 were converted to resectability by radiological criteria.

After surgical resection 5 had R0 resections, 1 had an R1 resection and 1 had unresectable disease. The remaining 10 patients went on to receive chemoradiotherapy; 5 remained with unresectable disease; and 3 were radiologically assessed as being potentially resectable after chemoradiotherapy and went on to have R0 resections. The overall R0 resection rate was 8 out of 18 or 44% (95% CI 22-69%) using this sequential combined bimodality approach. The 1-year PFS was 93% (95% CI 59-96%) and the 1-year OS was 100% (95% CI 85-100%). The estimated 1-year PFS was not significantly different for the patients who achieved R0 resections (88%; 95% CI 47-100%) versus those who did not (80%; 95% CI 44094%, p=0.27). However, chemoradiation, including FOLFIRINOX, appears to be feasible in patients with LAPC.

7.4 Summary of known and potential risks and benefits

Most common grade 3 or 4 adverse events occurring in more than 5% of patients with metastasized disease in the FOLFIRINOX trial (171 patients) were: Neutropenia (45.7%), Febrile neutropenia (5.4%), Thrombocytopenia (9.1%), Anemia (7.8%), Fatigue (23.6%), Vomiting (14.5%), Diarrhea (12.7%), Sensory neuropathy (9.0%), Elevated level of alanine aminotransferase (7.3%) and Thromboembolism (6.6%).

7.5 Description and justification of route of administration and dosage

See point 7.6 for dose and administration routes of FOLFIRINOX treatment.

7.6 Dosages, dosage modifications and method of administration

FOLFIRINOX, a combination of systemic chemotherapy agents. FOLFIRINOX consists of oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m2 given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg/m2, given as a 90-minute intravenous infusion through a Y-connector. This treatment is immediately followed by fluorouracil at a dose of 400 mg/m2 administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg/m2 over a 46-hour period every 2 weeks. Primary prophylaxis with G-CSF will be prescribed after every cycle of FOLFIRINOX.

Dose adjustments should be based on the worst preceding toxicity, graded using the National Cancer Institute Common Toxicity Criteria (version 4.0). For details on dose adjustment see section 9.

7.7 Preparation and labelling of Non Investigational Medicinal Product

The FOLFIRINOX chemotherapy combination is prepared in the pharmacy of the Erasmus MC Cancer Institute following their standard operating procedures. Since this is standard of care FOLFIRINOX does not need to be labelled as study medication.

7.8 Drug accountability

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

- overall survival

8.1.2 Secondary study parameters/endpoints

- toxicity of chemotherapy according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4)
- toxicity of radiotherapy according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4)
- radiological response rates after chemotherapy and radiotherapy (RECIST criteria)
- resection rate
- time to locoregional progression
- time to distant metastases
- determine prediction value of a set of biological markers (miRNAs)

8.1.3 Other study parameters

Not applicable.

8.2 Randomisation, blinding and treatment allocation

Not applicable.

8.3 Study procedures

Pre-treatment evaluation (pre-screening)

Once the diagnosis of pancreatic cancer is suspected, diagnostic workup will be performed. Staging of the tumor and irresectability will be determined by tri-phase helical CT-scan (Pancreas) and endoscopic ultrasound in specific cases in which vascular involvement cannot adequately determined by CT-scan. Endoscopic ultrasonography with Fine Needle Aspiration/Biopsy is performed to obtain a pathological diagnosis.

The following procedures will be performed during the evaluation:

- Obtaining informed consent
- *Tri-phase helical CT-scan of thorax and abdomen*. Tumors with more than 90 degrees of contact with the celiac axis or hepatic or mesenteric artery or more than 270 degree of contact with the portomesenteric vein and in case of occlusion of these veins, will be defined as irresectable locally advanced.
- *Endoscopic ultrasonography with Fine Needle Aspiration*. To obtain a cytological/histological diagnosis and/or more information regarding vascular involvement in specific cases patients will undergo endoscopic ultrasound with Fine Needle Aspiration/Biopsy. The specificity of FNAB is around 100%, the sensitivity however is between 60-70%. Hence, EUS/FNAB will be repeated at most three times, until a definite pathological diagnosis is obtained, without a definite pathological diagnosis patients cannot enter the study protocol.
- *Diagnostic laparoscopy and placement of porth-a-cath* In patients with locally advanced disease and confirmed pathological diagnosis without evidence of metastatic disease on CT-scanning a diagnostic laparoscopy will be performed in order to exclude metastatic disease. During the same procedure a porth-a-cath will be placed for easy venous access during the chemotherapeutic regimen.
- *Biliary stenting.* In case of obstructive jaundice (defined as bilirubin >50 µmol/l), placement of a metal biliary stent should be performed prior to start of treatment .
- *Laboratory tests*. Hemoglobin, WBC, platelets, ALAS, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium, CEA and tumormarker CA 19.9.
- *Additional blood sampling*. Two additional tubes (SST) will be drawn for miRNA biomarker analysis (2x10 ml).

Initial visit to the outpatient clinic (baseline)

- Assessment of Medical History.
- Assessment of nutrient intake and possible associated weight loss.
- Pain score (VAS).
- Assessment of concomitant pain medication.
- Assessment of adverse events

- Vital signs (Height, weight, pulse, respiration frequency).
- Contrast enhanced spiral-CT scan of thorax and abdomen (if not available within 1 month prior to start of therapy).
- Endoscopic ultrasound if not yet performed during evaluation period.
- Laboratory tests. Hemoglobin, WBC, platelets, ALAS, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium, CEA and tumormarker CA 19.9.
- Additional blood sampling. Two additional tubes (SST) will be drawn for miRNA biomarker analysis (2x10 ml if not yet done before laparoscopy. See schematic representation on page 34.

FOLFIRINOX treatment period (cycle 1,2,3,4,5,6,7 and 8)

- FOLFIRINOX treatment
- Staging helical CT scan of abdomen after cycle 4 and 8. Evaluation will be performed according to RECIST 1.1. In case of partial response and stable disease consecutive CT or RT will be performed. In case of progressive disease under chemotherapy, i.e. at least a 20% increase in the longest diameter of the target lesion or the appearance of any new tumor lesion distant from the primary tumor, consecutive treatment will be aborted and patients will not be eligible for stereotactic radiation treatment.
- Assessment of nutrient intake and possible associated weight loss.
- Pain score (VAS).
- Assessment of concomitant pain medication.
- Assessment of adverse events
- Vital signs (Weight, pulse, respiration frequency).
- Laboratory tests. Hemoglobin, WBC, platelets, ALAS, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium and tumormarker CA 19.9.
- Additional blood sampling. Two additional tubes (SST) will be drawn for biomarker analysis (2x10 ml) before 2nd cycle, after 4th cycle/before 1st CT evaluation and after the 8th cycle/before 2nd CT evaluation. For details also see schematic representation on page 34.

Stereotactic radiation pre-treatment visit (only for non-metastatic patients)

- Placement of “fiducial” markers.

- 4D CT (hospital standard CT) scan one week after placement to determine exact radiation area.
- Assessment of nutrient intake and possible associated weight loss.
- Pain score (VAS).
- Assessment of concomitant pain medication.
- Assessment of adverse events
- Vital signs (Weight, pulse, respiration frequency).
- Laboratory tests. Hemoglobin, WBC, platelets, ALAS, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium and tumormarker CA 19.9.

Stereotactic radiation treatment period (dosing days 1,2,3,4 and 5)

- 4D CT scan just before the treatment fraction in treatment position at dosing day 1, day 2 and day 3.
- Stereotactic radiation (8 Gy per radiation) dose
- Assessment of nutrient intake and possible associated weight loss.
- Pain score (VAS).
- Assessment of concomitant pain medication.
- Assessment of adverse events
- Vital signs (Weight, pulse, respiration frequency).
- Laboratory tests. Hemoglobin, WBC, platelets, ALAS, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium and tumormarker CA 19.9.

Follow up period (FU visit 1 to FU visit 9)

Follow up visits will take place at the following time points after the last radiotherapy (RT) is given:

FU visit 1: 6 weeks after RT
FU visit 2: 3 months after RT (including staging helical CT scan (Pancreas and abdomen) and blood sampling)
FU visit 3: 6 months after RT (including staging helical CT scan (Pancreas and abdomen)
FU visit 4: 9 months after RT
FU visit 5: 12 months after RT
FU visit 6: 15 months after RT

FU visit 7: 18 months after RT
FU visit 8: 21 months after RT
FU visit 9: 24 months after RT

- Staging helical CT scan of pancreas and abdomen 3 and 6 months after last radiotherapy. Additional CT scans can be performed on judgment of physician.
- Assessment of tumor resectability. Patients with at least stable disease and the following criteria are offered an exploratory laparotomy with intent of resection

	SMA	**Celiac axis**	**CHA**	**SMV-PV**
Exploratory laparotomy (minimally one required)	contact < 90°	contact < 90°	contact < 90°	contact > 270°
Definitive irresectable (minimally one required)	contact > 90°	contact > 90°	contact > 90°	occlusion

- Assessment of nutrient intake and possible associated weight loss.
- Pain score (VAS).
- Assessment of concomitant pain medication.
- Assessment of adverse events for late toxicity effects.
- Vital signs (Weight, pulse, respiration frequency).
- Laboratory tests. Hemoglobin, WBC, platelets, ALAS, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium and tumormarker CA 19.9.
- Additional blood sampling. Two additional tubes (SST) will be drawn for biomarker analysis (2x10 ml) at follow up visit 2 (week 32). For details also see schematic representation on page 35.

Study overview treatment period

Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Week	-4	0	2	4	6	8	EVAL 1 (9)	10	12	14	16	EVAL 2 (17)	18	20	20	20	20	20
Informed consent	X																	
staging CT-scan	X	X*					X					X	X	X	X			
EUS-FNAB	X	X*																
Diagnostic laparoscopy	X																	
Porth-a-cath placement	X																	
Fiducial marker placement													X					
FOLFIRINOX			X	X	X	X		X[4]	X[4]	X[4]	X[4]							
Stereotactic radiotherapy														X[4]	X[4]	X[4]	X[4]	X[4]
Resectability assessment																		
Resection																		
Medical history		X																
Vital signs, weight, height**		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X
Pain score (VAS)		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X
Concomitant medication		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X
Adverse events		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X
Hematology	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		X[1]	X[1]	X[1]	X[1]		X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Chemistry	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]		X[2]	X[2]	X[2]	X[2]		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Tumor markers (CEA and Ca19.9)	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X
Serum storage (mL)	6	6*		6			6					6						

X*	If not yet performed at pre-treatment evaluation
X**	Height only at baseline
Hematology[1]	Hemoglobin, WBC, platelets
Chemistry[2]	ALAT, ASAT, Alkaline Phosphatase, GGT, creatinin, ureum, albumin, sodium,potassium, calcium
X[4]	Only for non-metastatic patients

Study overview follow-up period

Visit	19	20	21	22	23	24	25	26	27
Week	FU 1 (26)	FU 2 (32)	FU 3 (46)	FU 4 (58)	FU 5 (70)	FU 6 (82)	FU 7 (94)	FU 8 (106)	FU 9 (118)
Informed consent									
staging CT-scan		X	X						
EUS-FNAB									
Diagnostic laparoscopy									
Porth-a-cath placement									
Fiducial marker placement									
FOLFIRINOX									
Stereotactic radiotherapy									
Resectability assessment		X							
Resection		X[4]							
Medical history									
Vital signs, weight, height**	X	X	X	X	X	X	X	X	X
Pain score (VAS)	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Hematology	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
Chemistry	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Tumor markers (CEA and Ca19.9)	X	X	X	X	X	X	X	X	X
Serum storage (mL)		6							

X*	If not yet performed at pre-treatment evaluation
X**	Height only at baseline
Hematology[1]	Hemoglobin, WBC, platelets
Chemistry[2]	ALAT, ASAT, Alkaline Phosphatase, GGT, creatinin, ureum, albumin, sodium,potassium, calcium
X[4]	Only for non-metastatic patients

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal

Not applicable.

8.5 Replacement of individual subjects after withdrawal

Not applicable

8.6 Follow-up of subjects withdrawn from treatment

Patients who withdraw from treatment will be offered to undergo standard of care treatment. They will be asked to participate in a final end of study visit which will consist of:

- Assessment of nutrient intake and possible associated weight loss.
- Pain score (VAS).
- Assessment of concomitant pain medication.
- Assessment of adverse events
- Vital signs (Weight, pulse, respiration frequency).
- Laboratory tests. Hemoglobin, WBC, platelets, ALAS, ASAT, Alkaline Phosphatase, gamma-GT, creatinin, ureum, albumin, sodium, potassium, calcium and tumormarker CA 19.9.

8.7 Premature termination of the study

If the sponsor decides to suspend or terminate the trial prematurely, the principal investigator must be informed as soon as possible. The principal investigator must inform the METC within 15 days after initial awareness of this event.

9. SAFETY REPORTING

9.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product or the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Chemotherapy Adverse Event Reporting

All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Radiation Adverse Event Reporting

All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Guidelines for dose adjustments due to adverse events

All dose adjustments should be based on the worst preceding toxicity, graded using the National Cancer Institute Common Toxicity Criteria (version 4.0).

The dose of leucovorin is not modified for toxicity, but is omitted if fluorouracil is omitted. Once a dose is decreased, re-escalation is not permitted. Patients are off study if they develop the same grade 4 toxicity despite a first dose reduction.

Hematologic toxicity

Do not retreat until the granulocyte count is ≥ 1.5 x 10^9/L and the platelet count is ≥ 75x10^9/L. See table 1 and 2 for details.

Table 1. Doses according to the blood counts at the beginning of a cycle (Day 1).

BLOOD COUNTS AT DAY 1	DELAY OF CYCLE	DOSES REDUCTION		
		Irinotecan	Oxaliplatin	Fluoraucil
granulocyte count is < 1.5 x 10^9/L	Hold treatment until granulocytes ≥ 1.5 x 10^9/L (one or two weeks if necessary). In case of non recovery after 2 weeks delay, stop treatment*	1st occurrence: reduction of dose to 150 mg/m² 2nd occurrence: maintain the dose at 150 mg/m² 3rd occurrence: treatment discontinu	1st occurrence : no reduction of dose 2nd occurrence: reduce the dose to 60 mg/m2 3rd occurrence: treatment discontinuation	1st occurrence: delete bolus 5FU
Platelets < 75 x 10^9/L	Hold the treatment until recovery (platelets ≥ 75 x 10^9/L). In case of non recovery after 2 weeks delay, stop treatment	1st occurrence: no reduction of dose 2nd occurrence: reduce the dose to 150 mg/m² 3rd occurrence: treatment discontinuation	1st occurrence: reduce the dose to 60 mg/m² 2nd occurrence: maintenance of the reduced dose 3rd occurrence: treatment discontinuation	1st occurrence: reduce both the bolus and the continuous infusion to 75% of the original doses

Table 2. Doses according to the low nadir blood counts or in case of infection.

ADVERSE EVENTS	REDUCTION OF DOSE FOR SUBSEQUENT CYCLES
Febrile neutropenia Grade 4 neutropenia during more than 7 days Infection with concomitant grade 3-4 neutropenia	1st occurrence: reduce the dose of irinotecan to 150 mg/m² and delete the bolus 5FU dose 2nd occurrence: reduce also the dose of oxaliplatin to 60 mg/m² 3rd occurrence: treatment discontinuation

Gastrointestinal toxicities

Patients are instructed to use loperamide as treatment for diarrhea, and have a supply of this drug upon starting FOLFIRINOX. Patients should not be retreated with irinotecan until recovery from diarrhea (without loperamide for at least 24 h) has occurred. See table 3 for details.

Table 3. Doses in case of persistent diarrhea.

ADVERSE EVENTS	REDUCTION OF DOSE FOR SUBSEQUENT CYCLES
Diarrhea grade 3-4 or Diarrhea + fever and/or neutropenia grade 3-4	1st occurrence: reduce the irinotecan dose to 150 mg/m2 and delete the bolus 5FU dose 2nd occurrence: reduce also the oxaliplatin dose to 60 mg/m² and reduce the dose of continuous 5FU to 75 % of the original dose 3rd occurrence: treatment discontinuation
Diarrhea ≥ 48 h despite high doses loperamide	No systematic reduction of the irinotecan, oxaliplatin or 5FU doses after complete recovery, unless grade 3-4 diarrhea, or diarrhea + fever, and/or concomitant neutropenia grade 3-4

Mucositis or "hand-foot" syndrome

In case of grade 3-4 toxicity, a reduction in dosages of 25% of both bolus 5FU and of continuous 5FU will be carried out for the subsequent cycles.

Cardiac toxicity

In case of angina pectoris or of myocardial infarction, 5FU has to be stopped.

Hyperbilirubinaemia

In case of elevation of bilirubin, it is suggested to exclude an obstruction of the biliary stent or a progressive disease and to postpone chemotherapy. If bilirubin is >1.5xULN, irinotecan is not recommended. If chemotherapy is medically indicated, it is necessary to provide a dose adjustment of irinotecan.

Other toxicities

Any other toxicity ≥ grade 2, except anemia and alopecia, can justify a reduction of dose if medically indicated, for example reduction of irinotecan to 150 mg/m² and/or oxaliplatin to 60mg/m² and/or 5FU of 25% depending of the type of adverse event.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation (elective surgery is not considered an SAE);
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

All life-threatening events (events, which in view of the investigator, place the patient at immediate risk of death from the reaction) or Grade 4 events that are definitely, possibly, or probably related to protocol treatment using chemo- or radiation therapy must be reported by telephone to 010-7033854 within 24 hours after occurrence.

All deaths during and within 30 days of completion of protocol chemoradiation therapy, regardless of attribution, must be reported by telephone within 24 hours after occurrence to 010-7041347. If the event is more than 30 days from completion of radiation treatment, but is felt to be definitely, possibly, or probably resulting from protocol chemoradiation therapy, this event should be telephoned to 010-7033854.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable.

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10. STATISTICAL ANALYSIS

End point: overall survival (OS) at 1 year (OS 1 yr). Historical control: OS 1 yr = 40% [19]. Estimated number of potentially eligible patients per year is 25. With a two-sided 5% significance test and a power of 80% a minimum of 51 patients need to be included in the study. If at least half of the included patients are alive 1 year after the start of treatment than this treatment deserves further study.

Depending on distributional properties, outcome measures will be expressed as means ± standard deviations (SD) or as medians with interquartile ranges (IQR). Missing follow-up data will be considered to be missing at randomAll reported P values will be two-sided and a value < 0.05 will be considered to be significant. Data will be analysed with SPSS 21, Statistical Package for the Social Sciences. SPSS Inc, Chicago, Illinois.

Endpoints are defined as follows:

- Overall survival is defined as the period of time between inclusion and death from any cause.
- Time to progression is defined as the period of time between inclusion and radiological evidence for locoregional progression or distant metastasis. Tumor time to progression will be evaluated using CT scan examination. The assessment of tumor status will be done six weeks after completions of chemoradiotherapy. Additional scans will be performed every three months until disease progression. The evaluation of a tumor is defined by the RECIST criteria (http://www.eortc.be/recist/).
  - Complete response (CR): disappearance of the target lesion for at least 4 weeks.
  - Partial response (PR): at least a 30% decrease in the longest diameter of the target lesion, confirmed after 4 weeks.
  - Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD)
  - Progressive disease (PD): at least a 20% increase in the longest diameter of the target lesion or the appearance of any new tumor lesion distant from the primary tumor.
- The toxicity of radiochemotherapy is defined according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4) (http://www.eortc.be/services/doc/ctc/).
- Resection rate is defined as the percentage of patients that actually underwent a resection.
- Time to locoregional progression is defined as the period of time without locoregional progression after completion of chemoradiation.

- Time to distant metastasis is defined as the period of time without evidence of metastasis after completion of chemoradiation.
- CA 19.9 response is only descriptive.

Statistical tests per endpoint:

- Overall survival (OS) will be determined by using a Kaplan-Meier survival curve
- Resection rate will be analyzed by a chi-square test
- Time to locoregional progression will be analyzed by a competing risk model
- Time to distant metastases will be analyzed by a competing risk model
- Toxicity of chemoradiation therapy will be described according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4)
- Predictive value analysis of miRNAs will be performed on normalized array data. Hierarchical clustering will be performed based on the mean centered and scaled miR expression levels.

10.1 Primary study parameters

- overall survival (OS)

10.2 Secondary study parameters

- toxicity of chemotherapy according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4)
- toxicity of radiotherapy according to Common Terminology Criteria for Adverse Events 4 (CTC-AE 4)
- radiological response rates after chemotherapy and radiotherapy (RECIST criteria)
- resection rate
- time to locoregional progression
- time to distant metastases
- determine prediction value of a set of biological markers

10.3 Other study parameters

Not applicable.

10.4 Interim analysis

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

The treating physician will inform eligible patients about the study and will explain the aims, methods, anticipated benefits, and potential hazards. Also, this information will be provided in print. Subsequently, patients will have at least 48 hours to decide if they want to participate in the study, by giving their written informed consent. If patients have any further questions they can also consult an independent physician

11.3 Objection by minors or incapacitated subjects

Not applicable.

11.4 Benefits and risks assessment, group relatedness

Patients participating in this study may experience side effects as defined in section *9.2.1 Adverse Events*. There is no increased risk compared to the standard treatment (defined as systemic chemotherapy and normal radiation therapy). Patients may benefit from this study since tumor size may decrease enough to perform resection of the primary tumor.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be handled confidentially. Each patient will receive an anonymous identification code. To trace data back to an individual patient, a subject identification code list will be used. The study coordinator will safeguard the key to this code. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet bescherming persoonsgegevens, Wbp). Data will be kept as long as 15 years, according to the WMO guidelines.

12.2 Monitoring and Quality Assurance

The sponsor and investigators will conduct the trial according to Good Clinical Practice (GCP) guidelines .

Data will be entered in an (e)CRF by the (co) investigators. In case sponsor deems monitoring necessary, the study will be monitored by an experienced monitor upon request by the sponsor by means of a personal visit to the investigational site. Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study at a frequency described in the monitoring plan. Each visit will include a review of essential clinical study documents as well as discussion on the conduct of the study with the investigators and staff.

12.3 Amendments

A ‘substantial amendment’ is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last follow up visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

12.6 Public disclosure and publication policy

Upon completion of the study, the principal investigator will be responsible for the public disclosure/publication of the study outcome. The results will be reported during symposia, national and international professional meetings, and submitted for publication to peer reviewed journals.

Authorship credit will be based on the Recommendations of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). The criteria for authorship are defined as 1. substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2. drafting the article or revising it critically for important intellectual content; and 3. final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

For this study patients will receive placing of fiducials to be able to correctly receive the dose of stereotactic radiation therapy. The placing of these fiducials is low risk with usually only minor side effects like stomach ache or nausea. The use of stereotactic radiation should exert less side effects than the standard radiotherapies which are used. Conventional radiotherapy usually leads to skin irritation while in stereotactic radiotherapy the skin is spared since the radiation is only focussed on the tumor site.
We classified this study as medium risk since the patients will also undergo several extra CT scans which will slightly increase the received amount of ionising radiation dose. In addition patients included in this study are physically not in optimal condition, the treatment given and the extra visits to the hospital can therefore be burdensome for them. Since several departments within the hospital need to cooperate in this study there is also a risk of protocol violations, however we anticipate that these violations will always be in the best interest of the participating patients.

13.2 Synthesis

The combination of both chemotherapy as well as stereotactic radiotherapy has already been studied in other trials and does not pose an additional risk to the patients.

Due to the treatment offered in this trial patients may benefit from the fact that tumor size will decrease enough to make resection possible.

Patient safety is regularly assessed during the study. Visits are planned frequently and at each visit patients are checked for adverse events and vital signs. In addition, regular CT scans will be performed to keep track of tumor characteristics during the treatment period. After the treatment period patients will undergo intensive follow up in the clinic so that any late events will be recognized immediately and treatment can be given if necessary.

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