ISRCTN35198481 https://doi.org/10.1186/ISRCTN35198481

Therapy of locally advanced rectal cancer of the upper third by quality controlled total versus partial mesorectal excision

Submission date	Recruitment status	[ ] Prospectively registered
18/01/2008	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
13/02/2008	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
13/02/2008	Cancer	[ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Study information

Scientific Title
Therapy of cUICC stage II/III rectal cancer of the upper third by quality controlled total versus partial mesorectal excision, followed by adjuvant chemotherapy

Acronym
GAST-05

Study objectives
The multicentric GAST-05 study aims at identifying the optimal surgical treatment of locally advanced (cUICC stage II/III) rectal cancer located 12 - 16 cm above the anocutaneous verge. Two established surgical techniques are compared:
1. Total mesorectal excision (TME), to completely eliminate affected and surrounding tissue, bears the risk of post-surgical complications
2. Partial mesorectal excision (PME) restricts surgery to the afflicted tissue and defined surroundings

PME may be equally effective in eliminating cancer while limiting post-operative complications. No clinical data have been raised to date that show if TME or PME is oncologically superior. To answer this requires a refocus on the principles of both resection techniques, including peri- and post-operative quality control. Post-surgical chemotherapy is identical in both trial arms. Primary endpoint is the disease-free survival after 3 years.

The GAST-05 study is an add-on study to the ongoing CAO/AIO/ARO-04 trial, which intends to optimise the pre-surgical chemoradiotherapy of cUICC stage II/III cancers in the lower two thirds of the rectum (0 - 12 cm). The comparison of the long-term outcomes of both studies (GAST-05: surgical procecures; CAO/AIO/ARO-04: intensified preoperative treatment) will influence future studies; they will apply the surgical procedure that is identified as being superior during the GAST-05 study. Additional gene expression analyses on pre-therapeutically taken tumour probes will show if gene profiling can help to predict individual prognosis.

The identification of the oncologically superior of two standardised surgical treatments (TME and PME) of cUICC stage II/III cancers of the upper third of the rectum has not been determined. The identification is a prerequisite for further studies, needed to reduce the side effects of optimised surgical treatments. If both techniques, TME and PME, turn out to be equivalent, that technique will be regarded as superior, which promises less comorbidities, a higher qualitiy of life, and lower health care costs (i.e. PME).

A cross-comparison of disease-free and overall survival data from the GAST-05 trial and the CAO /ARO/AIO-04 trial will further allow judgement on the need for further studies on multimodal therapies for rectal cancers of the upper third. If the rate of local and distant metastases turns out to be equal or lower in the GAST-05 trial (upper third, no neoadjuvant RT/CT, PME/TME) than in the CAO/ARO/AIO-04-trial (lower two thirds, intensified preoperative treatment), further trials may be unnecessary which test multimodal therapies in cancers of the upper third. Patients with cUICC stage II/III cancers of the upper third of the rectum will then be spared potentially ineffective preoperative radiochemotherapy with its toxicities.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the Georg-August-University Gottingen Ethik-Kommission der Medizinischen Fakultat on the 17th January 2007 (ref: 21/11/06).

Study design
Open, multi-centric, prospectively randomised phase II trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Rectal cancer

Interventions
For all procedures, standard operating procedures (SOPs) are available.

Experimental intervention:
1. Arm A: total mesorectal excision (TME) including surgical and pathological quality control, followed by standard adjuvant chemotherapy. The mesorectum is completely excised downwards to the pelvic floor:
1.1. Dorsally: entire retro-rectal fat body with the lymph tissue under consideration of the fascial system
1.2. Ventrally: including the spatium prerectale along the Denonvilliers-fascia
1.3. Laterally: entire area up to pelvis

2. Arm B: Partial mesorectal excision (PME) including surgical and pathological quality control, followed by adjuvant chemotherapy. PME follows the same surgical principles as in TME with the following exception: the mesorectum is transected at a right angle to the rectal wall 5 cm beyond the gross distal margin of the tumour, as measured in situ

In both trial arms, surgery is followed by adjuvant chemotherapy:
1. Folinic acid: 400 mg/m^2, 2-hour infusion, day 1
2. Oxaliplatin: 100 mg/m^2 2-hour infusion in 500 ml glucose 5%, day 1
3. 5-Fluorouracil: 2400 mg/m^2 as 46-hour infusion

Perioperative assessment of mesorectal excision (TME/PME):
Staining of the specimen via inferior mesenteric artery, photo-documentation:
Class 1: no leakage, optimal TME/PME
Class 2: punctual leakage(s), good TME/PME
Class 3: extensive leakage(s), incomplete TME/PME

Standardised pathological assessment of TME/PME (in addition to established TNM/UICC criteria):
Extent: TME/PME?
In case of PME:
1. Distance between macroscopically visible distal margin of tumour and distal transection margin measured in centimetres. Measuring method:
1.1. Fresh, non-stretched specimen
1.2. After fixation (non-pinned)
1.3. After fixation (pinned, non-stretched)
2. Coning (distal transaction in a plane at 90° to the rectal wall): no, yes
3. Macroscopic assessment of the specimen surface in all cases:
3.1. Intact, smooth (lipoma-like)
3.2. Circumscribed defect(s) no greater than 5 mm
3.3. Extensive defect(s), muscular layer of the rectum invisible

3.4. Extensive defect(s), muscular layer of the rectum visible
3.5. Incision into the tumour or tumour torn open

Pathological quality assessment of the specimens after TME/PME:
1. Complete: intact mesorectum, no defects larger than 5 mm, no PME-coning, smooth circumferential resection margin on slicing
2. Moderate: irregular mesorectal surface, moderate PME-coning, muscularis propria invisible with the exception of area of insertion of levator muscles, moderate irregularity of the circumferential resection margin
3. Incomplete: little bulk of mesorectum with defects down into mucularis and/or very irregular circumferential resection margin, PME-coning

Control intervention:
None

Duration of intervention per patient: 32 weeks
Follow-up per patient: 3 years

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Folinic acid, oxaliplatin, 5-Fluorouracil

Primary outcome(s)
Disease-free survival after 3 years (local and/ or distant recurrences).

Key secondary outcome(s))
1. R0-rate of resection
2. Post-operative 30-day lethality
3. Post-operative morbidity (especially rate of anastomotic insufficiencies)
4. Cumulative incidence of local relapses and distant metastases
5. Survival after 3 and 5 years
6. Acute and late toxicity of the chemotherapy according to the Common Toxicity Criteria of the National Cancer Institute (NCI CTC version 2.0)
7. Post-operative late complications (defaecation problems, anastomotic stenoses, loss of sphincter function)
8. Quality of TME and PME as assessed
9. Quality of life according to the European Organisation for Research and Treatment of Cancer (EORTC)-Questionnaire QLQ-30 (3.0)

Assessment of safety: TME, PME, and adjuvant chemotherapy are established procedures.

Completion date
30/06/2013

Eligibility

Key inclusion criteria
1. Histologically confirmed advanced primary rectum carcinoma at a level 12 - 16 cm above the anocutaneous verge (as measured by rigid endoscopy), endosonographically classified as uT3-4 or uN+ carcinomas, no evidence for synchronous distant metastases
2. Patients aged 18 - 85 years, either sex
3. No preliminary treatment of rectum carcinoma

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Successfully treated secondary malignoma with the exception of basal cell carcinoma of the skin and in situ cervix carcinoma, respectively, The inclusion of patients with other tumours, that have been treated successfully and have not reappeared during the last 5 years, has to be discussed with the principal investigator
2. Simultaneous therapy with other anti-cancer drugs
3. Chronic colonic diseases

Date of first enrolment
01/10/2007

Date of final enrolment
30/06/2013

Locations

Countries of recruitment
Germany

Study participating centre
Georg-August University of Gottingen
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Sponsor information

Organisation
Georg-August University of Gottingen (Georg-August-Universitat Gottingen, Universitatsmedizin) (Germany)

ROR
https://ror.org/01y9bpm73

Funder(s)

Funder type
Government

Funder Name
German Research Council (Deutsche Forschungsgemeinschaft [DFG]) (Germany) (ref: 518)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration