A Phase II study combining short course radiotherapy, chemotherapy and resection of the rectum and metastases in primary metastasized rectal cancer.

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1. Curative treatment of primary metastasized rectal cancer includes resection of primary tumor and metastases; 2. Primary tumors in case of metastasized disease are often locally advanced and need downsizing before resection; 3. Systemic...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON27950

Bron
NTR

Verkorte titel
M1-study

Aandoening

rectal cancer, primary metastasized, stage IV
rectumcarcinoom, primair gemetastaseerd, stadium IV

Ondersteuning

Primaire sponsor: K. Havenga, M.D. Ph.D.
Overige ondersteuning: Unrestricted research grant: Roche BV and Sanofi-Synthelabo BV, the Netherlands

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The percentage of complete resection or ablation (R0) of all primary and metastatic tumor.

Toelichting onderzoek

Achtergrond van het onderzoek

Prognosis of patients who present with metastasized rectal cancer is poor. Without treatment, median survival is estimated at six months. Treatment options are available for the primary tumor and the metastatic disease. The primary tumor may be resected or treated with radiation therapy. Resection of the primary tumor is controversial, as it may not improve the quality of life in patients with a poor prognosis due to the metastatic disease. As the majority of patients with primary stage IV rectal cancer present with a locally advanced primary tumor, resection of the primary tumor would necessitate preoperative radiation therapy.
Metastatic disease may respond to chemotherapy. In recent years, advances in chemotherapy have increased the response rate to 40 percent. Some patients presenting with liver or lung metastases are candidates for resection of their metastatic disease. Neoadjuvant chemotherapy may increase the fraction of patients with resectable metastatic disease, or may allow for smaller resections for metastatic disease.

In case of primary stage IV rectal cancer, resection of the primary tumor and metastatic disease may result in an overall survival of 30 percent. However, as the majority of primary tumors in primary stage IV rectal cancer are deep T3 or N+ lesions, preoperative radiation therapy is required for downstaging effect to obtain R0 resections. Long course radiation therapy schemes are used for this goal, usually combined with chemotherapy as radiosensitizers. Radiosensitizing chemotherapy doses are too low to have an effect on metasatatic disease.

To overcome the logistical problem of combining radiation therapy to the pelvis with adequate doses of neoadjuvant chemotherapy for systemic disease we propose to give preoperative radiation therapy (5x5 Gy), followed by combination chemotherapy (bevacizumab (Avastin®), capecitabine (Xeloda®) and oxaliplatin (Eloxatin® concentrate).

The main criteria for including patients in this study are resectable primary metastasized rectal cancer, a good performance score and no co-morbidity.

The main objective of this phase II study is to evaluate the efficacy of the proposed regimen.

Primary endpoint is the fraction of patients who undergo an R0 resection of all tumor sites. Secundary endpoints include two-year survival, two-year recurrence rate, and treatment associated toxicity. Fifty patients will be included in this study.

Doel van het onderzoek

1. Curative treatment of primary metastasized rectal cancer includes resection of primary tumor and metastases;

2. Primary tumors in case of metastasized disease are often locally advanced and need downsizing before resection;

3. Systemic treatment is desired to enhance resectability, to eradicate micrometastases and to identify incurable patients who progress under chemotherapy;

4. Traditional long course radiation delays administration of effective systemic chemotherapy;

5. 5x5 Gy radiation therapy has a similar biological effective dose as long course radiation.

Onderzoeksopzet

1. Week 1: radiation therapy;

2. Week 3: first cycle chemotherapy;

3. Week 6: second cycle chemotherapy;

4. Week 9: third cycle chemotherapy;

5. Week 12: fourth cycle chemotherapy;

6. Week 15: fifth cycle chemotherapy;

7. Week 18: sixth cycle chemotherapy;

8. Week 25: resection of primary tumor/metastases.

Onderzoeksproduct en/of interventie

1. 5 x 5 Gy radiation therapy;

2. Capecitabine 2 x 1000 mg/m2, day 1-14;

3. Oxaliplatin 130 mg/m2;

4. Bevacizumab 7,5 mg/m2;

5. Resection of rectum and metastases.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

DISEASE CHARACTERISTICS:

1. Histologically verified adenocarcinoma of the rectum;

2. Initial evaluation 4 weeks or less before inclusion.

PRIMARY RECTAL TUMOR:

1. Palpable rectal tumor OR;

2. Tumor below the level S1-2 as judged by sagittal CT or MRI slides;

3. R0 resection (circumferential margin > 1 mm) possible at time of presentation OR;

4. Locally advanced primary tumor in which an R0 resection is feasible after 5x5 Gy radiation therapy and a waiting period. This criterium will be judged based on CT scan or MRI of the pelvis. In general, tumors with lymph node metastases in the obturator fossa or above the promontory are not resectable, even after downsizing.

METASTATIC DISEASE:

1. Resectable or ablatable liver metastases. This criterium is judged on the following criteria:

A. No metastatic disease adjacent to or apparently involving all three major hepatic veins, the portal vein bifurcation or the retro hepatic vena cava;

B. No metastatic disease adjacent to or involving the main right or main left portal vein and the main hepatic vein of the opposite lobe;

C. No metastatic disease that would require more than a right or left trisegmentectomy;

D. No presence of six or more metastatic lesion distributed diffusely in both lobes of the liver;

E. No metastatic liver disease that would require a resection that would jeopardize postoperative liver function.

2. Resectable lung metastases. This criterium is judged on the size, number and location of lesions and on the condition and lung capacity of the patient;

3. No metastatic disease in more than two organs, based on CT scan or FDG-PET scan;

4. No peritoneal metastases as demonstrated on CT scan, FDG-PET scan or during laparotomy;

5. No clinical signs of brain metastases.

PATIENT CHARACTERISTICS:

1. GENERAL:

A. 18 years and above;

B. ECOG performance status 0 or 1;

C. Ability to withstand major operative procedure;

D. Written informed consent obtained prior to any study specific screening procedures;

E. Patient must be able to comply with the protocol.

2. HEMATOPOIETIC:

A. White blood cell count at least 3000/mm3.

B. Platelet count at least 100.000/mm3;

C. No bleeding diathesis or coagulopathy.

3. HEPATIC:

A. Total bilirubin less than 1.5 x upper limit of normal;

B. ASAT/ALAT less than 2,5 times upper limit of normal;

C. INR less than 1,5 (for patients receiving coumarin derivates).

4. RENAL:

A. Creatinine normal OR;

B. Creatinine clearance at least 50 ml/min;

C. Negative urine dipstick for protein OR;

D. Protein less than 1 g on 24-hour urine collection.

5. CARDIOVASCULAR;

A. No history of cerebrovascular attack or transient ischemic attack;

B. No uncontrolled hypertension (i.e., blood pressure > 150/100 mm Hg on medication);

C. No unstable angina pectoris;

D. No myocardial infarction within the past year;

E. No New York Heart Association class II-IV congestive heart failure;

F. No serious cardiac arrhythmia requiring medication;

G. No peripheral vascular disease ≥ grade II;

H. No other clinically significant cardiovascular disease;

I. No other unstable or uncompensated cardiac disease.

6. OTHER:

A. No unstable or uncompensated respiratory disease;

B. No pregnant or lactating women;

C. Fertile patients must use effective contraception;

D. No previous or concomitant malignancies within five years other than non-melanoma of the skin or carcinoma in situ of any organ;

E. No serious non-healing wound, ulcer, or bone fracture;

F. No significant traumatic injury within the past 28 days;

G. No serious active infections.

PRIOR AND CONCURRENT THERAPY
CHEMOTHERAPY:

1. No prior fluorouracil-based therapy for any malignancy;

2. No other concurrent chemotherapy.

ENDOCRINE THERAPY:

1. No concurrent hormonal therapy except the following:

A. Steroids for adrenal failure or allergic reactions;

B. Hormones for non-disease-related conditions (e.g., insulin for diabetes);

C. Intermittent dexamethason as an antiemetic.

RADIOTHERAPY:

1. No prior pelvic radiotherapy.

SURGERY:

1. More than 28 days since prior major surgery or open biopsy, surgical wounds should be completely healed;

2. More than 7 days since prior biopsy (except rectal cancer);

3. More than 7 days since prior placement of vascular access device;

4. No other concurrent planned major surgery.

OTHER:

1. More than 10 days since prior full-dose oral or parenteral anticoagulant or thrombolytic agents (except to maintain patency of preexisting, permanent indwelling IV catheters);

2. No prior treatment for this malignancy;

3. No concurrent chronic aspirin use (more than 325 mg/day);

4. No concurrent nonsteroidal anti-inflammatory medications (of the kind known to inhibit platelet function at doses used to treat chronic inflammatory diseases);

5. No other concurrent investigational agents.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

See inclusion criteria.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Factorieel
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-04-2006
Aantal proefpersonen:	50
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	28-09-2009
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1912

Register	ID
NTR-old	NTR2029
Ander register	METC UMC Groningen : METc2005/270
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A