Final report NORWAIT Trial

"Watch and Wait" in patients with complete clinical response (cCR) after neo-adjuvant chemoradiotherapy for primary locally advanced rectal cancer. Open population-based observational study on behalf of the Norwegian Gastro-Intestinal Cancer Group – Colorectal (NGICG-CR)"

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English translation of the final study report submitted on March 6, 2024 to and accepted by the Regional Ethics Committee Western Norway (REK-vest, April 19. 2024). The report adheres to the legal requirements for health research as well as the order by the Norwegian Board of Health Supervision to exclude those patients from outcome analyses that had entered the study in discrepancy with the protocol.

Summary

Background

About 40% of patients with rectal cancer receive preoperative radiotherapy (neoadjuvant treatment) before curative surgery. In 10–15% of these, the tumour is no longer visible on clinical examination (i.e., clinical complete response; cCR). According to the literature, clinical observation in a close follow-up programme, called "Watch and Wait (W&W)", can be an alternative to surgery, which may lead to significant complications and adverse late effects. Around 30% of patients with cCR may have regrowth of the tumour and can then undergo surgery with good results, without increased incidence of metastases. However, this treatment option is not sufficiently documented, and the literature has been characterised by a high degree of selection and varying criteria for the use of neoadjuvant treatment internationally. The NORWAIT study aimed to investigate whether W&W in case of a clinical complete response can be a treatment option for patients with cCR after neoadjuvant treatment in Norway.

Methods

Prospective national cohort study originating from the Norwegian Gastrointestinal Cancer Group Colorectal (NGICG-CR). Inclusion criteria were patients >18 years of age with histologically proven adenocarcinoma in the rectum with cCR after neoadjuvant treatment assessed 6–8 weeks after the end of treatment and reassessed after 12–14 weeks in the case of near-cCR after 6–8 weeks. Patients in W&W were observed in a standardized follow-up programme consisting of clinical examination, endoscopy with imaging, MRI and CEA, as well as standard follow-up for metastases. Clinical assessments were performed every two months in the 1st year, every 3 months in the 2nd year, every six months in the 3rd year, after 4 and 5 years, and then according to national guidelines up to 8 years. The primary endpoint was the regrowth rate in patients with cCR who were followed with W&W, to calculate the positive predictive value of the diagnosis of cCR. Among the secondary endpoints were the rate of metastases and survival. The study was conducted at all Norwegian university hospitals and Kristiansand Hospital Trust.
The study was stopped earlier than planned due to an unexpected high incidence of regrowth combined with metastases at one site. Deviations from the protocol were found at one study site, which led to an inquiry by the Public Health authorities, which concluded that results from this study site could not be used for analysis of results.

Results

97 patients were considered for inclusion, of which 86 were included in the study. Of these, 31 patients were excluded following the decision from the Norwegian Health Authorities, and the remaining 55 included patients form the basis for this analysis. Clinical suspicion of regrowth was found in 32 patients. All underwent surgery, 31 with rectal resection, and one with local removal of the tumour. In 29 of the 32 patients, residual tumour was histologically confirmed, i.e. that 53% of the patients had regrowth. Of the 28 who had a rectal resection performed, 26 had a radical operation (R0).

Nine patients (16%) developed metastases, of which 7 were in combination with regrowth. Five of the patients with metastases had a positive finding of extramural vascular invasion (EMVI) on MRI at the time of primary diagnosis.

Estimated 5-year overall survival was 83.4%, and disease-specific survival was 96%.

Analysis of a similar national cohort with stage I-III rectal cancer who received neoadjuvant treatment followed by surgery showed an incidence of metastases of 26.7%, and among patients without residual tumour in the surgical specimen the incidence was 8.2%. There was a clear association between a positive finding of EMVI at diagnosis and the development of metastases in the national cohort (HR 1.49, 95% CI 1.08 – 2.06), in patients receiving standard surgery after neoadjuvant treatment in the national cohort (HR 2.09, 95% CI 1.29 – 3.40) and in patients in the NORWAIT study (HR 5.58, 95% CI 1.22 – 25.52). There was a lower estimated 5-year overall survival (77%) and disease-specific survival (85%) in the national cohort.

Conclusion

Results from the NORWAIT study show a higher incidence of regrowth (53%) than expected. This may be related to the fact that Norwegian criteria for neoadjuvant treatment are to a greater extent reserved for patients with higher disease stages compared to published studies. Metastases (16%) occurred often in combination with regrowth. There was a significant correlation between a positive finding of EMVI at diagnosis and the occurrence of metastases both in NORWAIT and in the national cohort. The diagnosis of cCR based on clinical examination in combination with MRI imaging seems to have a low diagnostic accuracy. Survival of patients included in the NORWAIT trial was not inferior compared to patients who received standard treatment in Norway during this time period. There is a need for large prospective studies of non-surgical management of rectal cancer.

Final report

Introduction

Surgery for rectal cancer is fundamental for treatment for cure and involves a major surgical intervention in the pelvis. About 40% of patients have their rectum permanently removed (permanent stoma) or perceive significant functional changes of the neorectum after restorative surgery that preserves the anal opening (1). In addition, urinary and sexual function can be affected, which may have a significant impact on quality of life.

Approximately 35–40% of patients considered for curative treatment of rectal cancer need radiotherapy before surgery, often combined with chemotherapy (neoadjuvant chemoradiotherapy, hereafter referred to as "neoadjuvant treatment"), with the aim of reducing the incidence of local recurrence after surgery (2). Neoadjuvant treatment is given according to specific criteria, based on the extent of the tumour, invasion into perirectal tissue, spread to lymph nodes or other risk factors (3). The criteria for neoadjuvant treatment vary between different countries. In some patients, the tumour regresses completely, and a publication with data from the Cancer Registry of Norway has shown that no remnants of tumour tissue were found in 10% of those operated on who had received neoadjuvant treatment, so-called *pathological complete response* (pCR, ypT0N0) (4). In 10–15% of patients, there is no detectable tumour during the clinical evaluation after neoadjuvant treatment, so-called *clinical complete response* (cCR, ycT0). Over the past 20 years, several studies have shown that a subgroup of patients with cCR can avoid an extensive operation, and rather participate in a follow-up programme with regular examinations (5-7). This treatment principle is known as "Watch & Wait" (W&W), or "non-operative management". In this way, the rectum is preserved. If there is regrowth of tumour tissue, the patient is operated on, basically according to the same method as was planned before the observation period.

The objections to organ preserving treatment have been the risk of regrowth and of distant spread, and the assessment of whether the treatment is safe, with comparable outcomes to standard treatment and can be used in a balanced risk-benefit assessment in clinical practice.

The literature on W&W largely consists of selected patient series with uncertain information about the selection and follow-up of the study cohorts (8-10). The studies often have included a relatively high proportion of patients with lower disease stages, and these patients are not given neoadjuvant treatment in Norway. When this study was planned, there was international agreement that W&W should be offered within clinical trials, and W&W was not part of established recommendations (11).

The NORWAIT study investigated whether W&W can be offered as a treatment option to patients with a clinical complete response after neoadjuvant treatment as an alternative to surgery.

Patients and methods

Study population and endpoints

The study was designed by the Norwegian Colorectal Cancer Group, that also served as the trial management group.
The study's main objective was to estimate the proportion of regrowth among patients with locally advanced rectal cancer after neoadjuvant treatment and clinical complete response, in order to calculate the positive predictive value of clinical complete response in a national cohort.

The primary endpoint was the proportion who had regrowth among patients with cCR who followed the W&W protocol after neoadjuvant treatment.

Secondary endpoints were
• the proportion of patients with a clinical complete response after preoperative chemoradiotherapy
• to calculate the diagnostic accuracy of the clinical diagnosis of complete response
• the incidence of metachronous metastases in patients in the W&W program
• the occurrence of metachronous metastases and local recurrence in patients with ypCR
• the overall and disease-specific survival in patients observed in a W&W program and in patients with ypCR after surgery for regrowth
• to estimate the proportion of patients who would otherwise have had a rectal amputation performed
• the health-related quality of life and rectal function with organ-preserving treatment
• to estimate the costs of W&W and of standard surgical treatment
• to examine the diagnostic accuracy of MRI for the diagnosis of cCR.
The study was designed as an open prospective national population-based cohort study and the protocol was approved by the Regional Ethics Committee of Western Norway (REK-vest; reference # 2017/935).

With an assumed incidence rate of 10% pCR in patients after neoadjuvant treatment, and approximately 1000 patients receiving neoadjuvant treatment over a period of 3 years, an inclusion target of 115 patients with cCR was set to be able to calculate the positive predictive value of the clinical diagnosis cCR using figures from the Norwegian Colorectal Cancer Registry.

Definitions

cCR was defined according to the so-called Habr-Gama criteria (5). It involved the absence of visible tumour or ulceration (mandatory), and a whitish color in the bowel wall corresponding to the tumour site or the development of telangiectasia (not mandatory). Patients with incomplete cCR, but more than 75% regression of the tumour were classified as near-complete response, ncCR.

Inclusion and exclusion criteria

Inclusion criteria

• Histologically verified adenocarcinoma in the rectum up to 15 cm from the anal opening measured with a rigid rectoscope
• Neoadjuvant treatment according to the criteria in national guidelines, such as radiotherapy or chemo-radiotherapy (25x2 Gy, at least 40 Gy), or 5x5 Gy with or without systemic chemotherapy (protocol amendment v. 1.2, 2020)
• Age ≥18 years
• Written informed consent
• Stage I-III rectal cancer, or patients with limited spread to the liver and who have had curative resection of metastases without adjuvant chemotherapy

Exclusion criteria were
• Absence of cCR
• Lack of consent competence
• Tumour growth assessed with MRI after neoadjuvant treatment
• Total radiation dose <40Gy for patients with planned CRT 2x25Gy
• Metastatic disease at diagnosis not eligible for resection with curative intent
• Previous malignant disease in the pelvis treated with chemotherapy and/or radiotherapy

Inclusion and follow-up

The study was opened in January 2018 in connection with a national kick-off meeting for all participating hospitals. Neoadjuvant treatment was recommended according to national guidelines. The patients underwent response evaluation 6–8 weeks after the end of neoadjuvant treatment with a new MRI and clinical examination that included digital rectal examination and rectoscopy with a rigid scope, and endoscopic image documentation at inclusion and further follow-up. MRI was evaluated according to the tumour regression grade scale and an assessment of the probability of complete response. The diagnosis of cCR was based on presence of the mandatory criteria, and assessment of MR response at multidisciplinary team meeting (MDT). Patients with cCR were invited to participate in the NORWAIT study and included by two dedicated surgeons at the study site. Patients with ncCR were invited to a new assessment with the same examinations 12–14 weeks after the end of neoadjuvant treatment, with the possibility of inclusion in the study if there was then a cCR. Patients who did not achieve cCR were recommended surgery. Patients in whom rectal exploration or MRI suggested tumour, although otherwise cCR, were offered surgery and included in the study without W&W. CEA was taken at inclusion.

Patients in W&W were followed up in a standardized follow-up programme consisting of clinical examination, endoscopy with imaging, MRI and CEA, as well as standard follow-up for metastases. Clinical assessment was every two months 1st year, every 3 months 2nd year, every six months 3rd year, then with MRI 4th and 5th year, and otherwise according to national guidelines up to 8 years. Study data were collected on a paper-based clinical registration form at each study site. Quality of life and rectal function were recorded in the form of EORTC-QLQ C30 questionnaires and LARS scores, i.e. measurement of rectal function after low anterior resection (12).

Neoadjuvant treatment in Norway during the study period

During the study period 01.01.2018–13.11.2020, 675 patients in Norway received neoadjuvant treatment for rectal cancer, Figure 1. The decision to give neoadjuvant treatment and response evaluation after neoadjuvant treatment was made in multidisciplinary team (MDT) meetings at the institutions. Assessment of clinical response in the Regional Health Authorities of Northern Norway, Central Norway and Western Norway was carried out at four university hospitals. At the Regional Health Authorities of Southern and Eastern Norway, patients at the Hospital of Southern Norway Hospital Kristiansand were offered neoadjuvant treatment and assessed for cCR locally. The other patients in that health region were assessed for neoadjuvant treatment at Oslo University Hospital Ullevål (OUS) with MDT meetings at Ullevål Hospital and the Norwegian Radium Hospital. Response evaluation was carried out at local hospitals or at OUS. The Norwegian Radium Hospital followed its own routine for response evaluation 4 weeks after the end of neoadjuvant treatment, and 166 of 339 (49%) patients in the South-Eastern region were selected for surgery at this hospital without assessment of cCR. The remaining patients were eligible for assessment for inclusion in NORWAIT. The process for evaluation after neoadjuvant treatment and assessment for possible inclusion in the NORWAIT study was thus handled nationally in different ways, with the possibility of a selection bias in the South-Eastern health region.

Course of the study and cessation of inclusion

In October 2020, one study site reported a higher incidence of regrowth in combination with metastases than expected. This led to the decision to stop inclusion, before the inclusion target was reached, as well as to an internal review of study data being carried out. This suggested a possible connection between tumour characteristics that indicated more aggressive disease (N1c [tumour deposits in the mesorectum], EMVI [extramural vascular ingrowth]) and regrowth/metastases.

A local monitoring of the inclusion was also carried out at each hospital, which revealed deviations from the study protocol at the study site which had reported a higher incidence of regrowth combined with metastases. This triggered an inquiry by the Norwegian Board of Health Supervision. A consequence of the supervisory case was that patient data from the relevant study site cannot be used for analysis of results together with results from the other institutions.

The Norwegian Colorectal Cancer Group in consultation with PI and the coordinating Hospital Trust decided the termination of the study, and to conclude with a final report as required by legislation. The Regional Ethics Committee set the requirement to apply a scientific format for the final report.

Analysis of study data

The final report was designed in accordance with STROBE guidelines for observational studies (13).
The inclusion and exclusion process are shown step-by-step by description of clinical characteristics for the entire study cohort that was assessed for inclusion, the group that was included in the study, and the remaining group for the final report after

exclusion in accordance with the decision of the Norwegian Health Authorities. This study cohort forms the basis for analysis of the results of the study's objectives.
The study's primary endpoint, proportion with regrowth and calculated positive predictive value of cCR in a national cohort with cCR after neoadjuvant treatment, cannot be answered, as the study was stopped before the inclusion target of 115 participants was reached and after exclusion of one study site. This analysis therefore focuses on the following endpoints:

- The regrowth rate after neoadjuvant treatment
- Occurrence of metachronous metastases in patients in the W&W programme
- Overall and disease-specific survival in patients in W&W and in patients with ypCR after surgery for regrowth

In addition, possible relationships between defined outcomes and clinical characteristics are analysed.

The results are also put into a national context with analyses of a patient cohort who received standard treatment with curative surgery after neoadjuvant treatment for rectal cancer stage I-III in the time from 2015–2022. Data are shown for the occurrence of metastases and disease-specific and total mortality. The same analyses were also performed for patients who had no residual tumour in the surgical specimen (ypT0N0).

The information was recorded by local project investigators at six of the seven participating study sites in an electronic database (Viedoc®), based on variables from the paper-based registration form and predefined variables for MR responses. Any ambiguities in the data set were clarified with the relevant project staff who carried out corrections in the Viedoc database. Aggregated information necessary for describing the inclusion and exclusion process was obtained from the study site that was excluded from the results analysis. MRI variables at primary diagnosis were used in the analysis as a basis for deciding on neoadjuvant treatment. MRI results for evaluation after neoadjuvant treatment were not reassessed by an independent radiologist and may be subject to a significant margin of error and were therefore only used descriptively.

The work on the final report was carried out by the Primary investigator in collaboration with representatives from the Norwegian Colorectal Cancer Group. Statistical analyses of study outcomes were done by a statistician at the Cancer Registry of Norway.

Statistical methods

Clinical variables were described using usual descriptive methods, including median and min-max for continuous variables and frequency distribution for categorical variables. Follow-up time was described using the median and interquartile range (IQR). Chi-square test was used to assess differences between categorical variables. To assess differences between continuous variables, the Mann-Whitney test was used based on a non-parametric distribution. Cumulative incidence was estimated using the Aalen-Johansen estimator which takes competing events into account. When estimating the cumulative incidence of death from rectal cancer, death from other causes was treated as a competing event. When estimating outcomes other than death, death regardless of cause was treated as a competing event. A possible relationship

between clinical and pathological EMVI and risk of distant metastases was estimated by univariable and multivariable Cox regression models. The multivariable models were estimated with the aim of adjusting for potential confounding effects of patient gender and age, in addition to tumour height and clinical TNM stage. P-values <0.05 were considered statistically significant. All analyses were performed in STATA version 18.0 and SPSS version 29.

Results

Inclusion and exclusion

During the study period, 97 patients were assessed for cCR, and 86 patients were included. Of these, 31 patients were excluded in accordance with the Norwegian Health Authority's decision, and the remaining 55 patients form the cohort for analysis of results (Figure 2). Patient and tumour characteristics and their distribution when assessed for cCR (n=97), inclusion (n=86) and after exclusion (n=55) are described in Table 1. After exclusion, there was a significantly higher proportion of males (p =0.044), a higher proportion with low comorbidity (ASA 1; p=0.014), and a lower proportion with tumours in the upper part of the rectum (p=0.044) in the patient group in the South-Eastern Health region compared to the other regions. Two study participants wanted to limit the follow-up to fewer controls during the study, without formally withdrawing from the study. The patients were followed about various outcomes (regrowth, metastases, death) until 30/06/2023, which gives a potential follow-up period of 66 months for those who were included the earliest and 32 months for those who were included last.

Neoadjuvant treatment of the study cohort

Neoadjuvant treatment and MRI findings at evaluation after neoadjuvant treatment are described in Table 2. Most patients, 48 of the remaining 55, received chemoradiotherapy. About a third were included after the first assessment 6–8 weeks after the end of treatment. All patients were followed up according to the protocol. Patients who were operated on for regrowth were followed up in accordance with national recommendations for follow-up.

Regrowth

In 32 of 55 patients in the W&W follow-up there was a clinical suspicion of regrowth. All underwent surgery, of whom 31 with a formal resection of the rectum and one with transanal endoscopic microsurgery (TEM), Table 3A and Figure 3. Twenty-nine patients (53%) had histologically proven residual tumour tissue, median time 4.7 months (IQR: 2.5–8.1) after inclusion. In 3 of those operated on, no residual tumour was found (ypT0N0). A radical resection (R0) was achieved in 26 of 28 patients with rectal resection, and two had signs of microscopic residual tumour (R1). Abdominoperineal resection was performed in 19 patients, and low anterior resection in 12 patients. There was no statistically significant relationship between the occurrence of regrowth and patient or tumour characteristics at diagnosis. Two patients had a local recurrence after R0 resection for regrowth.

Table 3B shows tumour characteristics at diagnosis in the remaining 23 patients with sustained clinical complete response (ycT0) at last observation and in 3 with pCR after

surgery for suspected regrowth (ypT0N0), and correspondingly for 176 patients with ypT0N0 in the national cohort. Based on coding practices in the national Colorectal Cancer Registry and/or lack of reporting, the figures cannot be compared directly.

Metastases

Nine patients (16%) developed metastases, median time 14.7 months (IQR: 6.3–31.3) after inclusion, Figure 4. Seven of nine patients (78%) developed metastases in combination with regrowth, 5 synchronous and 2 metachronous, while two participants had metastases without detection of regrowth. Localization of metastases and relation to clinical characteristics are indicated in Table 4a.

Survival

Five-year overall survival, or the probability of being alive after 5 years, was 83.4% (95% CI 68.9–91.6). The probability of dying from rectal cancer during the first 5 years was estimated at 4.0% (95% CI 0.8–12.2), corresponding to a 5-year disease-specific survival rate of 96%. The probability of dying from other causes in the same period was estimated at 11.6% (95% CI 4.9–24.1), corresponding to a 5-year disease-free survival of 88.4%. Thus, most of the deaths were related to causes other than rectal cancer.

National background figures and the study cohort

The cancer registry extracted a national cohort consisting of patients who received neoadjuvant treatment for rectal cancer stage I-III followed by resection with curative intent in the period 2015–2022, which corresponds to standard treatment for cure of rectal cancer in need of neoadjuvant treatment (Figure 5 and Table 5). Of 1655 patients with stage I-III who received neoadjuvant treatment and surgery, 176 (10.6%) had a pathological complete response (ypT0N0). The figures form the basis for national figures for the occurrence of metastases and mortality, and thus constitute background information for outcomes in the NORWAIT cohort.

Figure 6a shows the cumulative incidence of metastases up to 5 years in patients operated on for rectal cancer after neoadjuvant treatment. In the national cohort, the probability of metastases at 5 years was 26.7% for patients in stages I-III (95% CI 24.1–29.4). For patients with a pathological complete response, the probability was 8.2% (95% CI 3.8–14.7). In the NORWAIT cohort, the probability of metastases at 5 years was 17.4% (95% CI 8.5–28.9). Figure 6b shows the mortality related to cancer in the study cohort and national cohort, and Figure 6c mortality related to other causes in the study cohort and in the national cohort. While cancer-related mortality in the national cohort was significantly higher than mortality from other causes, mortality in the NORWAIT cohort was mainly related to causes other than rectal cancer.

From the NORWAIT cohort, Figure 7a shows the occurrence of metastases in relation to a positive finding of EMVI at diagnosis, while Figure 7b shows mortality from rectal cancer and Figure 7c mortality from other causes in relation to a positive finding of EMVI at diagnosis. Of 9 patients who developed metastases, 5 had a positive finding on EMVI at diagnosis and had metastases in combination with regrowth. Four of these developed metastases during the first year.

Figure 8 shows estimates for the occurrence of metastases and mortality in the national cohort stratified for clinical EMVI status at diagnosis. Figure 9 shows corresponding estimates for patients in the national cohort based on histological diagnosis after surgery. Multivariable analysis showed that patients with a positive EMVI status at the time of diagnosis had a significantly higher risk of developing metastases both in the national cohort and in the NORWAIT cohort, Table 4b. There was no significant correlation between other clinical characteristics and the development of metastases.

Discussion

This final report is a scientific analysis of 55 patients who met the requirement of the protocol after exclusion of 31 patients in accordance with decisions made by the Norwegian Health Authorities and regional Ethics Committee. It follows the STROBE guidelines to satisfy scientific requirements for reporting cohort studies in a transparent manner (13) and gives a thorough account of patients who were assessed for inclusion, patients who were included, and the patient group that remained for analysis of results after exclusion, with corresponding changes in the composition of patient characteristics in this process (STROBE statement). Characteristics and results from these 55 patients are described in more detail in this report (Table 1). The results are based on a total number that is significantly lower than what was calculated to be necessary to answer the primary endpoint, and the results described are thus based on small numbers with correspondingly wide confidence intervals. Care must therefore be taken when interpreting findings.

One of the secondary endpoints was incidence of cCR. Assessment for inclusion in the study was handled according to different routines for patient flow in the South-Eastern Health Care region than in the other regions (Figure 1). This very likely results in a selection bias, and the number of included patients cannot be used as a basis for any estimate of the incidence of cCR.

The proportion of patients who were diagnosed with regrowth was higher than expected based on the available literature when the study was planned. All patients with suspected regrowth were operated on according to protocol, and 29 out of 32 operated on had histologically confirmed tumour tissue in the surgical specimen. This higher proportion of regrowth may be due to the fact that patients who, according to national guidelines, are eligible for neoadjuvant treatment and thus eligible for inclusion in a W&W programme, had a higher disease stage compared to the stage distribution in published studies describing W&W. This literature has essentially been based on cohorts from individual institutions (14) or international databases with a heterogeneous composition of patients and a relatively higher proportion of patients with earlier disease stages, and without available information to assess selection (10). This report, however, gives an account of the entire Norwegian patient population who received neoadjuvant treatment during this period as the backdrop for the interpretation of the results, and the proportion of patients included and followed with W&W in the NORWAIT trial (Figure 1).

The higher incidence of regrowth than expected suggests that the clinical assessment of clinical complete response is uncertain, even when it is also based on MRI findings and CEA as described in the protocol. Recent literature suggests that there are large differences between how clinicians assess clinical complete response based on endoscopic images (15). Moreover, response to neoadjuvant treatment is also an important factor, and Hole et al (16) showed in a material from the Norwegian Radium Hospital that response evaluation after neoadjuvant treatment can overestimate tumour regression, as there may be remaining islands of tumour cells in irradiated tissue. This may have been a contributing factor to the higher incidence of regrowth in the NORWAIT cohort, where the patients had more advanced disease than in other publications (10).

There was an unexpectedly high incidence of metastases in the analysed study cohort compared to other published studies on W&W (10), or in patients with histologically proven pathological complete response (4). In seven of the nine patients who developed metastases, it occurred synchronous in combination with regrowth. The analysis showed that the occurrence of extramural vascular ingrowth (EMVI) at the time of diagnosis was an independent risk factor for the development of metastases (Table 4a and b). This connection between EMVI and risk of metastases was also shown in national data for patients who were operated on after neoadjuvant treatment (Figures 8 and 9). This may indicate that there are other factors than the primary treatment of the tumour that are linked to the development of metastases. The prognostic significance of EMVI was unclear when the study was planned, but EMVI has now subsequently been established as a predictor of metastatic disease (17, 18). Current guidelines recommend more intensive chemotherapy in the primary treatment of EMVI-positive disease (19). The relationship between EMVI and risk of metastases also came to light in the national review of preliminary study results after stopping inclusion. In a more recent ongoing study for organ-preserving treatment of rectal cancer at an early stage, EMVI is an exclusion criterion (20). It remains to be seen to what extent new treatment algorithms can contribute to reducing the proportion of patients who develop metachronous metastases after radical treatment for rectal cancer.

Smith et al (21) published a retrospective cohort of patients with cCR in a W&W program, and patients with pCR. There was regrowth in 22 of 113 patients in the W&W program, and 8 (36%) of them developed metastases. The authors hypothesize that a subgroup of patients with cCR may have a more aggressive tumour biology with an increased risk of metastases, suggesting that local tumour response and the potential for distant spread are two independent biological processes. This observation seems to coincide with findings in the NORWAIT cohort.

In another American publication of the W&W approach in patients with a clinical complete response and who did not want operative treatment, Beard et al (22) describe a correlation between a high incidence of metastases and residual tumour manifestations in the mesorectum with only endoscopically diagnosed cCR after neoadjuvant treatment ("unaddressed mesorectal disease"), but without further definition of this term. This suggests that MRI can provide important additional information for assessment of cCR, even though MRI diagnostics after neoadjuvant treatment can also have relatively poor diagnostic accuracy (23).

The clinical diagnosis of complete response after neoadjuvant treatment still appears difficult. Several studies show the importance of tumour biological factors. El Sissy et al (24) found agreement between the immune response in tumour tissue and the effect of neoadjuvant treatment. Future studies of the W&W approach for patients with cCR after neoadjuvant treatment as part of a curative treatment goal should probably be based on other diagnostic assessments/criteria in addition to visual assessment of clinical complete response and MRI findings.

Survival in the NORWAIT cohort was apparently higher than in the dataset national from the national cohort with standard treatment (Figure 6b+6c). Most deaths in NORWAIT were related to causes other than rectal cancer, and the disease-specific survival in NORWAIT was better than in the national cohort.

This final report shows that the patients who were included in the NORWAIT study had a higher incidence of regrowth than expected. All patients suspected of regrowth were operated on according to protocol. This may indicate that the clinical assessment of complete response has greater uncertainty than previously thought, and there is a need for comprehensive assessment including better biomarkers to assess clinical complete response after neoadjuvant treatment for locally advanced rectal cancer. The incidence of metastases was higher than expected and appeared to be related to tumour-biological factors. It does not appear that survival was worse in NORWAIT than in patients who received standard treatment in Norway during this period.

Whether organ preserving treatment of rectal cancer with cCR after neoadjuvant treatment can be a good treatment option, and for which patient group, is still an important question. It is also actualized by newer treatment methods such as immunotherapy for selected patient groups (25). To answer this question, large prospective studies are needed with better selection of patients based on a broad assessment of risk factors, better criteria for assessing cCR, and optimal follow-up of the patient group.

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Legend to figures

Figure 1

Flow diagram for 675 patients who received neoadjuvant treatment for stage I-III rectal cancer for cure in Norway, with distribution across the four healthcare regions. In the Southern and Eastern region, 49% of irradiated patients were selected for surgery at the Radium Hospital without assessment for complete clinical response after completion of treatment.

Figure 2

Flow chart for inclusion in the NORWAIT study. Of 97 assessed patients, 86 were included for follow-up with the Watch & Wait program. Of these, 31 patients were excluded as decided by the Norwegian Health Authorities, and the remaining 55 patients represent the study cohort for analysis of results.

Figure 3

Cumulative incidence of histologically proven regrowth of primary tumour in 29 out of 55 patients with clinical diagnosis of complete response after neoadjuvant treatment for rectal cancer among included in the Watch & Wait program.

Figure 4

Cumulative incidence of metastases in 9 out of 55 patients observed in the W&W program after clinical diagnosis of complete response after neoadjuvant treatment for rectal cancer.

Figure 5

Flow diagram for description of national cohort with neoadjuvant treatment and curative surgery for rectal cancer in stages I-III in the period 2015–2022.

Figure 6

Incidence of metastases (6A), cancer-related mortality (6B), and mortality from other causes (6C) for patients operated on for rectal cancer in a national cohort (blue line; cTNM I-III), with pathological complete response (red line, cTNM I-III, ypT0N0) and in the NORWAIT cohort (black line, n=55).

Figure 7

Incidence of metastases (7A), cancer-related mortality (7B), and mortality from other causes (7C) for 55 patients included in the W&W program after presumed clinical complete response stratified by clinical EMVI status at diagnosis (blue line, cEMVI negative; red line, cEMVI positive).

Figure 8

Incidence of metastases (8A), cancer-related mortality (8B), and mortality from other causes (8C) in national cohort stratified by clinical EMVI status at diagnosis (cEMVI; blue

line, cEMVI negative; red line, cEMVI positive). cEMVI was reported to the Cancer Registry for 812 out of 1655 patients.

Figure 9

Incidence of metastases (9A), cancer-related mortality (9B), and mortality from other causes (9C) in national cohort stratified by pathologic EMVI status (pEMVI; blue line, pEMVI negative; red line, pEMVI positive). pEMVI was reported to the Cancer Registry for 442 out of 1655 patients.

Participating institutions

Stavanger University Hospital
Stavanger, Norway
Coordinating institution

University Hospital of North Norway
Tromsø, Norway

St. Olavs hospital
Trondheim University Hospital
Trondheim, Norway

Haukeland University Hospital
Bergen, Norway

Kristiansand Hospital Trust
Kristiansand, Norway

Oslo University Hospital
Oslo, Norway

Akershus University Hospital
Lørenskog, Norway

Cancer Registry of Norway
Oslo, Norway

Table 1

Demographic and clinical characteristics of patients evaluated for inclusion (n=97), included to the W&W programme (n=86), and after exclusion of 31 patients (n=55), and the eventual changes of distribution of the various characteristics.

	Evaluated for inclusion N=97	**Inclusion to W&W** N=86	**After exclusion** N=55
Patient characteristics			
Sex			
Males	65	59	37[a]
Females	32	27	18
Age, median (min-max)	68 (38–85)	67 (38–85)	66 (41–85)
ASA			
1	55	52	30[b]
2	27	22	17
3	12	9	7
Missing	3	3	1
ECOG			
0	80	72	46
1	11	8	7
2	4	4	2
Missing	2	2	0
Tumour characteristics			
CEA median (min-max)	2.5 (0–67)	2.6 (0–67)	3 (0–28)
Tumour level			
Lower (0–5 cm)	48	42	30[c]
Mid (6–10 cm)	38	34	20
Upper (>10 cm)	10	9	5
Missing	1	1	0
Clinical T-stage			
T1/2	16	15	12
T3a/b	53	46	30
T3c/d	17	15	6
T4a	5	5	4
T4b	6	5	3
Clinical N-stage			
N0	42	39	27
N1	25	22	18
N2a+b	17	12	10
Missing[d]	13	13	0
N1c positive	20	18	5
EMVI positive	32	18	11
Distance to MRF[e], mm, median (min-max)	0 (0–25)	0 (0–25)	0 (0–6)
Clinical M-stage			
M0	95	84	53
M1[f]	2	2	2

[a] Significantly higher proportion of males in Regional Health Authority Southern-Eastern, p=.044 (after exclusion of 31 patients):

	South-East	Other regions	Total
Males	23	14	37
Females	6	12	18
Total	29	26	55

[b] Significantly higher proportion of patients with ASA 1 - status in South-Eastern Health Region, p=.014 (after exclusion of 31 patients)

	South-East	Other regions	Total
ASA 1	21	9	30
ASA 2	4	13	17
ASA 3	4	3	7
Unknown	0	1	1
Total	29	26	55

[c] Significantly higher proportion of patients with lower tumour level in South-Eastern Health Region: 0 tumours in upper rectum vs. 5 in the regions outside uptake area of the Norwegian Radium, p=.044 (after exclusion of 31 patients)

	South-East	Other regions	Total
Lower	18	12	30
Mid	9	11	20
Upper	0	5	5
Total	29	26	55

[d] 13 patients reported as N1c positive only, and without information on N1-2

[e] Mesorectal fascia

[f] Surgical resection of metastatic disease for cure

Table 2

Details on neoadjuvant treatment given and MR evaluation after end of neoadjuvant treatment, for all included patients (n=86) and the remaining 55 patients after exclusion of 31 patients. MRi examinations have not been reviewed by independent radiologists, and outcomes are shown for descriptive, but not analytical purposes.

	At inclusion N=86	**After exclusion** N=55
Chemoradiotherapy,2 Gy x 25	72	48
Radiotherapy 5 Gy x 5 + chemotherapy	3	2
Radiotherapy 5 Gy x 5	7	4
Radiotherapy 2 Gy x 25	4	1
Clinical yT-stage[f]		
T0	40	34
T1/2	20	13
T3a/b	19	6
T3c/d	4	1
T4a	1	1
T4b	1	0
Unknown	1	0
Clinical yN-stage		
N0	72	50
N1	11	4
N2a+b	0	0
Unknown	3	1
Clinical yN1c		
Positive	1	1
Clinical yEMVI		
Positive	6	1
Unknown	2	1
Tumour regression grade (TRG) based on MR[g]		
1	37	33
2	29	16
3	13	3
4	3	0
Unknown	4	3
Time of inclusion		
6–8 weeks	37	17
12–14 weeks	49	38
Time periods, days; median (min-max)		
Diagnosis to inclusion	134 (188–224)	139 (100–220)
Duration of neoadj. treatment	34 (5–123)	35 (5–123)
End of treatment to inclusion	67 (38–149)	74 (38–149)

[f] Prefix y indicates clinical staging after neoadjuvant treatment

[g] TRG 1 – radiological complete response

TRG2 –no residual tumour or regrowth likely

TRG3 – uncertain residual or regrowth of tumour

TRG4 – residual tumour or regrowth likely

TRG5 – radiological evidence of residual tumour/regrow

Table 3A

Clinical characteristics of patients with tumour regrowth. Thirty-two of 55 patients had clinical findings indicating regrowth. Of those, 31 underwent rectal resection and one patient had an R0 transanal endoskopic microsurgery (TEM) procedure. In 29 patients, regrowth was histologically proven, and 3 patients had no evidence of regrowth (ypT0N0). Results are shown for patients with rectal resections. There were no significant associations between clinical characteristics and regrowth.

	ypT+ N=28	**ypT0N0** N=3
cT-stage at diagnosis		
T1/2	7	0
T3a/b	15	1
T3c/d	2	0
T4a	2	2
T4b	2	0
cN- stage at diagnosis		
N0	15	1
N1	8	1
N2	5	1
N1c- stage at diagnosis		
Positive	1	0
EMVI- stage at diagnosis		
Positive	6	0
Tumour level		
Lower	17	1
Mid	8	0
Upper	3	2
Distance to MRF[h]		
<2 mm	25	3
>2 mm	3	0
Operation for regrowth		
Low anterior resection	10	2
Abdomino-perineal excision	18	1
Radikality of procedure		
R0	26	-
R1	2	-

[h] MRF=mesorectal fascia

Table 3B

Tumour characteristics of 26 patients at diagnosis included in NORWAIT trial with sustained clinical (n=23, ycT0Nx[i]) or pathological complete response (n=3, ypT0N0), and in 176 patients in a national cohort who underwent rectal resection for stadium I-III after neoadjuvant treatment with pathological complete response (ypT0N0). Due to the coding practice applied by the Cancer Registry of Norway and/or incomplete reporting subgroups for cT3 are not reported, and the figures for N1c- og EMVI-status may be incomplete. Accordingly, the national data should be seen as background information and direct comparisons with study data should not be made.

	ycT0/ypT0N0 N=26	**ypT0N0 national cohort** N=176
cT-stage		
T1/2	5	32
T3a/b	14	102[h]
T3c/d	4	-
T4a	2	20
T4b	1	22
cN- stage		
N0	11	65
N1	10	66
N2	5	42
N1c- stage[i]		
Positive	4	7[k]
EMVI- stage		
Positive	5	35[l]
Tumour level		
Lower	12	71
Mid	12	73
Upper	2	20
Unknown	0	12
Distance to MRF		
<2 mm	21	120
>2 mm	5	18
Ukjent	0	38

[i] ycN-stage uncertain in patients with sustained clinical response and thus unavailable histological data.

[h] cT3 stage reported without subgroups by the Cancer Registry of Norway

[k] Patients with both tumour deposits and lymph node metastases are coded as N1-2-a or N1-2b by the Registry. Consequently, the reported N1c value is likely to be incomplete. N1c-stage was negative or unknown in 169 patients.

[l] EMVI is not recorded if cN = 0. EMVI was negative or unknown in 141 patients.

Table 4A
Clinical characteristics associated with the occurrence of distant metastases in patients in the W&W programme with clinical complete response after neoadjuvant treatment for rectal cancer.

	Antall N=9	**p-verdi**
Site of metastases		-
Liver	2	
Lung	3	
Others/multiple	4	
cT-stage at diagnosis		.480
T1/2	1	
T3a/b	6	
T3c/d	2	
T4a	0	
T4b	0	
cN- stage at diagnosis		.183
N0	2	
N1	4	
N2	3	
N1c- stage at diagnosis		.184
Positive	2	
EMVI- stage at diagnosis		.011
Positive	5	
Tumour level		.078
Lower	2	
Mid	5	
Upper	2	
Distance to MRF		.604
<2mm	7	
MR-regression grade		.588
1	5	
2	2	
3	1	
4	0	
5	0	
Unknown	1	
Metastases combined with regrowth		
Yes	7	.193

Table 4B

Uni- and multivariable analysis of EMVI as risk factor for metastatic disease in the study cohort.

As backdrop information for study outcomes, the estimates for the risk based on clinical preoperative EMVI-status and pathological EMVI-status in surgical specimens reported to the Cancer Registry of Norway (CRN) in 2015-2022.

	Univariable		**Multivariable***	
	HR (95% CI)	**p-verdi**	**HR (95% CI)**	**p-verdi**
NORWAIT	7.95 (2.12–29.85)	0.002	5.58 (1.22–25.52)	0.027
CRN: clinical EMVI +	1.46 (1.07–1.98)	0.017	1.49 (1.08–2.06)	0.015
CRN: pathological EMVI +	2.05 (1.29–3.25)	0.002	2.09 (1.29–3.40)	0.003

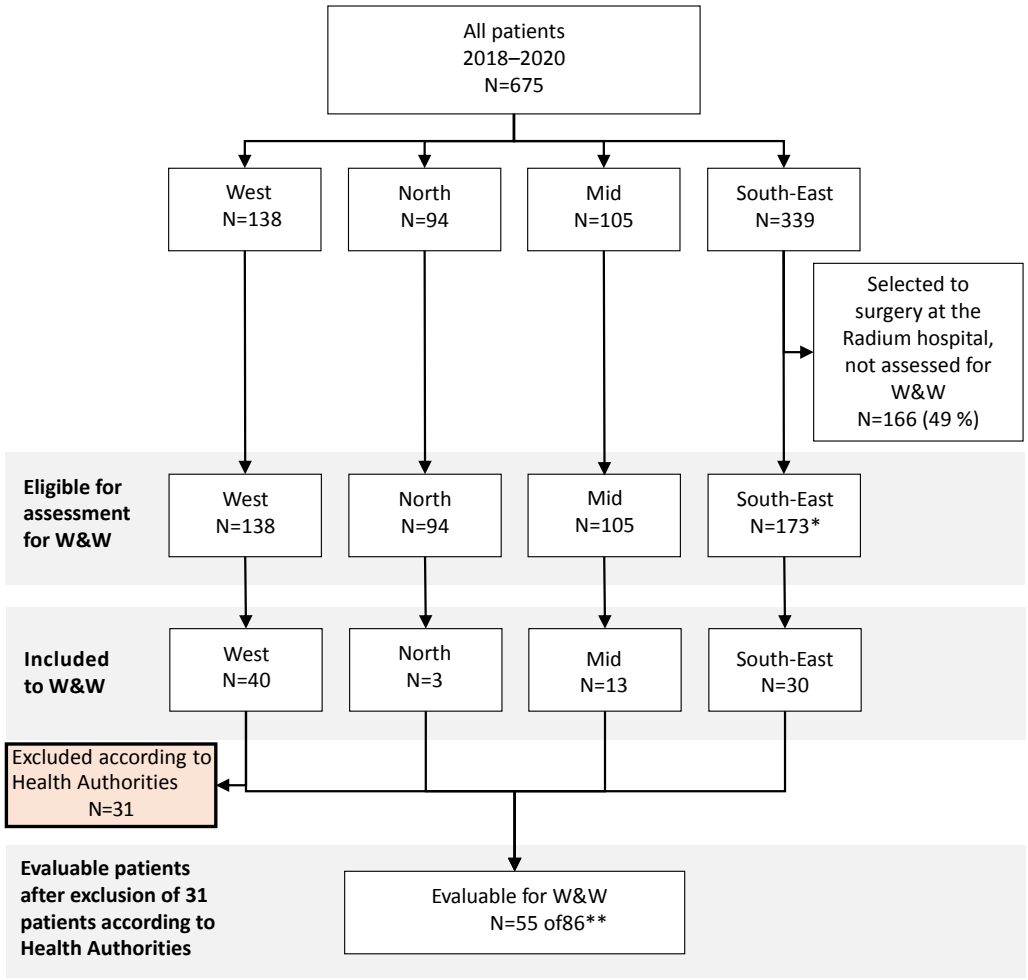
*Adjusted for age, sex, cTNM and tumour level

Table 5
Clinical Characteristics of 1655 patients who were operated on for stage I-III rectal cancer after neoadjuvant treatment in Norway in 2015–2022.

	CRN cTNM I–III N=1655
Age, median (IQR)	67 (58–74)
	n (%)
Sex	
Females	669 (40.4%)
Males	986 (59.6%)
cTNM	
I	94 (5.7%)
II	499 (30.2%)
III	1062 (64.1%)
ASA	
1	134 (8.1%)
2	960 (58.0%)
3	452 (27.3%)
4	21 (1.3%)
Unknown	88 (5.3%)
ECOG	
0	1002 (64.7%)
1	395 (25.5%)
2	58 (3.7%)
3	14 (0.9%)
4	2 (0.1%)
Unknown	79 (5.1%)
Tumour level	
Lower	638 (38.6%)
Mid	577 (34.9%)
Upper	254 (15.4%)
Unknown	186 (11.1%)

Figure 1

Flow diagram for 675 patients who received neoadjuvant treatment for stage I-III rectal cancer for cure in Norway, with distribu on across the four healthcare regions, i.e., regions of Northern, Mid, Western and South-East Norway . In the South-eastern region, 49% of irradiated patients were selected to surgery at the Radium Hospital without assessment for complete clinical response after completion of treatment.

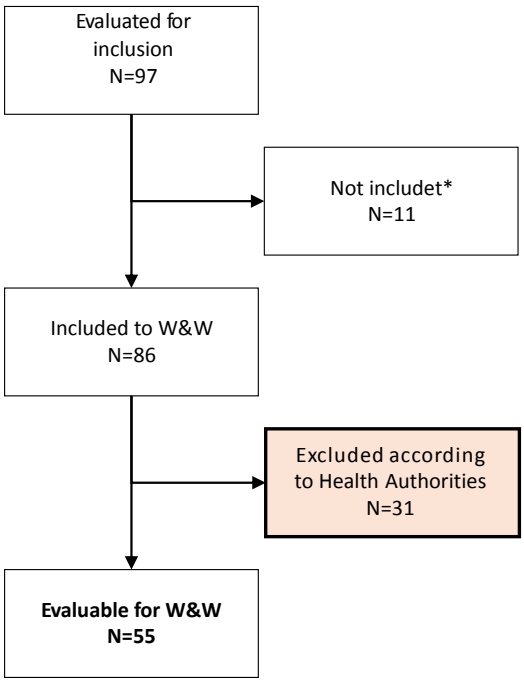


* In the South-Eastern Health region 173 of 339 (51 %) patients were eligible for inclusion. The remaining 166 were selected to surgery at the Radium Hospital without assessment for W&W

**115 estimated as target for inclusion for analysis of primary endpoint

Figure 2

Flow chart for inclusion in the NORWAIT study. Of 97 assessed patients, 86 were included for follow-up with the Watch & Wait program. Of these, 31 patients were excluded as decided by the Norwegian Health Authorites, and the remaining 55 patients represent the study cohort for analysis of results.



* Ten out of 11 patients did not have clinical complete response, and og 1 patient with assumed did not wish to participate

Figure 3

Cumulative incidence of histologically proven regrowth of primary tumor in 29 out of 55 patients with clinical diagnosis of complete response after neoadjuvant treatment for rectal cancer among included in the Watch & Wait program.

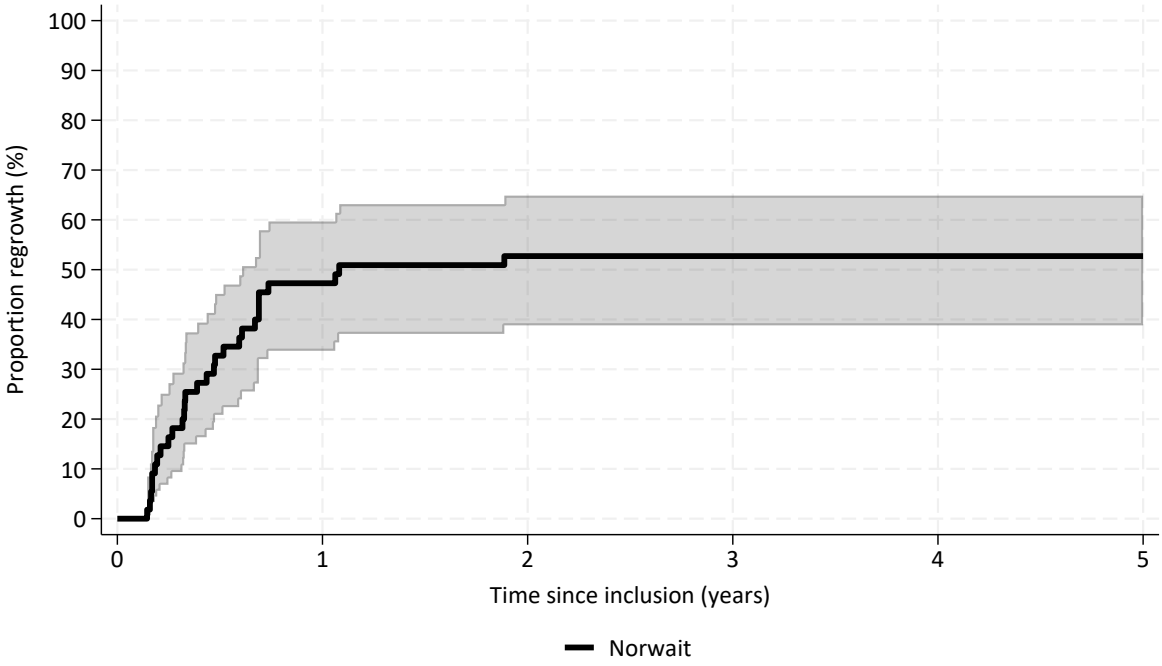


Figure 4

Cumulative incidence of metastases in 9 out of 55 patients observed in the W&W program after clinical diagnosis of complete response after neoadjuvant treatment for rectal cancer.

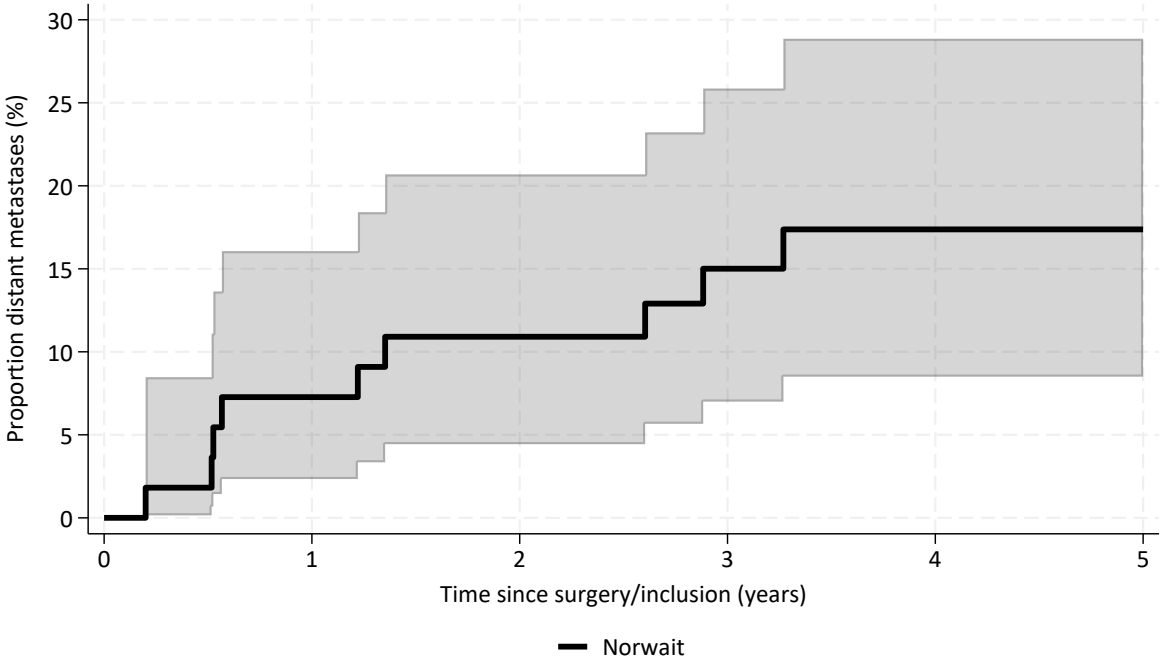


Figure 5

Flow diagram for description of national cohort with neoadjuvant treatment and curative surgery for rectal cancer in stages I-III in the period 2015–2022.

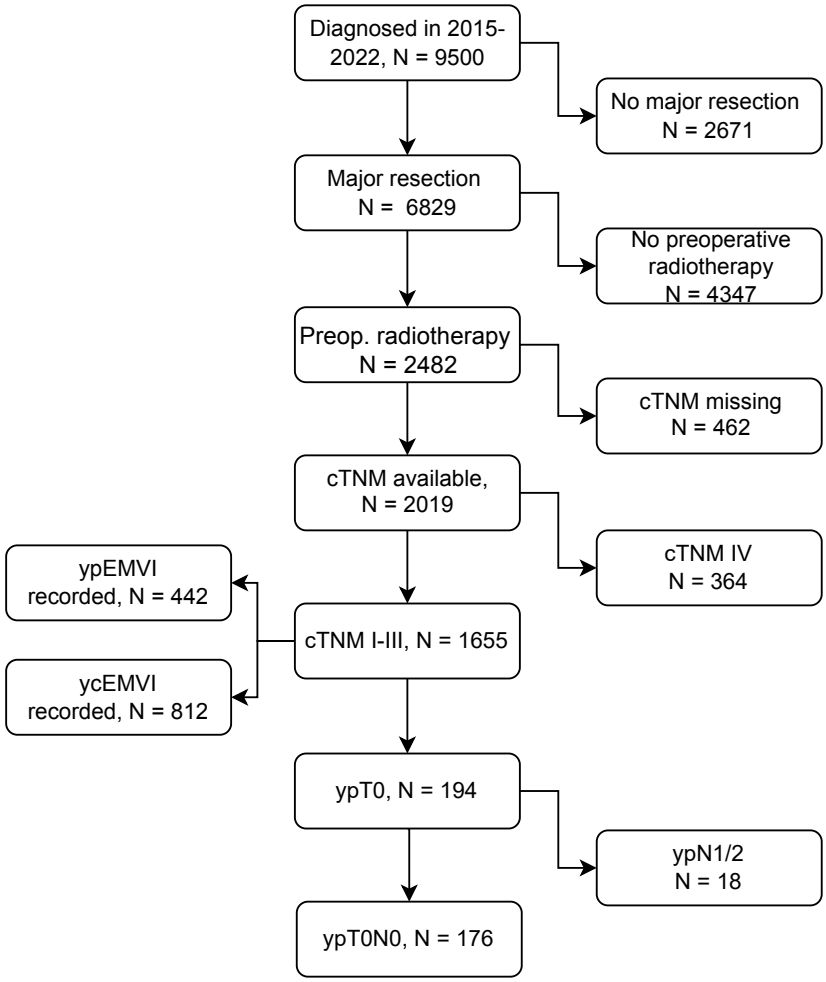


Figure 6

Incidence of metastases (6A), cancer-related mortality (6B), and mortality from other causes (6C) for patients operated on for rectal cancer in a national cohort from the Cancer Registry of Norway (CRN) (blue line; cTNM I-III), with pathological complete response (red line, ypT0N0) and the NORWAIT cohort (black line, n=55).

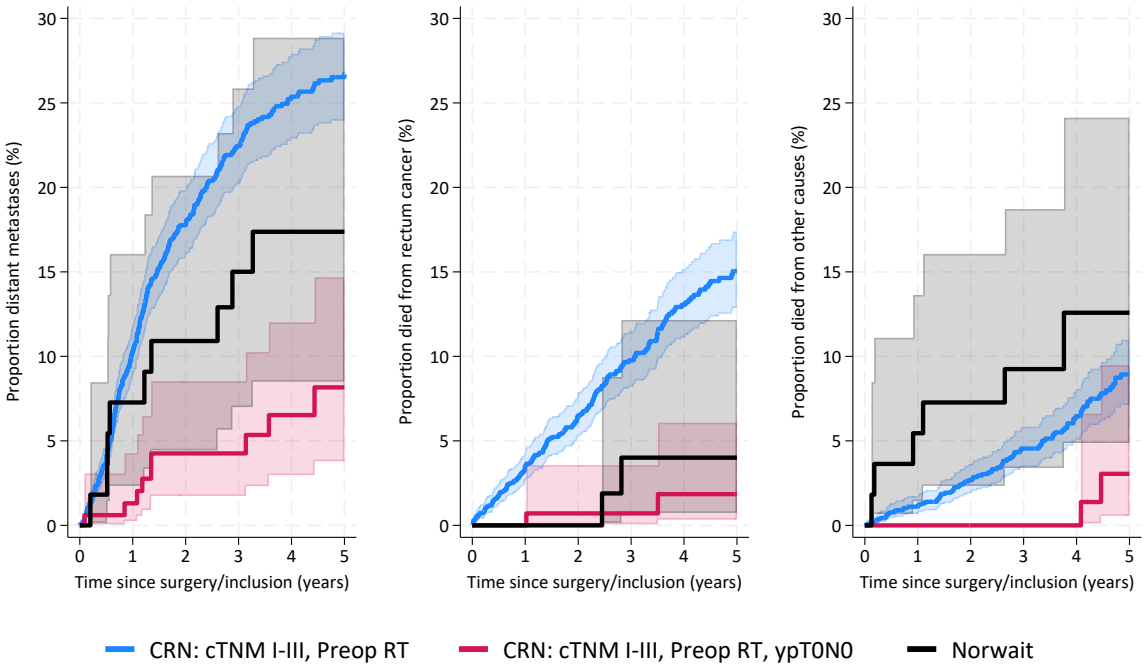


Figure 7

Incidence of metastases (7A), cancer-related mortality (7B), and mortality from other causes (7C) for 55 patients included in the W&W program after presumed clinical complete response stratified by clinical EMVI status at diagnosis (blue line, cEMVI negative; red line, cEMVI positive).

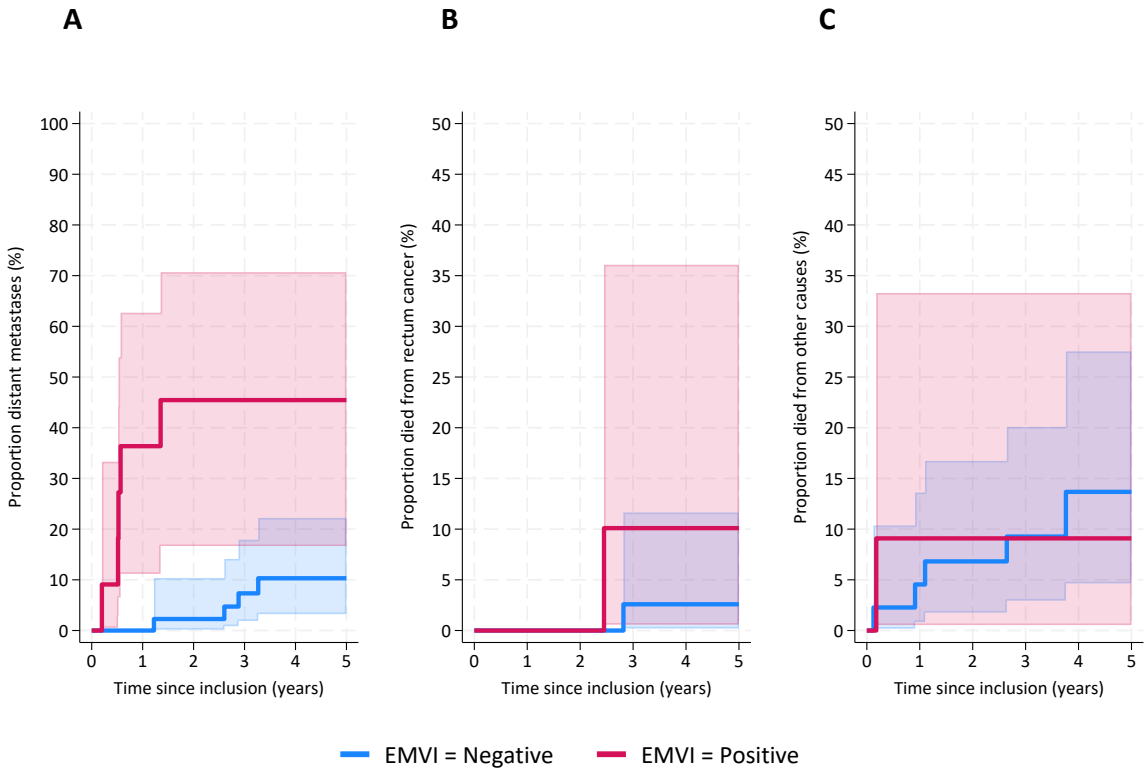


Figure 8

Incidence of metastases (8A), cancer-related mortality (8B), and mortality from other causes (8C) in national cohort stratified by clinical EMVI status at diagnosis (cEMVI; blue line, cEMVI negative; red line, cEMVI positive). cEMVI was reported to the Cancer Registry for 812 out of 1655 patients.

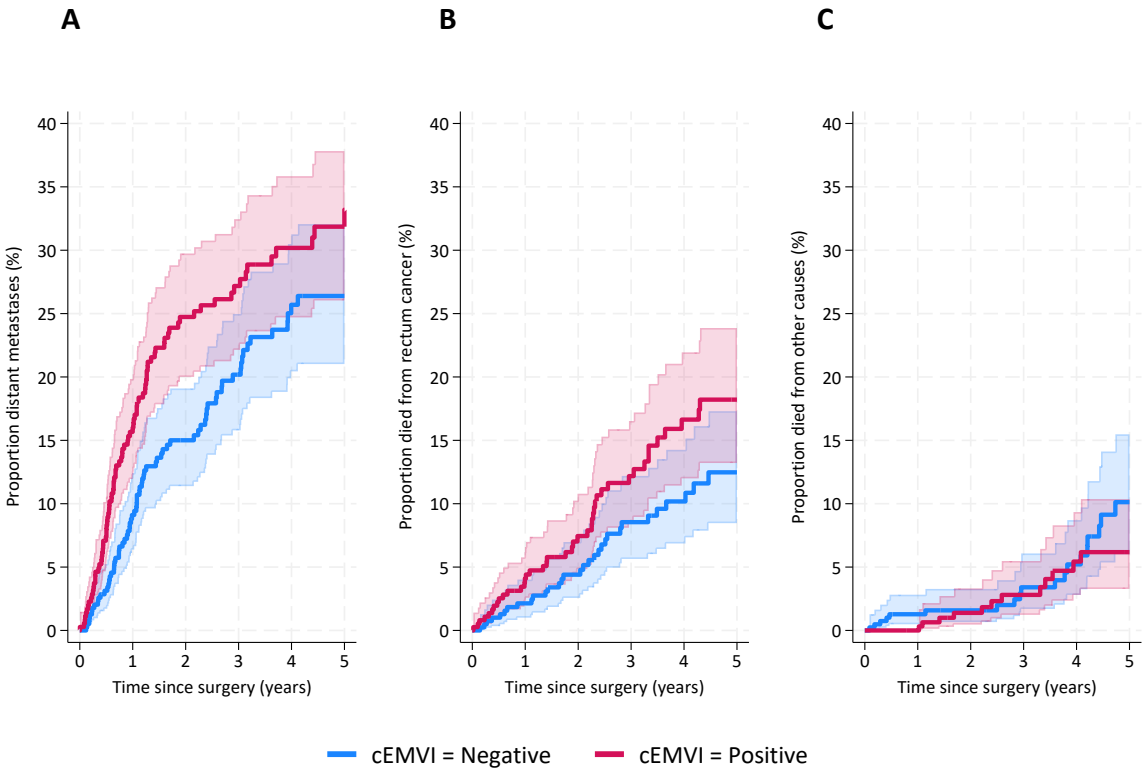
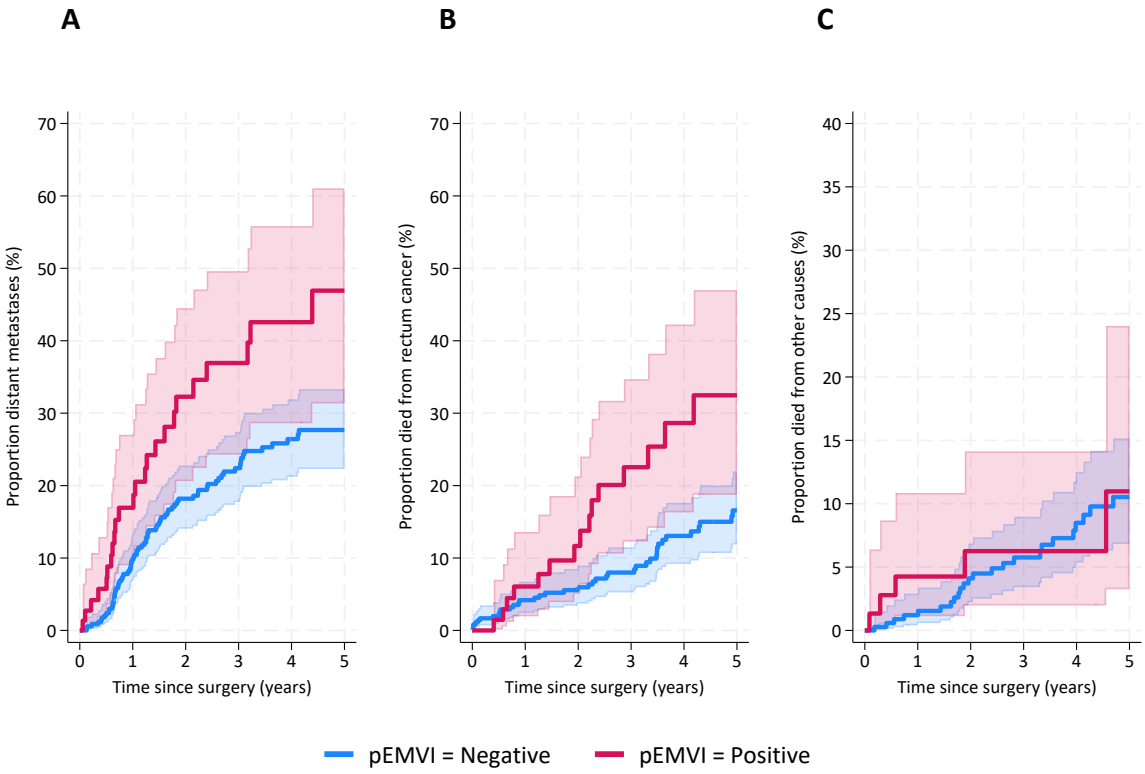


Figure 9

Incidence of metastases (9A), cancer-related mortality (9B), and mortality from other causes (9C) in national cohort stratified by pathologic EMVI status (pEMVI; blue line, pEMVI negative; red line, pEMVI positive). pEMVI was reported to the Cancer Registry for 442 out of 1655 patients.



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract *The title provides the required information*
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found *The abstract provides the required information*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported *Explained on page 4*
Objectives	3	State specific objectives, including any prespecified hypotheses *Explained on page 4*
Methods		
Study design	4	Present key elements of study design early in the paper *See section "Pasienter og metode"; National prospectice unselected cohort study.*
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection *See section "Pasienter og metode" with subheadings*
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. *Criteria for in- and exclusion are presented on page 5*
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed *n.a.*
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable *See information on these items on page 6*
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group *Variables for analysis of the Norwait study cohort are clearly described based on the study protocol and CRF, including criteria for assessment of clinical complete response. Variables describing the national cohort drawn from the cancer Registry of Norway are separately described. These two cohorts are analysed and described separately without direct comparisons.*
Bias	9	Describe any efforts to address potential sources of bias *Sources of bias are described in Figure 1 and Table 1. The exclusion process of 31 patients from one study site is described in a separate section on page 7/8.*
Study size	10	Explain how the study size was arrived at *See Figure 1 and 2*
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why *See subheading on statistics in the section "Pasienter og metode". Variables describing the national cohort drawn from the cancer Registry of Norway are separately described. These two cohorts are analysed and described separately without direct comparisons, according to item 8.*
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding *See subheading on statistics in the section "Pasienter og metode".*
		(*b*) Describe any methods used to examine subgroups and interactions

		See subheading on statistics in the section "Pasienter og metode".
		(*c*) Explain how missing data were addressed *The dataset of the Norwait cohort is 100% complete.*
		(*d*) If applicable, explain how loss to follow-up was addressed *n.a.*
		(*e*) Describe any sensitivity analyses *n.a.*
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed *See Figure 1 and 2, and Table 1*
		(b) Give reasons for non-participation at each stage *See Figure 1 and section "Resultater" on page 8*
		(c) Consider use of a flow diagram *Flow diagrams are provided (Figure 1 and 2)*
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders *These characteristics are given for the respective cohorts in Table 1, 2 and 5*
		(b) Indicate number of participants with missing data for each variable of interest *n.a.*
		(c) Summarise follow-up time (eg, average and total amount) *Follow-up time is summarised by median of months and interquartile range.*
Outcome data	15*	Report numbers of outcome events or summary measures over time *See results section and Tables 3 and 4, and Figures 3, 4, 6, 7, 8 and 9*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included *See Table 4 b and results section*
		(*b*) Report category boundaries when continuous variables were categorized *These are reported for tumor level in the rectum and distance to mesorectal fascia (Table 1)*
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period *n.a.*
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses *n.a.*
Discussion		
Key results	18	Summarise key results with reference to study objectives *Key results are discussed, se pages 10-13*
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias *Types and sources of bias are clearly discussed*
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence *These aspects are discussed in the results section*
Generalisability	21	Discuss the generalisability (external validity) of the study results

		The issues affecting external validity are part of the discussion section.
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based *The study was economically supported by the Folke Hermansens Fund (https://www.folke-fondet.org), grant # 424519.*

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.