WoW
Watch and wait: Clinical complete response after (chemo)radiotherapy in advanced rectal cancer:

A multicentre prospective national cohort study.

WoW

En klinisk studie om icke operativ behandling vid ändtarmscancer efter strål- och cellgiftsbehandling

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1. STUDY ORGANISATION

1.1 Planning group:

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1.2 Principal investigator:

Eva Angenete

1.3 Deputy principal investigator:

Anna Martling

1.4 Study secretariat

The study secretariat will be situated at SSORG/Göteborg, Department of Surgery, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University. Much clinical data will be retrieved from the Swedish ColoRectal Cancer Registry. Biopsies will be collected at selected centers and then gathered at Sahlgrenska University Hospital/Östra.

1.5 Study committee

Anna Martling, Eva Angenete, Bengt Glimelius, Anders Johnsson, Ingvar Syk, Kenneth Smedh, Peter Mathiessen, Olof Hallböök, Joakim Folkesson, Wilhelm Graf, Lennart Blomqvist, Markku Haapamäki. The committee decides on the final version of the protocol, changes in the protocol (if any) as well as about analyses to be made. The committee can include other researcher at will.

1.6 Scientific framework

The study is organised and performed within the framework of both the Scandinavian Surgical Outcomes Research Group, as the Swedish Colorectal Cancer Study Group. It will also involve researchers within the Swedish ColoRectal Cancer Registry (SCRCR), a Swedish multidisciplinary collaboration of surgeons, radiologists, pathologists and oncologists.

1.7 Writing committee

In agreement with internationally accepted guidelines for authorship the members of the planning group and scientific committee who are active in planning and running the study, in analysing results and in writing can be a part of the writing committee. All authors must fulfil the Vancouver criteria and final decision regarding authorship will be made by the PI and the deputy PI.

Publication of results is planned to be in international ”peer review” scientific journals.

2.0 PROTOCOL

2.1 Background

The prognosis for rectal cancer has improved in the last decades and the risk of local recurrence and chances for long term survival have improved. This is probably due to improvements in many areas, including preoperative diagnostics, surgical technique, pathology and oncologic treatment.

The surgical procedure alone is associated with a high risk for complications. According to the Swedish ColoRectal Cancer Registry (SCRCR) 40% of the patients have a postoperative complication and patients receiving neoadjuvant treatment have the highest risk of postoperative complications both in short- and long-term (1).

Reports from Evangelita Habr-Gama in Brazil have indicated that non-surgical approach is possible in a selected group of patients receiving chemoradiotherapy and a succeeding complete tumour regression (response) (2). This has been referred to in the literature as "watch and wait". Later reports have shown similar results, but it is mainly seen in selected case series with possible selection bias and uncertain external validity (3-5). There are no prospective studies comparing a watch and wait protocol with standard surgical treatment. However, data indicates that patients that have complete response to chemoradiotherapy have a better prognosis if they are subject to surgery, compared to patients that did not respond as well to their neoadjuvant treatment (6, 7). Furthermore, it is possible that older patients may benefit more from a "watch and wait" protocol, where they may eventually avoid the serious complications from surgery (8). Patients who would otherwise need an abdominoperineal excision could be the best candidates as they might avoid a stoma, but patients planned for a low anterior resection are at risk for life-threatening anastomotic leaks and severe functional bowel dysfunction indicating that avoiding surgery may be beneficial for this group as well.

The radiation schedules used in recent "watch and wait" report vary, but 45-53 Gy are the most common doses used. Also chemotherapy treatment varies, but in Habr-Gama's reports most patients receive intravenous 5-Fluoruracil with leucovorin but the use of oral capecitabine (Xeloda®) has also been described.

In early rectal cancer (T1-T3, N0 with clear mesorectal margins on MRI) it is not standard treatment in Sweden to use (chemo)radiotherapy. The relative 5-year survival for these patients treated with standard surgery is 98 and 80% for patients with stage I and stage II respectively. The risk for local recurrence is then approximately 2-3.4%(1). The watch and wait approach has been suggested for this patient group, and currently several clinical trials are investigating this matter. The StarTrec study (Saving the rectum by watchful waiting or TransAnal surgery after (chemo)Radiotherapy versus Total mesorectal excision for early Rectal Cancer) (ISCRTN14422743) will soon start. Another study is the CARTS study, that reported 30/51 patients with complete or near complete response (9). However, in this group of patients that could be safely treated with surgery alone, there is a risk of over treatment of patients including increasing rates of complications at surgery.

In patients with more advanced tumours (chemo)radiotherapy is as an established treatment to perform tumour downstaging/downsizing prior to surgery (neoadjuvant treatment) and to lower the risk of

local recurrence. There are several reports regarding complete response in this patient group. In the different studies there is a case-mix with a clear selection with tumours included such as cT1-T2 tumours which would not automatically receive neoadjuvant treatment in Sweden. (3). Of all cases with primary non resectable or locally advanced rectal cancer that receives (chemo)radiotherapy complete response is seen in 10-15% (5, 10, 11), but the numbers are believed to increase with addition of further oncologic treatment. (12). Approximately 10-20% of patients with complete response treated in a "watch and wait" protocol will have regrowth of the tumour within a few years, many of which can be treated with surgery.

At present there are two randomized trials in Sao Paolo (n=150, NCT00952926 and NCT01941979) and a prospective evaluation of function is underway in Maastricht (n=100, NCT02278653) including patients with more advanced tumours. The latter includes manometry and QoL but has no control group. A prospective registration of patients is currently ongoing at Royal Marsden Hospital (UK) (n=45, NCT01047969) and in Vejle (Denmark) (n=100 NCT00952926 and n=105, NCT02438839).

There are no markers in blood or tumour tissue that has been known to predict tumour response to (chemo)radiotherapy that can be brought into clinical practice although studies indicate that acute phase inflammatory response proteins, plasma apolipoproteins and coagulation factors are up regulated (13). CEA has been suggested as a marker, although data is scarce regarding specificity and sensitivity (14, 15). In the tumour tissue there are possible markers such as thymidylate syntetase and epidermal growth factor polymorphisms, the gene p21 and several others, but none have been convincing (16, 17).

The normal tissue changes after radiotherapy have been studied and it is clear that there is an effect on normal tissue with an inflammatory response (18, 19) such as urokinase plasminogen activator (uPA) and calprotectin (20). Histologic examinations of Ki67 can assess stem cells in the cryptae as well as fibrosis and colitis development (18). In plasma citrulline and lipopolysaccharides can be markers for tissue damage due to radiotherapy (21-23).

2.2 Hypotheses

It is possible to avoid surgery in a selected group of patients with complete response after neoadjuvant (chemo)radiotherapy for rectal cancer with similar or better oncologic outcome at three years as compared with patients without complete response treated with surgery?

2.3 Primary endpoint

- 3-year disease free survival. Thus, this includes patients that have had regrowth and been operated for their tumour. Patients that have had metastatic surgery are included as well.

2.4 Secondary endpoint

- Percentage of re-growth during follow-up (10 years).
- Local recurrence after salvage surgery due to regrowth
- Results after surgery for re-growth
- Long-term survival

- Number of patients with no response, partial response and complete response according to MRI and pathology, this will include patients with biopsies at selected centers as well as using the Swedish ColoRectal Cancer Registry.
- Anorectal function measured by LARS score(24) and other questions in QoL questionnaires.
- HRQoL 0, 6, 12, 24 months
- Health economic evaluation
- Endpoints for a substudy:
    - Identifying biomarkers for complete response
    - Identifying biomarkers for normal tissue damage

2.5 Overall study design

A national cohort study with all patients scheduled for neoadjuvant treatment with (chemo)radiotherapy or short course radiotherapy with delayed surgery (6-8 weeks) for rectal cancer according to national guidelines staged as cT4bNX/anycTanycN and cMRF+/anycTanycN and lateral lymph nodes on MRI and patients that have been offered short course raditotherapy with delayed surgery due to various reasons such as a protocol according to Stockholm III(25). The tumours should be positioned in the rectum. The patients are offered this treatment after recommendations from their local multidisciplinary tumour board, and will be informed and offered to participate in the study. Patients scheduled for short course radiotherapy with immediate surgery cannot be included.

2.5.1 The biopsy substudy:

- Biopsies and blood from patients with rectal cancer subject to neoadjuvant treatment with (chemo)radiotherapy or radiotherapy 5x5 Gy with at least 6-8 weeks wait until surgery.

All patients will undergo scheduled (chemo)radiotherapy according to national guidelines. The patients with (chemo)radiotherapy or radiotherapy with delayed surgery will be evaluated at 6 (-8 weeks) weeks after completed treatment (26) with pelvic MRI, endoscopy and rectal palpation. If the patients have received 5x5 Gy and four or six doses of chemotherapy (as described in the Rapido study or Larctus){Bahadoer, 2021 #9429} then the evaluation is set at 4 weeks after completed chemotherapy. If signs of complete response are present, the patient will be referred to a regional hospital for further evaluation with a new assessment of the MRI, a new endoscopy and rectal palpation within another 2 weeks.

In case of signs of near complete response the patient will be offered a new evaluation four to six weeks later (12 weeks after cessation of 5x5Gy or (chemo)radiotherapy. This can be iterated once, thus a new evaluation at 16 weeks after completed treatment. If the patient still shows no complete response surgery should be recommended and the patient is no longer within the study.

All patients that are considered to have complete response at evaluation at regional hospital will be offered a "Watch and wait" approach with follow-up according to the protocol. They will then be followed at one of the Regional University Hospitals within their catchment area or at Västmanlands sjukhus in Västerås.

All patients that do not achieve complete response will serve as control and will be treated with surgery as planned prior to initiation of (chemo)radiotherapy.

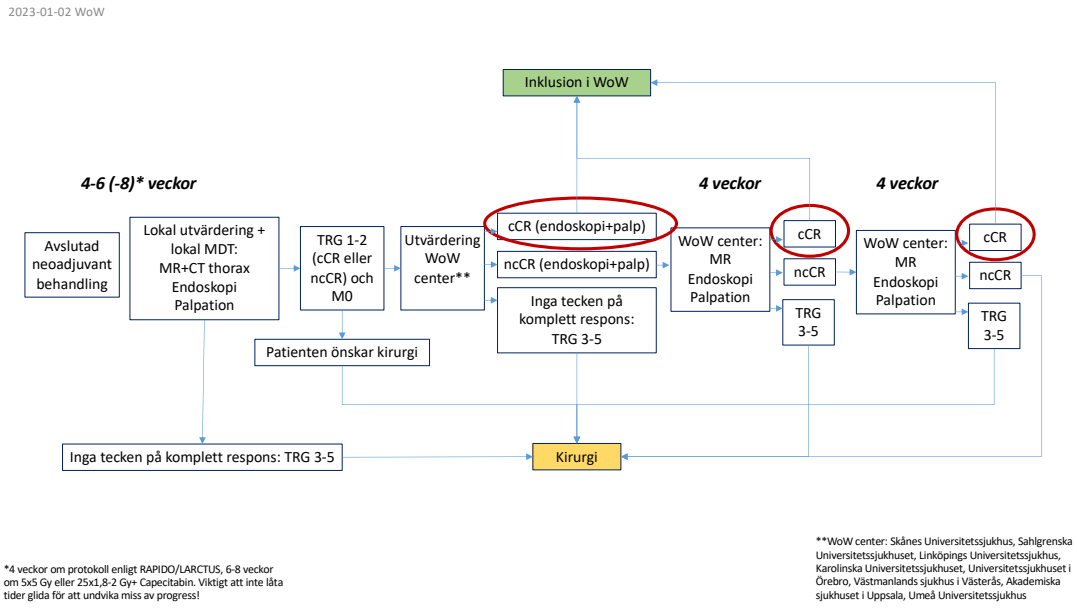

Figure 1. Patients that receive neoadjuvant treatment (CRT=chemoradiotherapy, RT=radiotherapy) will be evaluated 6 weeks after termination of treatment with (MRI=magnetic resonance imaging, CT=computer tomography) and will undergo evaluation at a local MDT (=multi-disciplinary tumour board). If TRG (=tumour regression grade) 1-2 the patients have suspected complete clinical response (=cCR) or near clinical complete response (ncCR) and will be evaluated at regional MDT. At the regional MDT a decision regarding ncCR or cCR or even no response will be made and the patients will be recommended treatment accordingly. DRE= digital rectal examination.

2.5.2 Definition of complete response

Patients with the indication of a complete response on follow-up MRI will undergo endoscopy, and digital rectal examination to ascertain complete response. MRI together with documentation from endoscopy will be reviewed at the Regional University Hospital to establish agreement regarding interpretation. All the below mentioned criteria must be fulfilled to be considered complete response:

1. No suspicious metastatic lymph nodes or evidence of remaining tumour on MRI. In the majority of cases a complete response on MRI will be seen as areas of homogeneous fibrosis. Absence of any remaining pathological tissue is seen in a minority of cases.
2. Endoscopic examination with white light and NBI (narrow band imaging). Presence of light/white mucosa or scar, telangiectasia. Presence of fibrosis and oedema. Absence of a clear neoplastic pattern on NBI images.
3. No palpable tumour on clinical examination (27) if the tumour was palpable initially.

2.5.3. Follow-up of the "Watch and wait" arm

All patients with radiological signs of complete response that after evaluation according to point 2.7.1 that still are considered complete response will initially be evaluated with a CT of the thorax and abdomen.

In addition, patients will be followed for ten years according to the schedule below. The evidence for how to follow these patients is scarce, but there are clinical suggestions (3, 28). The follow-up schedule is illustrated in the appendix (appendix A). Details from the follow-up schedule will be registered in clinical record forms including information on the endoscopic findings, MRI findings and digital examination.

Patients will be followed every third month for the **first two years** as follows:

- PET-CT is optional, but can be performed at inclusion
- Pelvic MRI including diffusion weighted imaging according to appendix C.
- Clinical examination
- Endoscopy (flexible sigmoidoscopy) with photo documentation
- CEA

After two years the patients will be followed every six months with:

- Pelvic MRI including diffusion weighted imaging according to appendix as at baseline
- Clinical examination
- Endoscopy with photo documentation
- CEA

The first and third year patients will also undergo:

- CT scan of the thorax and abdomen (can be replaced by MRI of the abdomen if this is the local routine) to ascertain that there are no metastases.

At three years and then every five years patients will undergo a colonoscopy according to the Swedish national guidelines.

After five years patients will be followed yearly up to ten years after diagnosis.

2.5.4 Details on the biopsy substudy

As mentioned above there will be a substudy with biopsies and plasma and blood samples in centres able and willing to participate. Biopsies will be taken for damages to the cell and cell nucleus and morphologic analysis prior to start of treatment to assess specific characteristics in the tumour to enable prediction of complete response in the future (16, 17). Biopsies will also be taken from seemingly normal tissue adjacent from the tumour but in the irradiated field to enable studies on the irradiation damage to normal tissue. All biopsies will be (approximately 20-40 mg wet weight) snap frozen in liquid nitrogen and stored at -70° until analysis. Biopsies will also be fixed in formalin for histology and immunohistochemistry.

Analyses will include histologic examinations of Ki67 (18), homogenized tissue for several markers for inflammation

and fibrosis as well as the presence of tight junctions (19). Blood samples will also be collected, analyzed for citrulline and lipopolysaccharides and other markers for tissue damage due to radiotherapy (21-23). Venous blood samples will be collected in a standardized manner and centrifuged, the plasma will be collected and frozen to -70°C until further processed.

After the patients have undergone (chemo)radiotherapy some will have achieved complete response. These patients will be followed with biopsies of irradiated mucosa to further evaluate long-term irradiation damage to the rectal mucosa.

Patients that have been included in the biopsy substudy that do not achieve complete response will be offered radical surgery. During surgery biopsies will be taken from the tumour tissue as well as irradiated adjacent mucosa. Plasma will also be collected.

We will also collect all diagnostic formalin fixed biopsies from the original diagnosis from each relevant pathology department to stain with immunohistochemistry for tumour infiltrating lymphocytes but also to extract RNA and DNA when applicable. This will not affect the treatment or require additional samples from patients. If patients have been subject to subsequent surgery biopsies from this occasion will be collected as well. The biopsies collected will also be analyzed using a small tissue core of about 0.6 mm to allow for tissue microarrays.

2.5.5 Signs of re-growth

If the follow-up indicates that there are signs of re-growth of the tumour, the patient will be discussed on a regular MDT-conference and offered surgical treatment with resection of the tumour. In most cases this will be an abdominoperineal resection. This should be performed at the University Hospital that has monitored the patient.

2.6 Inclusion criteria

For the WoW part of the study all patients with rectal cancer that achieve complete response after neoadjuvant treatment evaluated at 6 weeks, 12 or 16 weeks (if signs of near complete response are present at first or second evaluation) according to the specified criteria above can be included in the Watch and Wait protocol. In detail this includes patients with:

- Patients with rectal cancer staged as cT4bNX/anycTanycN and cMRF+/anycTanycN and lateral lymph nodes on MRI and planned schedule for chemoradiotherapy according to the Swedish National Program for rectal cancer scheduled for neoadjuvant therapy are possible to include.
- Patients with rectal cancer staged as cT4bNX/anycTanycN and cMRF+/anycTanycN and lateral lymph nodes on MRI or anycTanycN considered appropriate for 5x5 Gy and 6-8 weeks of wait prior to surgery according to Stockholm III (29). (the indication for this regime according to Stockholm III could be logistics, co-morbidity and advanced age)

In the biopsy substudy the aim is to identify tumour and plasma markers for complete response, thus all patients that will receive (chemo)radiotherapy in the neoadjuvant setting are included to provide a control for the biopsies.

Patients not willing to participate will be treated according to local and national guidelines but will be offered to answer the same QoL questionnaires.

Patients will be included by the treating surgeon. Patients receive information and sign informed consent.

As soon as a patient has given informed consent this is communicated by phone to the secretariat at SSORG at a specific phone number, and then the treating surgeon receives a study number for the patient that will enable registration in the web-CRF without further identification.

Patients with complete response but with metastases where the clinician chooses to follow the patient according to the algorithm in the study are not formally included in the study but will be registered in the database to be able to perform a separate evaluation of that patient group.

After the initial 200 patients have been included data will be analyzed but to ascertain a rigid control of this rare patient group until long term data is available (Primary end-point is three year follow-up) patients with complete response identified after full accrual will be offered to enter the study and the registry after providing informed consent. Questionnaires will continue to be sent out to improve the statistical power of the secondary analyses of health related quality of life.

2.7 Exclusion criteria

- No informed consent received for participation.
- Contraindication for MRI such as presence of non-compatible metallic implants or claustrophobia.

2.8 Exclusion of included patients

- If a patient withdraws his/her consent after inclusion treatment will be performed according to the National guidelines for rectal cancer.

2.9 External validity

External validity is ascertained by identifying the population through the Swedish Colorectal Cancer Registry. All patients with a cT4bNX/anycTanycN and cMRF+/anycTanycN and lateral lymph nodes or anycTanycN considered appropriate on MRI considered appropriate for 5x5 Gy and 6-8 weeks of wait prior to surgery according to Stockholm III (29) or a palpable rectal cancer staged as cT4bNX/anycTanycN and cMRF+/anycTanycN and lateral lymph nodes on MRI registered in the SCRCR and subject to surgery will be used as control.
Patients with complete response that do not wish to participate in the trial are included in the Swedish Colorectal Cancer Registry and will be possible to evaluate through the registry.

2.10 Near complete response (ncCR)

Patients with near complete response should be asked for participation in the study as well to allow for registration of clinical and radiological data. They will then not be included in the analysis of cCR if they do not obtain a complete response.

At centers where patients have been reviewed for near complete response but not asked for participation in the study we will try to identify patients through out-patient listings and then obtain data on the patients retrospectively (clinical data, radiological data, radiation field plans and details on chemotherapy) to enhance the understanding of clinical aspects determining complete response or not.

2.11 Patient information and informed consent

All patients that fulfil the inclusion criteria will receive oral and written information at their treating hospital.

For the biopsy substudy patients will be included after the initial multidisciplinary tumour board.

For patients that possibly have a complete response after treatment the patients they will be assessed at a multidisciplinary board. If they are considered to have a complete response, they will be offered a watch and wait approach and will then be asked to fill in informed consent and QoL questionnaires.

2.12 Participating hospitals

All hospitals that treat patients with rectal cancer are invited to participate. Patients will be monitored and followed according to watch and wait protocol at their Regional University Hospital. All hospitals will have to adhere to the evaluation schedule after completed chemoradiotherapy.

2.13 Questionnaires

The patient's self-estimate of health and wellbeing will be identified using a specific questionnaire, developed for patients with rectal cancer (30). Patients included in the biopsy substudy will commence this at the initiation of the neoadjuvant treatment. Patients in the WoW study will commence answering questionnaires at inclusion after complete response and at 6, 12, 24 and 60 months. Patients who experience tumour regrowth and have surgical treatment, at any time during follow up, will continue to answer questionnaires at surgery, 6, 12, 24 and 60 months after surgery.

In-depth interviews with patients with rectal cancer have been performed to identify important areas for patients at time of diagnosis, at 6 months, 1, 2 and 5 years. The basis for the construction of this specific questionnaire is the “Steineck concept” with questions about symptoms and their duration, intensity and severity as well as impact on future life. Questions about socioeconomic details are included as well as EQ5D, to facilitate a health economic evaluation.

2.14 Work plan and organisation

All hospitals in Sweden that treat rectal cancer can include patients, but as the number of patients is low follow-up will be performed in selected centres, mainly Regional University Hospitals. At a consensus meeting in April 2016 the following centres were suggested:

1. Umeå (Markku Haapamäki)
2. Göteborg (Eva Angenete)

3. Stockholm (Anna Martling)
4. Västerås (Kenneth Smedh)
5. Linköping (Olof Hallböök)
6. Örebro (Peter Matthiessen)
7. Malmö (Ingvar Syk)
8. Uppsala (Joakim Folkesson)

From the fall of 2016 MRI-workshops will be undertaken to discuss the study, the study protocol, perform case discussions on MRI and examples of tumour regression evaluations. All referral centres that will monitor patients once complete response has been established will participate in these workshops with their selected radiologists.

The study will commence in the end of 2016 and during 2017.

2.15 Statistical methods and power calculation

Approximately 300-400 patients are diagnosed yearly with a non-metastatic advanced rectal cancer that will render them eligible for neoadjuvant (chemo)radiotherapy. According to the literature 10-20% of these patients will have a complete response after treatment. However, not all of these patients have a tumour that can be reached by digital examination. Approximately 30-80 patients will be possible to include yearly.

In this trial the primary end-point is three-year disease-free survival. It can be estimated that 10-20% of the patients in the surgery group will develop distant metastases during the first three years.

In a randomized controlled trial, it could have been estimated to have a reduction of disease at three years from 20% to 10% in the WoW group. This would require 199 patients in each group with a significance level of 5% and a power of 80%. However, as this is a prospective non-randomized trial we aim to include and evaluate 200 patients with complete response.

As there will be a lag-time of three years before the primary endpoint can be assessed we plan to continue including patients to ascertain a secure follow-up.

2.16 Data retrieval and registration

The secretariat for the clinical record forms will be at the Scandinavian Surgical Outcomes Research group in the Department of Surgery, Område 2, Sahlgrenska University Hospital, Göteborg.

The study will be registered at "Patientombudet" and is registered at Clinical Trials NCT03125343.

2.17 Statistical Analyses

When the database is completed, a plan for each of the analyses will be worked out prior to analysis and fully described in an analysis plan.

The analyses will be made on datasets designed to include all data needed to answer a specific research question according to the analysis plans described above. Such data sets will be withdrawn from the database. Handling of the database, after registration, will exclusively be by the data manager.

2.18 Health economic aspects

All out-patient visits will be registered including findings on these. This will be used together with other clinical data to perform a health economic evaluation. Details on each patient in the WoW group will be collected from patient charts and CRFs. Details on the patients in the control group will be collected from the SCRCR.

2.19 Ethical consideration

The study is approved by the Ethical Committee (Etik Prövnings Nämnden) in Gothenburg, EPN Dnr 566-16.

2.20 Financing

The study is supported by regional agreement on medical training and clinical research (ALF) between the Gothenburg county council at Sahlgrenska University Hospital (Eva Angenete). Additional financial support will be applied for.

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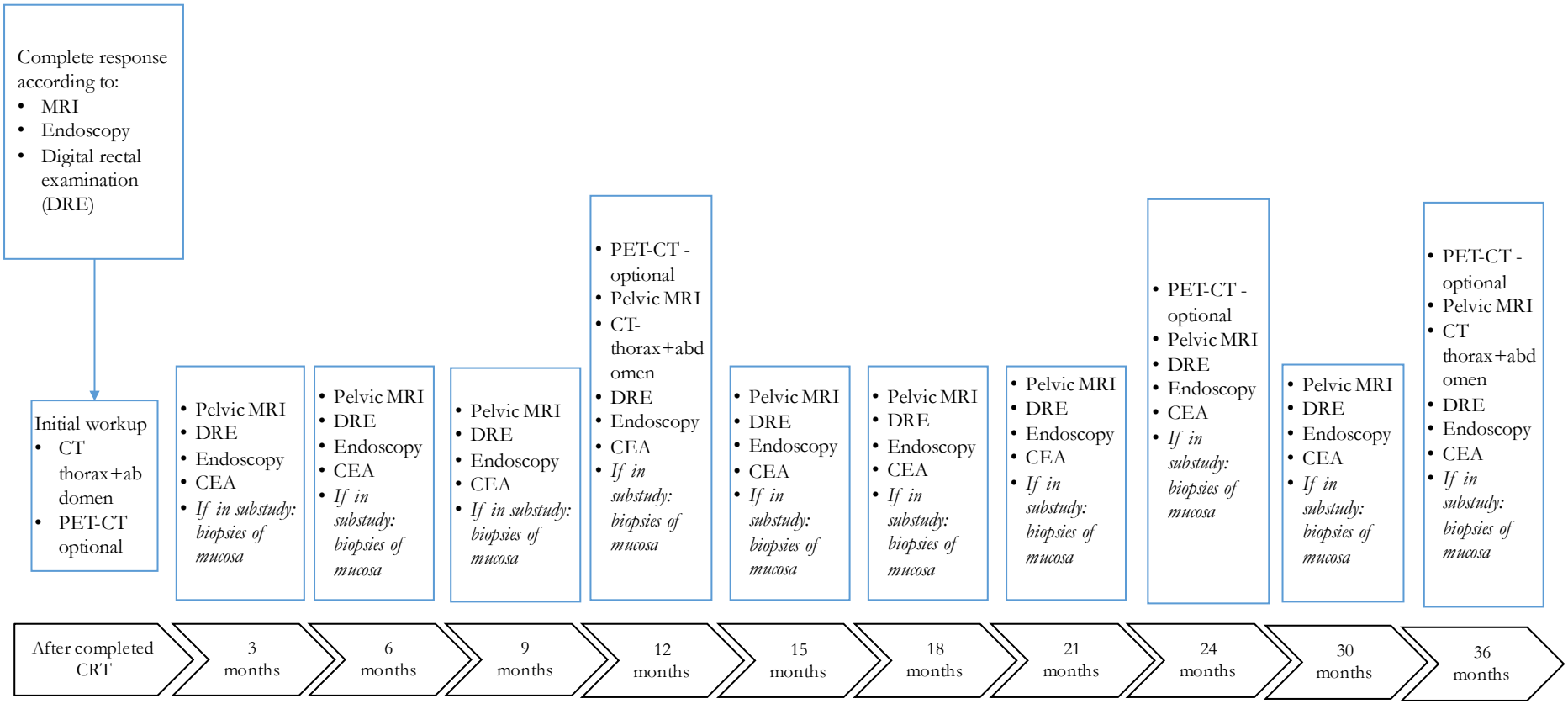
Appendix A - Follow-up schedule the first 3 years.



Appendix B - Radiology protocol for MRI

Ver 8 Oct 2020 – changes from last version in **bold**

Technical Requirements

1.5T or 3T MR equipments

Phased-array receiver coils for pelvic-/body imaging

Preparations: Four hours fasting , rektal emptying with

Mikrolax or likewise prior to examinations

Antispasmodic agents advocated if no contraindications

No endoluminal or intravenous contrast agents

Image sequences

T2-weighted high resolution sequences in at least three different planes (sagittal, transaxial and oblique planes) where at least one imaging sequence is perpendicular to the rectum at the level of the tumour interleaved without interslice gap with maximum 3 mm section thickness with a voxel size of maximum 3x0,8x0,6 mm (1). If low tumours, additional oblique sequences including the tumour parallel and perpendicular to the anal canal are performed with same prerequisites for spatial resolution.

An echo-planar diffusion weighted sequence of the pelvis should be performed in the same anatomical position as the axial T2-weighted sequence of the pelvis. Voxel size should not exceed 5x2x1,5 mm. The diffusion weighted sequence should include at least three b-values including the values b=0, 50 and 800 s/mm^2 as well as an ADC-map calculated from the b=50 and b=800 sequences.

T1-weighted axial sequence of the pelvis is suggested but not mandatory.

MRI reporting

Baseline examination before neoadjuvant treatment

Level of the tumour

The distance of the tumour from the anorectal junction and/or from the anal verge is measured by electronic calipers on sagittal images. The length of the tumour is measured and reported. It is also stated whether the tumour is above, at or below the level of the peritoneal reflection. For low tumours it is stated whether the tumour is within a mm from the levator muscles or not, whether there is involvement of the intersphincteric plane and the external sphincter.

Morphology

Morphology of the tumour is described whether the tumour is polypoid, (semi)annular. If there is evidence of a mucinous tumour indicated by typical high signal intensity on T2-weighted images, this is also reported.

Depth of extramural spread

The maximum depth of extramural depth from the outer edge of the muscle layer to the outer edge of the tumour is measured on high resolution images perpendicular to the rectum at the level of the tumour (1)

Extramural vascular invasion (EMVI+ if present)

EMVI is recorded when there is tumour extension along a vessel as a serpentiguous extension of tumour signal within a vascular structure. Criteria according to Smith et al are used to define whether extramural vascular invasion is present or not (2) .

Mesorectal Fascia

Potential involvement of the mesorectal margin is defined as tumour extending within 1 mm of the mesorectal fascia or closer. In low tumours, the mesorectal margin consists of the fascia covering the levator muscles.

Perforation of the peritoneal reflection by tumour

Peritoneal involvement is reported when nodular extension of tumour beyond the peritoneal reflection is found (3)

Mesorectal lymph node metastases

The total number of mesorectal lymph nodes is reported and the number of lymph nodes regarded as metastatic according to ESGAR consensus guidelines (12). In these quidelines, the size of the lymph nodes deteremines the number of morphological criteria needed (less than 5 mm three criteria, 5-8 mm two criteria and 9 mm or more with either irregular outer border or heterogeneous signal). To note is that a modification from these criteria is that at least one malignant morphological criterium is required for a metastasis regardless of lymph node size.

Extramesorectal lymph node metastases

Presence of suspected metastatic inguinal, lateral pelvic lymph nodes should be reported. Metastastic extramesorectal lymph nodes or pelvic sidewall lymph nodes are defined by morphological criteria same as mesorectal lymph nodes although it is important to note the presence, size and location of all extramesorectal lymph nodess.

Evaluation post chemo-irradiation

When MRI is performed after neoadjuvant treatment, the post treatment MRI is compared with MRI at baseline. Viable tumour (high signal intensity) is separated from post treatment fibrosis (low signal intensity) on T2-weighted images and/or presence of reamaing impeded diffusion on high b-value diffusion weighted images. For mucinous

tumours, remaining or increasing pure mucin pools may not necessary indicates progressive disease.

Length of tumour and tumour and fibrosis if these are not clearly separated is measured as in baseline on sagittal T2-weighted images.

MR tumour regression grading based on T2-weighted images (mrTRG) is performed according to Patel et al (9). This is a five graded scale for this study modified to include diffusion weithged images as follows:

mrTRG1 - no remaining tumour on T2- or diffusion-weighted images (DWI) and normal bowel wall. **A remaining more or less flat fibrotic scar with homogeneous low T2-w signal intensity is common in these cases**

MrTRG2 -the majority of the tumour converted to fibrosis with homogeneous low signal intensity on T2-weighted images **with minor areas of impeded diffusion on high b-value DWI.**

MrTRG3 -mixture of more or less equal amounts of fibrosis and tumour signal with or without areas of restricted diffusion on high b-value DWI

mrTRG4 -corresponds to predominantly tumour signal with remaning restricted diffusion on high b-value DWI.

mrTRG5 - no visible treatment effect neither on T2-weighted images or or high b-value DWI

A clinical complete response (CR) or near CR is defined as mrTRG1-2 together with no or minor areas of impeded diffusion on high b-value diffusion weighted images and a clear reduction in tumour size post-pre treatment (10). To note is that remaining TRG2 after a second or third follow up MRI more than 8 weeks after completion of CRT should be regarded suspicious for non complete response.

Regarding lymph nodes, the short axis diameter of mesorectal and extramesorectal lymph nodes is measured. Lymph nodes with malignant morphogical features pre treatment and a short axis diameter post treatment of equal to or more than 5 mm are considered malignant.

Note:

Role of volume reduction

The changes in size of tumour is only visually qualitatively assessed as the difference in length pre -post treatment and evaluated together with changes in signal on T2-weighted images and DWI.

(The length (L), width (W) and thickness(T) of the tumour can be measured and tumour volume (V) before (pre) and after (post) radiochemotherapy can be estimated as L x W x T /2 . Percentage volume reduction of tumour after treatment can be calculated as 100x (Vpre-Vpost)/Vpre. A volume reduction of at least 80 % is highly predictive of CR but should be evaluated together with the other MR imaging findings (11).)

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Appendix C - Quality of Life Questionnaire

See separate file.