“Watch and Wait” in patients with complete clinical response (cCR) after neo-adjuvant chemoradiotherapy for primary locally advanced rectal cancer

Study protocol

Open population-based observational study on behalf of the Norwegian Gastro-Intestinal Cancer Group – Colorectal (NGICG-CR)

NORWARECT trial
NORwegian Watch And wait in clinically complete response after neo-adjuvant treatment for RECTal cancer

Study group

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Cooperating hospitals

All hospitals within the four health regions of Norway that survey and treat patients with rectal cancer after neo-adjuvant treatment at one of the radiation centres are encouraged to participate and contribute to assessment and inclusion of patients with possible complete or near-complete response. Each cooperating hospital will define a responsible clinician at the respective institution.

Writing group

The writing group will consist of those who created the idea of this national multicentre study (Hans Wasmuth, Gerd Tranø, Arne Færden), an oncologist involved in the design of the protocol (Marianne Guren) and the primary investigator (Hartwig Kørner). Publication of the core endpoints of the study will be done as a research collaboration that includes all site investigators at university hospitals and collaborating hospitals. The writing group will act as principal author with the responsibility for the process from data analysis to submission of the manuscript. For other manuscripts derived from this study protocol, eligibility for authorship will be considered by the steering group in due time according to the Vancouver criteria for authorship in biomedical publishing. All other participants who do not fulfil criteria for authorship will be acknowledged in all potential publications from this study.

Steering group

The study will be conducted and published on behalf of the Colorectal subgroup of the Norwegian Gastro-Intestinal Cancer Group (NGICG-CR). The steering group of the NGICG-CR will act as steering group for this project.

Abbreviations

CR	Complete response
cCR	Clinical complete response on clinical examination
ypCR	Pathological complete response after neoadjuvant treatment
W&W	Watch and Wait protocol
CRT	Chemoradiotherapy
TME	Total Mesorectal Excision
CRF	Clinical report form
MDT	Multidisciplinary team
LR	Local recurrence
DRE	Digital rectal examination
MRI	Magnetic resonance imaging

Background

During the past three decades, preoperative radiotherapy (RT) and chemoradiotherapy (CRT) was introduced to reduce the high rates, i.e. 25-30%, of local recurrences (LR) after primary resection of adenocarcinoma of the rectum (1-3). For the same reason, a huge effort was done by others to refine the surgical technique of rectal cancer surgery based on better anatomical understanding of the mesorectum and the importance of the mesorectal fascia for optimal surgical treatment – the concept of *total mesorectal excision* (TME) (4).

In Norway, the implementation of TME as the new gold standard of surgical approach was clearly associated with a significant reduction of LR without the need of neoadjuvant treatment (5). This was, however, not true for very low tumours of the rectum, advanced tumours (i.e., those involving the mesorectal fascia and/or T4 stage), and not for every centre (6). In other countries like Sweden and the Netherlands, preoperative short-course radiotherapy was used in a much larger scale together with the introduction of TME surgery, showing that RT could halve the LR rate (2, 7). The combination of radiation with chemotherapy resulted in downsizing, and thus often down-staging of the tumour (1). Consequently, the use of preoperative CRT has increased in Norway during the years (8). Notably, it appeared that in some of the specimens after resection the tumour had disappeared completely and was not longer detectable by histopathology, indicated as pathological complete response (ypCR) (9).

In the late 1990ies the Brazilian group of Habr-Gama (10) identified the concept of *clinical* complete response (cCR), characterised by four clinical post CRT features: 1. Flattening of the tumour site, 2. No ulceration, 3. Whitening of the tumour and 4. Telangiectasia. These four clinical characteristics indicated a true complete response (CR) following CRT as definitive treatment. In their study, as well as described by others, no surgery was performed and the patient was included in a “watch and wait” (W&W) protocol in order to identify potential regrowth at an early stage. (11-14).
The results from the Habr-Gama group inspired several other centres, such as the Maastricht group in the Netherlands (15) and the Vejle group in Denmark (16) to study the phenomenon of cCR and the non-operative treatment strategy. Moreover, an international collaboration (*International Watch&Wait Database*, http://www.iwwd.org) has been established to register and monitor patients with cCR in order to assess the oncological outcomes in large patient groups undergoing this treatment.
Currently, it is agreed that true CR can be achieved after different protocols of chemoradiotherapy. The CR rates in specimens after radical surgery vary with tumour stage, being 30-35% for T1, 15-25% for T2, 12-15% for T3, and <10% for T4 stage. The frequency of complete response after surgery (ypCR) has been reported to be 10% in Norway (17).
The main problem is how to detect those tumours that are radiosensitive and will be highly likely to result in CR by CRT only, thus eliminating the need for major surgical resections with

considerable surgical morbidity and impairment of functions, in addition to late postradiation effects.

cCR is currently defined by the four clinical characteristics as described by the Habr-Gama group. At present, it remains unclear whether the additional use of Magnetic Resonance Imaging (MRI) may increase the predictive value of cCR, and conflicting results are reported (18, 19). This may, however, change with future improvements of diagnostic imaging tools and protocols. Further, tissue sampling during observation after CRT has currently no place in enhancing the sensitivity or specificity of cCR (15). Moreover, there are at present no molecular or other tumour characteristics that can predict CR.

According to the Norwegian guidelines – like others – the recommended waiting time before surgery is at least 6 -8 weeks, and up to 10-12 weeks after CRT. A waiting time of 12-13 weeks after long course CRT in tumours that respond is associated with an increased rate of cCR without any impaired prognosis (20). Thus, tumours with a near cCR at 6-8 weeks might result in a cCR at 12-13 weeks, and the patients who do not achieve cCR after 12-13 weeks and then undergo surgery will according to current knowledge not have inferior prognosis compared to those operated at 6 -8 weeks.

There are only a few studies in the literature that report on more than 50 – 100 patients in single centre series (21, 22). Due to the nature of the disease and treatment, such studies are not easy to conduct. Furthermore, the inclusion and exclusion criteria used in the various studies differ considerably, and the study populations are heterogeneous. The protocols vary with regard to the use of CRT and the waiting time for assessment of the response. Therefore, studies based on population based registries, such as the Cancer Registry of Norway or the Norwegian Colorectal Cancer Registry, are highly likely to provide important information.
The W&W has gained great interest, as it provides the possibility to cure the patients without the need of major surgery and its consequences on functional outcomes and lifelong morbidity, and thus preventing overtreatment. However, this treatment concept is currently regarded as experimental and has not yet become part of commonly accepted guidelines. There is a need to increase the knowledge on the concept of cCR and CR in a population based patient cohort with a standardized treatment algorithm and follow-up.

Aim of the study

The aim of this study is to estimate the rate of regrowth among patients with locally advanced rectal cancer treated with neoadjuvant treatment with radiotherapy or chemo-radiotherapy, where complete clinical response has been obtained, and thus to determine the positive predictive value of cCR in a national cohort.

Objectives and endpoints

Primary endpoint is the *rate of regrowth* among patients with cCR who follow the W&W protocol after preoperative radiotherapy or chemo-radiotherapy, in order to determine the positive predictive value of cCR.

Secondary endpoints are

- The rate of cCR after preoperative CRT
- To calculate the diagnostic accuracy of the clinical diagnosis of complete response
- The rate of metachronous distant metastases in patients following the W&W protocol
- The rate of metachronous metastasis and recurrence rate after ypCR
- Overall and cancer-specific survival of patients with cCR following the W&W protocol compared to patients with ypCR, i.e. patients with complete pathologic response after resection.
- Assess the rate of patients who otherwise would have had an APR
- Patient-reported outcome measures, such as Low anterior resection syndrome (LARS) and quality of life (QoL)
- To calculate the costs of treatment for W&W after cCR as compared to surgical treatment
- To assess the diagnostic accuracy of MRI in the diagnosis of complete response

Design

The current study is designed as an open prospective population-based study. All patients diagnosed and treated with radiotherapy or chemo-radiotherapy for rectal cancer in Norway will be eligible for this study, provided signed informed consent given before inclusion.
All patients will be diagnosed according to national guidelines, and treatment decisions with regard to the need for neo-adjuvant chemo-radiation therapy will be made according to national guidelines in the setting of multidisciplinary team (MDT) meetings. Indication for preoperative radiotherapy or chemo-radiotherapy will follow up-to-date treatment guidelines at any time, and will not be extended to new groups of patients who are currently not offered neo-adjuvant treatment with the intention to achieve complete clinical response (cCR).
Patients who participate in the study will be followed closely according to a defined schedule as described below. Patients diagnosed with regrowth during follow-up will be scheduled for surgical resection as described below.

STROBE guidelines (23) form the base of the design of the study, as well as the analysis and publication of results. These guidelines intend to ensure best possible transparency of cohort studies, and helping to identify and report possible confounders that are inherent to this study design.

Inclusion criteria into the study

- Histologically verified adenocarcinoma of the rectum within 15 cm from the anal verge measured by rigid proctoscopy
- Patients who have completed neoadjuvant treatment according to national guidelines for rectal cancer, i.e., radiotherapy or chemo-radiotherapy (at least 40 Gy) or short-course radiotherapy combined with chemotherapy
- Patients aged ≥18 years of age are eligible for inclusion. However, patients aged ≤40 years are recommended to undergo surgery on the theoretical base of a possibly more aggressive tumour disease in this age group, and will be asked to participate in the study by consenting to recording of data. Those patients who insist on W&W approach after careful consideration and well-documented informed consent are eligible for entering the W&W protocol.
- Given informed consent
- Stage I-III rectal cancer; however, patients with limited liver metastases who undergo primary liver surgery as part of a "liver first" treatment approach may be included

The following patients will be offered inclusion into the Watch & Wait protocol

- **Complete clinical response** at 6-8 weeks after neoadjuvant treatment includes two *negative signs*, i.e., the disappearing of the visible tumour leaving a flattening of the mucosa on the inner bowel wall, no tumour is seen, and the disappearing of any ulcer. These signs are *mandatory*. Two other criteria include *positive signs*, i.e., whitening of the previous tumour site appearing almost as a small white spot to merely a great area, and development of telangiectasia. These positive signs depend to a higher degree on time and individual interpretation, and are *not mandatory*:

    1. Flattening of the tumour site (mandatory)
    2. No ulcer visible (mandatory)
    3. Whitening of the tumour site (not mandatory)
    4. Visible telangiectasia (not mandatory)

- **Near Clinical Complete Response (near-cCR)** is defined as a nearly complete disappearance of the tumour and/or the ulcer of more than 75% at 6-8 weeks post RCT as determined by the clinician. A near-cCR may result in cCR after 11-12 weeks post CRT, and in this case the patient will be eligible for inclusion into the W&W

protocol at that time. Otherwise, the condition is not a cCR and surgery is offered immediately.

Patients with cCR after preoperative CRT who decline the W&W protocol and wish to undergo surgery, or patients with near, but not complete clinical response will be asked to give consent to participate for registration in the database as controls.

Exclusion Criteria

- Patients without cCR
- Patients unable to give informed consent
- Patients with short course radiotherapy (5x5 Gy) without additional chemotherapy, or patients receiving less than 40 Gy in long course CRT
- Patients with cCR but with increasing tumour growth on MRI after preoperative treatment
- Patients with metastatic disease at the time of diagnosis with the exception of those who are eligible for “liver first” treatment approach as part of an intention to cure approach.
- Patients previously diagnosed and treated for malignant disease in the pelvic region with radio- or chemoradiotherapy
- Other circumstances that may interfere with successful participation in the W&W protocol

Radiation and chemoradiation

Neoadjuvant treatment will be given based on a decision by the MDT and according to national guidelines that apply at any given time during the study period. Preoperative radiotherapy is currently given as long course radiotherapy to 50 Gy with concomitant chemotherapy (capecitabine or 5-fluorouracil). Patients treated with short-course 5x5 Gy with combination chemotherapy are also eligible for participation. Neoadjuvant treatment with any modifications due to patient-related factors are acceptable as far as the effect of received treatment is considered to be at least 80% of standard treatment.

Response evaluation before enrolment in the study

All patients who receive preoperative CRT will be evaluated for treatment response at approximately 6 weeks after the last radiation treatment by MRI and clinical examination, including digital rectal examination (DRE) and rigid proctoscopy.
Patients with cCR (i.e., ycT0N0) will be invited for participation in the study.

Patients with near-cCR will be invited to undergo a second evaluation for cCR at 12 weeks for participation in the study. State of clinical tumour regress will be documented by endoscopic photography imaging when cCR is concluded. Patients with initial near-cCR, but without cCR at 12 weeks will be advised to undergo surgery according to current guidelines. The accuracy of DRE in cCR is not evident. When either DRE and/or MRI suggest a tumour in patients who otherwise fulfil cCR criteria, they are offered surgery and asked for inclusion into the study without W&W protocol.
Patients who fulfil the criteria for cCR as defined at 6 weeks or 12 weeks will be asked for participation in the W&W protocol. All other patients who were considered for cCR without a final diagnosis of cCR will not be eligible for the W&W protocol, but they will be asked to participate in the study by recording their data of treatments and outcomes in order to calculate the necessary statistics (e.g., sensitivity, specificity or likelihood ratios of possible prognostic or predictive factors for the study endpoints). These patients will be offered systematic follow-up as described in national guidelines.

Treatment course of the included patients and follow-up

Patients eligible for the present study will be recruited from all patients undergoing neo-adjuvant treatment for rectal cancer within 15 cm distance from the anal verge according to national guidelines. Treatment decisions will be made at multidisciplinary team meetings according to national guidelines, and after information and discussion with the individual patient based on individual informed consent.

Evaluation after neo-adjuvant treatment and eventual inclusion into the cCR protocol will be done after 6 weeks based on clinical and radiological examinations as indicated in the flow chart below. Blood tests at inclusion include analysis of CEA, B-RAF and K-RAS biomarkers.

In case of persistently elevated or increasing serum CEA levels, the presence of synchronous distant metastases has to be ruled out, and the conclusion of cCR has to be thoroughly reconsidered.

Radiological response evaluation

Multiparametric MRI for estimating tumour response and tumour regrowth after CRT is a developing diagnostic tool and consists of many different techniques. In this population-based multicentre study, the MRI protocol needs to be standardized and based on the best-explored and most robust MRI parameters; T2W and diffusion weighted imaging (DWI).
The two most promising parameters for estimating cCR are tumour volume reduction, measured at T2W, and loss of tumour signal assessed at both T2 and DWI. Volume reduction has a high sensitivity for prediction of cCR (19) and will be assessed by the *MR Tumour*

Regression Grade (mrTRG), appendix I. Maas *et al* have shown that disappearance of tumour signal at T2W and DWI indicated cCR and furthermore that the diagnostic performance improved if MRI and clinical assessment were combined (15). A five-point confidence level scale (appendix II) will be used to record the tumour signal disappearance at T2&DWI. T2&DWI is also promising for early detection of regrowth in a *watch and wait* (W&W) program (24) and will also be recorded using a five-point confidence level scale, see appendix I.
Minimum required sequences in the MRI examination are:

- Transversal, sagittal and coronal 2D T2W *or* an isotropic 3D T2W
- Hi-resolution T2W TSE perpendicular to the tumour/bowel wall interface
- Transversal DWI with at least two b-factors 0 -1000

To reduce susceptibility artefacts from bowel air, a rectal enema should be administrated prior to the MRI examination.
For a more detailed MRI protocol se appendix II.

Follow-up of the patients in the W&W protocol will be done according to the schedule outlined below, and up to 8 years, as some recurrences or regrowths may occur later than within the 5 year period commonly used for follow-up of patients with rectal cancer.

Flow chart of W&W protocol

Neo-adjuvant treatment according to national guidelines

- Rectal adenocarcinoma within 15 cm above the anal verge
- Any T-stage or other lesions (tumour deposits, involved lymph nodes) threatening the circumferential resection margin (CRM) as defined by diagnostic MRI
- All T4 tumours
- No distant metastases (M0), or limited liver metastases eligible for ”liver first” approach
- Radiotherapy with concomitant chemotherapy according to the decision of the MDT

↓

Evaluation 6 weeks after completed radiation

1. MRI evaluation
   a. tumour regression
   b. stable disease
   c. progression
2. Clinical evaluation according to criteria by rectoscopy and digital examination
   a. complete clinical response (cCR, at least two mandatory criteria)
   b. near cCR (near-cCR; ≤75% estimated shrinkage of tumour and/or ulceration)
   c. stable disease
   d. progression

No biopsies required, ultrasound evaluation at the discretion of the surgeon
Endoscopic imaging of the tumour when cCR or near-cCR diagnosed
Serum CEA

↙ ↘

Tumour progression or lack of sufficient response
(1.b/c and/or 2.c/2.d)

Proceed to surgical resection

Tumour regression - 1.a and/or 2.a/2.b

- **near cCR – 2.b:**

Further observation until new assessment at 12 weeks, preliminary scheduling for resection

- **cCR – 2.a:**

Written informed consent

- to participate in W&W protocol
- to participate in data collection when not taking part in cCR protocol and surgical resection is planned

Mandatory registration in CRN/NCCR
Registration in cCR database according to consent

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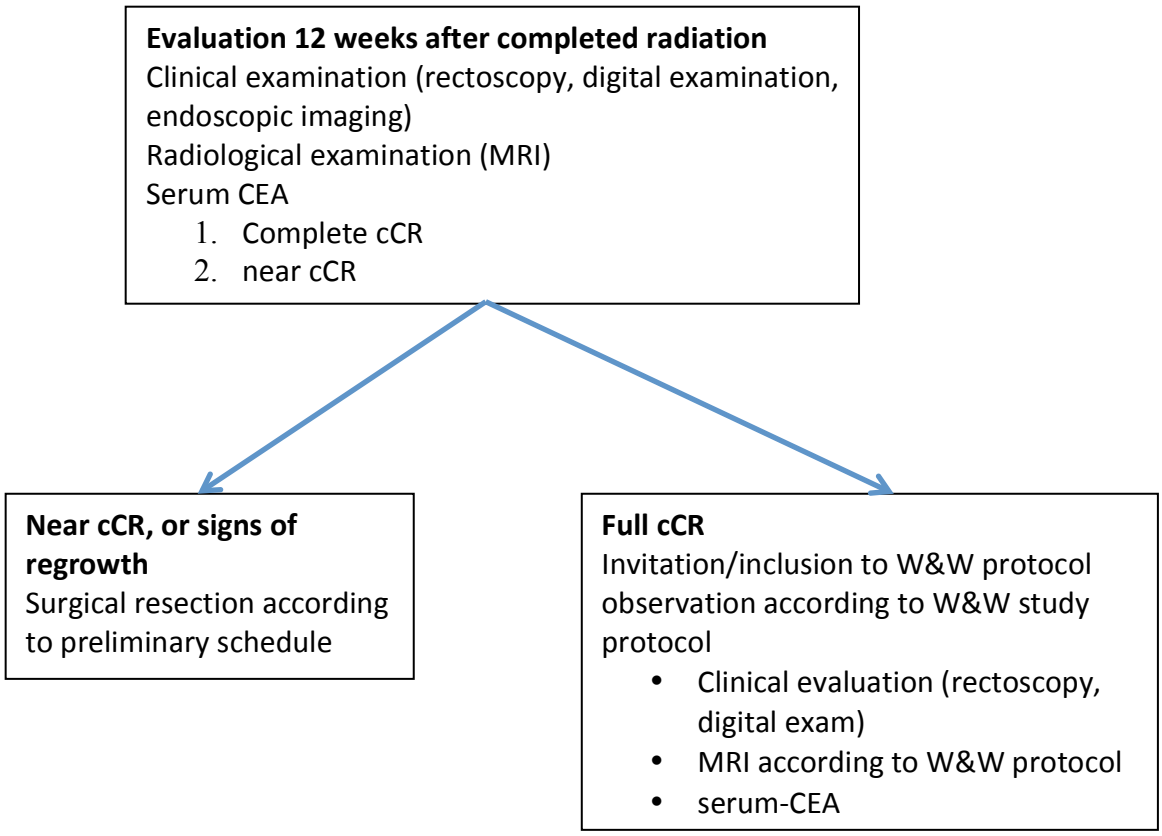

Schedule for W&W protocol:

Clinical evaluation

- Every second month 1. year
- Every third month 2. year
- Every sixth month 3. year
- Thereafter routine systematic follow-up according to national guidelines extended up to 8 years

MRI evaluation

- Every second clinical evaluation the 1. and 2. year, then every sixth month

Serum-CEA measurement

- At all clinical examinations

Systematic follow-up for distant metastases according to national guidelines for systematic follow-up extended to 8 years

Analysis of biological material

In addition to clinical outcomes, it will be of great interest to analyse available biological material with regard to biological markers that may indicate a clinical response, or a regrowth. This is particularly important for the current study as a national multicentre study. For this purpose, it will be of great interest to perform molecular-biological analyses of tissue specimens obtained from diagnostic procedures and surgical specimens after resection. This will be limited to tissue obtained in routine diagnosis, and when patient consent is given.

Patient-reported outcomes

PROMs will be assessed with the LARS score (see Appendix III), and the QLQ-C30 and QLQ-CR29 scores. EORTC-QoL C30 and C29 are generally accepted tools for measuring the quality of life of patients with colorectal cancer. According to the user agreement as defined by the EORTC group, the scores are not displayed in the protocol.

Patients will complete these questionnaires at the time of inclusion, and thereafter at 1, 3 and 5 years follow-up.

Withdrawal from the study

Patients enrolled in the W&W protocol can withdraw from the study at any moment without giving any reason. Data that have been registered as part of the study will not be deleted, unless the patient requests this specifically. Data that are part of mandatory public registration to the Cancer Registry of Norway will be recorded consecutively according to national legislation.

Adverse events

Adverse events (AE) are defined according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (published: May 28, 2009 v4.03: June 14, 2010).
An Adverse Event (AE) is any unfavourable and unintended sign (including a laboratory finding), symptom, temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily life

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily life

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Serious adverse events (SAE, grade 3-5 AE) will be recorded in the CRF and reported to the steering group of the trial:

- Description of event
- Time of first symptoms
- Severity: Evaluation of degree
- Relation to investigation (probable, improbable, uncertain)
- Action taken or planned for investigation
- Time of abatement/stabilization of condition

The steering group will decide on possible consequences for the trial.

International collaboration

In addition to the current national protocol, an international collaboration has been established to collect a large international database of patients who undergo a W&W treatment after cCR – the **International Watch & Wait database** (http://www.iwwd.org). Every Norwegian institution has the opportunity to provide the IWWD with its own data, and on its own initiative and responsibility.

Study population and sample size

The study population is intended to include most, and ideally all, patients who undergo neo-adjuvant treatment for rectal cancer and achieve a cCR and/or ypCR during the study period. Annually about 50 patients are registered at the CRN/NCCR database in Norway with ypCR after long course radiotherapy with or without concomitant chemo sensitization.

Estimation of sample size is based on the aim of this study to detect the sensitivity (i.e., true positives) and specificity (i.e., true negatives), as well as 1-sensitivity (false positives) and 1-specificity (i.e., false negatives) in order to characterize the ability to correctly diagnose patients with cCR with a minimum of regrowth (i.e., false negatives) or unnecessary resections (i.e., false positives). Based on these estimations, it will be possible to achieve the primary endpoint of the study, i.e. the rate of regrowth, and to calculate positive predictive value of the diagnosis of cCR among patients who follow the W&W protocol after preoperative chemoradiotherapy.
As the present study is a prospective observational study, and not a clinical trial that aims to prove the superiority or non-inferiority of a specified treatment, power calculations that result in *numbers needed to treat or to harm*, do not apply here for the estimation of number of patients to include.

By including patients into the study who wish to undergo surgical resection despite the clinical finding of cCR, and decide not to follow the W&W algorithm, it will be possible to calculate these parameters based on a 2x2 table on the following assumptions based on results from current literature:

- During this time period, a tenfold/approx. 1000 patients will receive neo-adjuvant treatment
- Of those, 100 patients with cCR to enter the W&W protocol
- Of those 100, it may be assumed that
    - 85 will have a true CR
    - 15 will have ypCR (i.e., ypT0) after surgical resection
    - of those 100 patients, up to 30 may have regrowth after initial cCR within the W&W protocol
- Finally, 900 of 1000 (i.e., 870 patients + 30 patients with regrowth) will have ypT1-4 after surgical resection

Accordingly, the study aims to include at least 100 patients with cCR who choose to follow the W&W algorithm.

	True CR	**No CR**	
W&W (cCR)	True positive N=85	False positive N=30 (regrowth)	**115**
No W&W (No cCR)	False Negative N=15	True Negative N=870	**885**
	100	**900**	**1000**

Based on these figures, it will be possible to calculate sensitivity, specificity, 1-sensitivity, 1-specificity, positive and negative predictive values, positive and negative likelihood ratios, and perform ROC curve analysis.
The study will include patients until a number of 100 patients has been entered the W&W protocol. Taking into account that 70% of all eligible patients with cCR patients will be identified, i.e. annually 31/50 will be included nationwide, an inclusion period of at least three years will be needed to achieve the goal of 100 study participants. Taking into account that some patients will reject participation in the study and/or decide to withdraw, or be lost to follow-up by other reasons, an inclusion period of up to 5 years might be necessary to achieve the inclusion goal.
One year after start of inclusion, the steering group will evaluate the recruitment with regard to the feasibility of the inclusion goal.

Data collection

Data collection will include clinically relevant variables that are part of common clinical practice independently of the cCR protocol, and that are part of the mandatory public registries (i.e., CRN and NCCR), such as:

- Patient characteristics
- Tumour characteristics (clinical, imaging, pathological and biological), values of blood tests
- Data on oncological treatment (radiation, chemotherapy)
- Surgical procedures
- Pathology reports
- Follow-up data, including possible regrowth, recurrence and metastases, and survival
- PROMs

Data will be collected and recorded at every patient visit and assessment. Given the limited number of patients, data will be collected on paper sheets temporarily at every participating study site under secure circumstances. After one year of inclusion a first interim analysis of all cases will be performed, and data entered into a suitable database provided by the NCCR.

Coupling with other national databases

To enhance data quality, or to increase the information available in the dataset, it will be useful to couple the current dataset with other national registries:

- Norwegian Patient Registry
- Cancer Registry of Norway
- Norwegian Colorectal Cancer Registry
- Norwegian Quality Registry for Gastro-intestinal Surgery (NoRGast)
- The Norwegian Prescription Database

The patients will be asked to consent to coupling to those registries. The study protocol requires the possibility to use indirectly identifiable data due to the coupling of databases.

Statistics

For analysis of the study, standard descriptive and analytic statistics will be applied when appropriate, and according to the distribution of the various variables. Multivariable analyses will be performed when appropriate with regard to relevant outcome variables, and in order to detect independent predictors of the outcome in question.
Survival analyses will be performed by Kaplan-Meier estimates and factors compared by using the log rank test. Multivariable analysis for time-dependent outcomes will be performed by Cox proportional Hazards analysis in order to detect independent predictors of the outcome in question.
The steering group has the necessary statistical knowledge and competency to provide appropriate statistic evaluation and analysis.

Organization

Patients with rectal cancer will be treated at all Norwegian hospitals that offer diagnosis and treatment for rectal cancer within the public specialist health service and according to national regulations and guidelines. When evaluation at 6 weeks after completed radiation indicates a possible full or near cCR, the patient will be referred to the cooperating University Hospital for further evaluation and recruitment to the W&W protocol when indicated, and informed consent will be obtained.

At each University Hospital, two dedicated colorectal surgeons will examine these patients, include in the W&W protocol and perform follow-up as described according to commonly agreed definitions. They will maintain the data entry forms and registration at the national registries.

In the case of equivocal or uncertain findings, these will be discussed in a collegial forum to achieve consent and decisions.

The W&W protocol will be referred to in the national guidelines as an ongoing study, and thus represent a treatment within a scientific study protocol. The study will be registered on public Norwegian websites such as https://kliniskestudier.helsenorge.no, and will be registered at clinicaltrials.gov.

Costs, finances and resources

The W&W protocol will be performed within the public specialist health care. Examinations that are part of the W&W protocol are mostly inexpensive clinical examinations or routine blood tests, with the exception of MRI examinations. However, the number of study participants is low, and as included patients will not need hospital consumptions related to surgery, the total economic load of the study is considered to be low.

The study group will apply for grants for financial support in order to cover expenses that are not covered by public health funding, such as development of CRF and study database, other costs related to collection of necessary data or information, research time for analysis, preparation of manuscripts and publication, including participation in international meetings, and if necessary, costs for supplemental data from other registries.

Insurance

Patients entering the W&W protocol will be covered by the ordinary liability insurance of the respective health trust and NPE (Norsk pasientskade erstatning) in line with any specialist health service. Every institution has the responsibility for its patients in line with relevant Norwegian legislation for specialist health care. Therefore, there will be no need for other insurances.

Time schedule

Recruitment will start as soon as possible when all permissions according to Norwegian law are obtained. The inclusion time will end when 100 W&W patients have enrolled the study, which is estimated to three to five years. Patients will be followed for 8 years.

Publication

The results will be published in international journals on behalf of the NGICG-CR. The writing group will consist of the persons as defined above, and the Vancouver guidelines and journal policies will apply. Results will be published regardless of the outcomes.

Ethical considerations

cCR is documented in scientific literature and applies for about 10, and maybe up to 20% of the patients. There is, albeit limited, evidence in the literature that a considerable proportion of patients with cCR followed with watchful waiting do fare well, and that treatment outcomes in patients operated on for tumour regrowth do achieve comparable results with regard to local recurrence and survival.

Current standard of surgical treatment, i.e. rectal resection or amputation, induces considerable short- and long-term comorbidity (surgical complications; low anterior resection syndrome, permanent stoma, chronic pain, bladder dysfunction, sexual dysfunction, or other injury of pelvic organs etc.), and may even lead to death. Thus, as a certain group of patients might be treated sufficiently with oncological treatment alone, these patients will possibly be subjected to over-treatment and may, thus, possibly be harmed by surgery. Moreover, avoidance of surgery after cCR will preserve rectal function and thus avoid a permanent colo- or ileostomy in those patients.

This has to be balanced against any under-treatment, i.e. the possible harms of the Watch & Wait strategy, such as tumour regrowth and possibly worse outcome after surgery for tumour regrowth.

There is a need for more knowledge on the concept of watchful waiting following cCR as a viable treatment alternative to surgery. The current study is expected to give important information, as the design of an open prospective population-based study will minimalize patient selection. Results will be reported according to the STROBE guidelines for observational studies, and thus, the results of the study will have a high degree of external validity.

The group of investigators as well as the steering committee therefore think that there is a strong need for this study, and that the potential benefits will outweigh the possible harms of the study.

User involvement

User involvement is secured according to national regulations. A user representative of the User involvement committee of Stavanger University Hospital has reviewed the study protocol as well as the patient information and consent form from a user perspective, and encourages the study.

Monitoring and patient security

The participating centres will establish a forum within the NGICG-CR for continuous communication on patients considered and included in the study with regard to findings, follow-up and possible adverse events. In this way, the group will maintain a continuous monitoring of the course of the study in order to secure inclusion, follow-up and treatment decisions in case of regrowth/recurrence according to the protocol and national guidelines.

References

1. Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008;26(22):3687-94.
2. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. 2005;23(24):5644-50.
3. Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926-33.
4. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg. 1998;133(8):894-9.
5. Wibe A, Moller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, et al. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. Dis Colon Rectum. 2002;45(7):857-66.
6. Wibe A, Eriksen MT, Syse A, Tretli S, Myrvold HE, Soreide O. Effect of hospital caseload on long-term outcome after standardization of rectal cancer surgery at a national level. Br J Surg. 2005;92(2):217-24.
7. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638-46.
8. Guren MG, Korner H, Pfeffer F, Myklebust TA, Eriksen MT, Edna TH, et al. Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010. Acta Oncol. 2015:1-9.
9. Manceau G, Panis Y. Is there a place for organ preservation in infiltrating rectal cancer? Minerva Chir. 2015;70(4):283-96.
10. Habr-Gama A, de Souza PM, Ribeiro U, Jr., Nadalin W, Gansl R, Sousa AH, Jr., et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. Dis Colon Rectum. 1998;41(9):1087-96.
11. Chawla S, Katz AW, Rauh SM, Monson JR. Can Surgery be Avoided After Preoperative Chemoradiation for Rectal Cancer in the Era of Organ Preservation? Current Review of Literature. Am J Clin Oncol. 2015;38(5):534-40.
12. Das P, Minsky BD. A watch-and-wait approach to the management of rectal cancer. Oncology (Williston Park). 2013;27(10):962-8.
13. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Bailao Aguilar P, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56(10):1109-17.

14. Hingorani M, Hartley JE, Greenman J, Macfie J. Avoiding radical surgery after pre-operative chemoradiotherapy: a possible therapeutic option in rectal cancer? Acta Oncol. 2012;51(3):275-84.
15. Maas M, Lambregts DM, Nelemans PJ, Heijnen LA, Martens MH, Leijtens JW, et al. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. Ann Surg Oncol. 2015;22(12):3873-80.
16. Appelt AL, Ploen J, Harling H, Jensen FS, Jensen LH, Jorgensen JC, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol. 2015;16(8):919-27.
17. Wasmuth HH, Rekstad LC, Trano G. The outcome and the frequency of pathological complete response after neoadjuvant radiotherapy in curative resections for advanced rectal cancer: a population-based study. Colorectal Dis. 2016;18(1):67-72.
18. Nahas SC, Rizkallah Nahas CS, Sparapan Marques CF, Ribeiro U, Jr., Cotti GC, Imperiale AR, et al. Pathologic Complete Response in Rectal Cancer: Can We Detect It? Lessons Learned From a Proposed Randomized Trial of Watch-and-Wait Treatment of Rectal Cancer. Dis Colon Rectum. 2016;59(4):255-63.
19. Bhoday J, Smith F, Siddiqui MR, Balyasnikova S, Swift RI, Perez R, et al. Magnetic Resonance Tumor Regression Grade and Residual Mucosal Abnormality as Predictors for Pathological Complete Response in Rectal Cancer Postneoadjuvant Chemoradiotherapy. Dis Colon Rectum. 2016;59(10):925-33.
20. Foster JD, Jones EL, Falk S, Cooper EJ, Francis NK. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Dis Colon Rectum. 2013;56(7):921-30.
21. Nyasavajjala SM, Shaw AG, Khan AQ, Brown SR, Lund JN. Neoadjuvant chemo-radiotherapy and rectal cancer: can the UK watch and wait with Brazil? Colorectal Dis. 2010;12(1):33-6.
22. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. 2015.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7.
24. Lambregts DM, Lahaye MJ, Heijnen LA, Martens MH, Maas M, Beets GL, et al. MRI and diffusion-weighted MRI to diagnose a local tumour regrowth during long-term follow-up of rectal cancer patients treated with organ preservation after chemoradiotherapy. Eur Radiol. 2016;26(7):2118-25.

Appendix I

Response evaluation: MRI Tumor Regression Grade, mrTRG

mrTRG 1	Radiological complete response. Linear scar in submucosa
mrTRG 2	Good response. Dense fibrosis, no residual tumor
mrTRG 3	Moderate response. > 50% fibrosis and mucin
mrTRG 4	Slight response. Little areas of fibrosis or mucin, mostly tumor
mrTRG 5	No response. Same appearance as original tumor

Response evaluation: Five-point confidence level scale for T2&DWI

1. Definitely complete response. Subtle or no hypointense wall thickening and no tumor signal on T2W and DWI
2. Probably complete response. Hypointense wall thickening, no tumor signal on T2W and DWI
3. Possibly residual tumor/possibly complete response. Irregular wall thickening with possible tumor signal on T2W and DWI
4. Probably residual tumor. Small residual tumor on T2W and DWI
5. Definitely residual tumor. Gross residual tumor on T2W and DWI

Regrowth detection: Five-point confidence level scale for T2&DWI

1. Definitely no regrowth. No visible tumor signal on T2W and DWI.
2. Probably no regrowth. Possibly minimal tumor signal on T2W or DWI
3. Possibly no/possibly regrowth. Minimal tumor signal on T2W and DWI
4. Probably regrowth. Small tumor volume on T2W and DWI
5. Definitely regrowth. Gross tumor signal on T2W and DWI

Appendix II

Recommended MRI protocol

T2W

Transversal, sagittal and coronal 2D T2W TSE. Voxel size ≈ 0.7 x 0.7 x 3-4 mm^3.
or (preferably) a 3D T2W TSE (SPACE,VISTA,CUBE). Voxel size ≈ 1.0 x 1.0 x 1.0 mm^3.
Hi- res T2W TSE perpendicular and parallel to the long axis of the tumor/bowel wall interface, voxel size: ⩾ 0.6 x 0.6 x 3 mm^3. An additional coronal T2W (parallel to the anal canal) should also be performed if tumor is low.

DWI

Transversal and sagittal DWI. Voxel size ≈ 2.0 x 2.0 x 4 mm^3. The optimal choice of b-values is not known. If the b-value is too low, T2-shine trough may be misinterpreted as residual tumor, if too high small amounts of tumor may disappear within noise. At least two b-values are recommended: 0 and 800-1000, preferably three or four; for instance 0-300-800 or 0-300-500-1000.
Adequate signal-to -noise ratio is crucial for high b-value images. At least 8-12 repetitions (NSA) are probably needed for most scanners in order to display small amounts of residual tumor. Small FOV reduces several artifacts in DWI. FOV ≈ 16-20 cm are therefore recommended. Saturation pulses should be used to prevent folding/aliasing, not oversampling.

T1W

Coronal T1W covering the whole pelvis is recommended.
3D T1W (SPACE, VISTA, CUBE etc) is especially suitable. If performed with a slightly lower resolution than the T2W, the scan time is only a few minutes. Voxel size:
Isotropic: 1.2 x 1.2 x 1.2 or 1.3 x 1.3 x 1.3 mm^3 or anisotropic: (faster) ≈ 1.0 x 1.0 x 2 mm.

Alternatively, a 2D T1W TSE can be performed. Voxel size ⩽ 0.8 x 0.8 x 4-5 mm^3.

Patient preparation

Bowel air generally causes serious degradation of DW images. Rectal enema should be given in order to reduce/remove bowel air. The patients administer the enema themselves at arrival at the radiology department approximately one hour prior to the examination. An additional benefit of the enema is that the induced mucosal edema makes it easier to discriminate residual tumor.
To reduce motion artifacts, antiperistaltic drugs such as butylscopolamin (Buscopan®) and/or glucagon should be administered iv. or im. The long 3D T2W sequence is particularly prone to artifacts from bowel motion. The most effective way to ensure good image quality from 3D T2W is to give butylscopolamine intravenously immediately before the start of the sequence.

Appendix III

Appendiks til Anne Karliczek, Bjørg Furnes, Frank Pfeffer.
Kartlegging av plager etter endetarmskirurgi.
Tidsskr Nor Legeforen 2016; 136: 212.
Dette appendikset er et tillegg til artikkelen og er ikke bearbeidet redaksjonelt.

Norsk versjon (1.0) av måleinstrument for lav fremre reseksjonssyndrom (Low anterior resection syndrome score, LARS score)

Spørreundersøkelse om tarmfunksjon

Formålet med denne spørreundersøkelsen er å vurdere din tarmfunksjon. For hvert spørsmål skal det kun settes ett kryss. Det kan være vanskelig å velge bare ett svar, siden vi vet at symptomene kan forandre seg fra dag til dag for noen pasienter. Vi ber om at du velger det svaret som best beskriver hverdagen din. Hvis du nylig har hatt en infeksjon som påvirket tarmfunksjonen din, ber vi om at du ikke tar hensyn til dette. I stedet vil vi at du svarer på spørsmålene slik at svarene best mulig gjengir din vanlige tarmfunksjon.

Hender det noen ganger at du ikke kan kontrollere din luftavgang (flatus)?
□ Nei, aldri
□ Ja, sjeldnere enn én gang i uken
□ Ja, minst én gang i uken

Hender det at du har ufrivillig lekkasje av flytende avføring?
□ Nei, aldri
□ Ja, sjeldnere enn én gang i uken
□ Ja, minst én gang i uken

Hvor ofte har du avføring?
□ Mer enn 7 ganger per døgn
□ 4-7 ganger per døgn
□ 1-3 ganger per døgn
□ Sjeldnere enn én gang per døgn

Hender det at du må ha avføring igjen innen en time etter forrige avføring?
□ Nei, aldri
□ Ja, sjeldnere enn én gang i uken
□ Ja, minst én gang i uken

Føler du noen gang så sterk trang til å ha avføring at du må skynde deg til toalettet?
□ Nei, aldri
□ Ja, sjeldnere enn én gang i uken
□ Ja, minst én gang i uken

Appendiks til Anne Karliczek, Bjørg Furnes, Frank Pfeffer.
Kartlegging av plager etter endetarmskirurgi.
Tidsskr Nor Legeforen 2016; 136: 212.
Dette appendikset er et tillegg til artikkelen og er ikke bearbeidet redaksjonelt.

Utregningsmal for skåringsskjemaet for lav fremre reseksjonssyndrom (LARS)

Legg sammen poengene for hvert av de fem spørsmålene til én samlet poengsum.

Hender det noen ganger at du ikke kan kontrollere din luftavgang (flatus)?

□ Nei, aldri	**0**
□ Ja, sjeldnere enn én gang per uke	**4**
□ Ja, minst én gang per uke	**7**

Hender det at du har ufrivillig lekkasje av flytende avføring?

□ Nei, aldri	**0**
□ Ja, sjeldnere enn én gang per uke	**3**
□ Ja, minst én gang per uke	**3**

Hvor ofte har du avføring?

□ Mer enn 7 ganger per døgn	**4**
□ 4-7 ganger per døgn	**2**
□ 1-3 ganger per døgn	**0**
□ Sjeldnere enn én gang per døgn	**5**

Hender det at du må ha avføring igjen innen en time etter forrige avføring?

□ Nei, aldri	**0**
□ Ja, sjeldnere enn én gang per uke	**9**
□ Ja, minst én gang per uke	**11**

Føler du noen gang så sterk trang til å ha avføring at du må skynde deg til toalettet?

□ Nei, aldri	**0**
□ Ja, sjeldnere enn én gang per uke	**11**
□ Ja, minst én gang per uke	**16**

Totalsum:
Tolkning:
0-20: Ingen LARS
21-29: Mild LARS
30-42: Alvorlig LARS