Chemoradiation and Consolidation Chemotherapy with or without oxaliplatin for distal rectal cancer and Watch and Wait. A multi-center prospective randomized controlled trial. (CCHOWW)

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Abstract:

Background: Neoadjuvant chemoradiation (nCRT) has been considered the preferred initial treatment strategy for distal rectal cancer. Advantages of this approach include improved local control after radical surgery but also the opportunity for organ preserving strategies (Watch and Wait - WW). Consolidation chemotherapy (cCT) regimens using fluoropyrimidine-based with or without oxalipatin following nCRT have demonstrated to increase complete response and organ preservation rates among these patients. However, the benefit of adding oxaliplatin to cCt compared to fluoropirimidine alone regimens in terms of primary tumor response remains unclear. Since oxalipatin-treatment may be associated with considerable toxicity, it becomes imperative to understand the benefit of its incorporation into standard cCT regimens in terms of primary tumor response. The aim of the present trial is to compare the outcomes of 2 different cCT regimens following nCRT (fluoropyrimidine-alone versus fluoropyrimidine+oxaliplatin) for patients with distal rectal cancer.

Methods: In this multi-centre study, patients with magnetic resonance-defined distal rectal tumors will be randomized on a 1:1 ratio to receive long-course chemoradiation (54Gy) followed by cCT with fluoropyrimidine alone versus fluoropyrimidine+oxaliplatin. Magnetic resonance (MR) will be analyzed centrally prior to patient inclusion and randomization. mrT2-3N0-1 tumor located no more than 1cm above the anorectal ring determined by sagittal views on MR will be eligible for the study. Tumor response will be assessed after 12 weeks from radiotherapy (RT) completion. Patients with clinical complete response (clinical, endoscopic and radiological) will be enrolled in an organ-preservation program (WW). The primary endpoint of this trial is decision to organ-preservation surveillance (WW) at 18 weeks from RT completion. Secondary endpoints are 3-year surgery-free survival, TME-free survival, distant metastases-free survival, local regrowth-free survival and colostomy-free survival.

Discussion: Long-course nCRT with cCT is associated with improved complete response rates and may be a very attractive alternative to increase the chances for organ-preservation strategies. Fluoropyrimidine-based cCT with or without oxaliplatin has never been investigated in the setting of a randomized trial to compare clinical response rates and the possibility of organ-preservation. The outcomes of this study may significantly impact clinical practice of patients with distal rectal cancer interested in organ-preservation.

Keywords: rectal cancer, consolidation chemotherapy, oxaliplatin, Watch and Wait, organ preservation

Introduction

Significant tumor response to neoadjuvant chemoradiation (nCRT) therapy has resulted in a dramatic change in distal rectal cancer management.[1] Observation of near-complete and complete tumor response to treatment has led surgeons to consider organ-preservation strategies to avoid the need for radical surgery. [2-5] Patients that achieve clinical complete response (cCR) defined by clinical, endoscopic and radiological criteria have been managed non-operatively and enrolled in a strict surveillance program (Watch and Wait – WW) with acceptable oncological outcomes.[6-9] These patients would ultimately avoid the risk of immediate postoperative morbidity and mortality in addition to the potential negative consequences of urinary, sexual and anorectal function frequently seen after total mesorectal excision (TME).[10-12] In addition, patients managed by WW would avoid the need for a temporary/definitive stoma – particularly relevant among patients with distal tumors.[13] In this latter group of patients, abdominal perineal resections (APR) with a definitive stoma or intersphincteric resections (ISR) with poor postoperative function are the surgical alternatives.[14,15]

Ultimately, organ-preservation has become an attractive alternative for patients with distal rectal cancers where APR or ISR are the radical surgical alternatives. In this setting, several attempts have been made to increase chances for achieving a clinical complete response and allowing for the opportunity of entering an organ-preserving pathway.[16] Several treatment-related features may affect complete tumor regression rates to neoadjuvant strategies in rectal cancer. [17-19] There is data to suggest that specific characteristics of both radiation and chemotherapy may influence complete tumor regression rates. Data provided from multiple studies using different radiation doses in rectal cancer suggests that there is an increase in complete response rates as total doses increase.[18] Radiosensitizing chemotherapy may also affect response rates to neoadjuvant treatment strategies. Incorporation of additional chemotherapy following radiation completion (consolidation chemotherapy) has also shown to significantly increase complete clinical and pathological response rates.[16,19-21] However, none of these studies were specifically designed to compare different radiosensitizing (or consolidation) chemotherapy regimens. Regimens including exclusively 5FU-based or 5FU + oxaliplatin regimens have been used in different studies using consolidation chemotherapy after CRT completion suggesting higher rates of pCR or cCR compared to historical cohorts.[19] However, there has never been a head-to-head comparison between 5FU-based alone versus 5FU-oxaliplatin in consolidation regimens. Earlier studies attempting to incorporate concomitant oxaliplatin into standard CRT regimens failed to demonstrate benefits in pCR rates while did result in excessive toxicity associated with the use of oxaliplatin.[22] However, when offered in a consolidation regimen, oxalipatin could potentially decrease its associated toxicity while effectively providing significant increase in response rates. For these reasons, we aimed to compare the outcomes of fluoropyrimidine-only consolidation chemotherapy to fluoropyrimidine + oxaliplatin in achieving a cCR after nCRT in this prospective randomized clinical trial.

Patients and Methods

Patients with distal rectal cancer will be eligible for the study after initial clinical, endoscopic and radiological assessment. At this point, patients will be offered to participate in the study and after informed consent, randomized to control or experimental arms as follows.

Eligibility and Inclusion Criteria

Patients will be eligible in the presence of the following inclusion criteria:

1. Age ≥18 years;
2. ECOG 0-2 or KPS≥70;
3. Primary rectal adenocarcinoma (biopsy confirmed) within the reach of digital rectal examination (at least lower tip/border) by the attending colorectal surgeon;
4. Endoscopic documentation;
5. Abdominal and chest CT scans showing no evidence of metastatic disease;
6. High-resolution magnetic resonance images performed at either 1.5T or 3.0T system using a phased array surface coil with: sagittal T2 images including the anal verge and the sacrum; axial oblique T2 weighted images acquired in a plane perpendicular to the long axis of the rectal wall guided by the sagittal images; coronal images acquired in parallel to the anal canal plane. Small field of view (16-18cm), 3mm section thickness, increased matrix size and increased number of signal averages are required;
7. Radiological defining criteria (centralized):
    a. Lower edge of tumor at the level (max. 1cm distance) or below the anorectal ring defined at sagittal or coronal views;
    b. mrT2, mrT3 (any subclassification)
    c. mrN0-1 (≤3 radiologically positive lymph nodes)
    d. mrEMVI: any status
    e. mrMRF: any status

Exclusion criteria:

1. Pregnancy
2. ECOG ≥3 or KPS<70
3. Unwilling to consent
4. Metastatic disease (any kind; internal iliac and obturator nodes are considered local disease and not metastatic disease and therefore will not be considered as exclusion criteria)
5. mrT4 or mrN2
6. Previous pelvic irradiation
7. Baseline neuropathy
8. Receiving treatment of other anti-cancer drug or methods
9. Presence of uncontrolled life threatening diseases

Endpoints

Primary endpoint: Decision to Watch and Wait due to clinical complete response achieved at 18 weeks from last date of radiation using clinical (DRE), endoscopic and radiological criteria (mrTRG grade) or near-complete clinical response (no progressive disease clinically, endoscopically or radiologically)

Definition of clinical complete response (cCR) available below and at the discretion of the attending surgeon.

Definition of radiological complete response as described below (centralized).

Patients will be counted as event if at 18 weeks the decision is to interrupt Watch and Wait and proceed to surgery (any kind) because of overt incomplete clinical response. In order to standardize assessment of response and reduce inter-observer variability, the decision to continue on Watch and Wait (or not) will be at the discretion of the central committee during central revision of studies.

Secondary endpoints:

- Surgery-free survival at 3 years
- TME-free survival at 3 years
- Distant metastases free survival at 3 years
- Local regrowth-free survival at 3 years
- Colostomy-free survival at 3 years

Definitions

Definition of cCR:

- Endoscopic: white scar, teleangiectasia, absence of ulceration and/or mass [6]
- Clinical: no irregularity, firm area with minor induration[6]
- Radiological: mrTRG1: fibrosis with low signal intensity seen on T2 weighted images replacing the primary tumor; no restricted diffusion on diffusion weighted images; no nodes with border irregularity or mixed signal intensity; no extramural vascular invasion[23-26]

Definition of near-complete response:

- Endoscopic: residual tumor size ≤2cm (or reduction of ≥70% original tumor volume/size) [4,27,28]
- Clinical: only superficial ulceration or minor (questionable) irregularities of the mucosal/rectal wall
- Radiological: mrTRG2 predominant fibrosis with low signal with foci of intermediate tumor signal intensity seen on T2 weighted images with or without restricted diffusion; mrTRG1: fibrosis with low signal intensity seen on T2 weighted

images replacing the primary tumor with restricted diffusion; no nodes with border irregularity or mixed signal intensity; no extramural vascular invasion [27]

Central Committee

The central committee is multidisciplinary group of surgeons, medical oncologists and radiologists previously appointed at the beginning of the recruitment of patients and with previous experience with organ preservation.[2, 21] This group of specialist will be responsible to assess the baseline staging and define if the patients fulfill all the inclusion/exclusion criteria prior to randomization. The committee will also be responsible to evaluate the endoscopic and radiological tumor re-assessment studies at 12 and 18 weeks from radiation completion. The definition to continue on the Watch and Wait pathway or not will be at the discretion of this committee.

Technical aspects of assessment tests:

Suggested MR protocol:

1.5T - FRFSE; TR/TE: 3300/120 (ms); slice thickness/gap: 3.0/0; Matrix: 256 x 256; NSA 8)
3.0T – FRFSE; TR/TE: 8000/150 (ms); slice thickness/gap: 3.0/0; Matrix: 288 x 288; NSA 5)
DWI – inclusion of a high b-value of at least 800

Suggested Endoscopic assessment:

Endoscopic assessment using a flexible scope (gastroscope preferred for retroflexion); direct endoscopic and retroflexion view of the primary tumor/scar; endoscopic biopsies at discretion of participating center.

Treatment arms

1) RT (54Gy) plus daily concomitant capecitabine 825mg/m2 bid, followed by mFOLFOX6 **or** XELOX for 4 cycles (12 weeks), starting 1 week after radiotherapy ended;

2) RT (54Gy) plus daily concomitant capecitabine 825mg/m2 bid, followed by capecitabine 2000mg/m2/day for 14 days in a 21 days cycle for 4 cycles (12 weeks), starting 1 week after radiotherapy ended;

Radiotherapy

Preoperative radiotherapy will be delivered on a linear accelerator in prone or supine position, preferably with full bladder. The use of a belly board is allowed.

Isocentric 3 or 4 fields, as well as an IMRT technique is allowed, as long as all beams are treated on a daily basis. The dose distribution and calculation should be performed on CT or MRI and specified according to the ICRU 50 guidelines.

Dose specification: All patients will receive 25 daily fractions of 1.8 Gy up to a total dose of 45 Gy to the pelvic field including the tumor bed with a margin and the regional lymph nodes. A field reduction after 45 Gy is recommended up to 54 Gy. The last 5 fractions will then be given to the tumor bed with a margin.

Target volume:
Pelvic CTV

- The primary tumor
- Mesorectum: Distally, only lymph nodes or tumor deposits up to 4 cm are included. For tumors in lower rectum this means that the entire mesorectum down to the pelvic floor is included.
- Presacral nodes and nodes along the rectal superior artery: Since local recurrences are very unusual above S1 – S2, lymph nodes above this level should not be included unless there are signs of radiologically positive lymph nodes presacrally. If this is the case, the cranial limit of CTV should be at least 1 cm above the most cranial radiologically positive lymph node.
- Lateral lymph node stations: Until they reach the level of the obturator canal Internal iliac artery up to the bifurcation from the external iliac artery. The cranial border for the CTV is in most cases just below the bifurcation of the internal and external iliac arteries. In most patients this is at the level of S1 – S2.
- Ischio-rectal fossa and the anal canal: Included in pelvic CTV only if the tumor grows into the levators or down into the anal canal.
- Lymph nodes along the external iliac artery: Included if the tumor grows into anterior organs like the prostate, urinary bladder, cervix, vagina or uterus to such an extent that the external nodes are at risk for metastases.

Boost GTV:
GTV is the visible primary tumor and radiologically positive lymph nodes.
CTV boost:
GTV boost plus a margin of 2 cm within the same anatomical compartment as the tumour is in, for the dose of 45 Gy, also around radiologically engaged lymph nodes.

PTV:
The above description relates to the CTV. A PTV should normally be defined and includes CTV and internal target volume (ITV) and a margin necessary for the setup. These margins are depending upon several factors that are related to the equipment at each radiotherapy center.

Chemotherapy Protocols

Concomitant chemotherapy:

Concomitant capecitabine: 825mg/m2 bid on the radiotherapy days only

Consolidation chemotherapy:

1. Consolidation capecitabine (alone): 1000mg/m2 bid, for 14 days, in a 3 week cycle, for 4 cycles
2. Consolidation options with oxaliplatin:
   2.1. mFOLFOX6: Oxaliplatin 85mg/m2 plus Leucovorin 400mg/m2 on a concomitant 2 hours infusion. 5FU 400mg/m2 on a bolus infusion, followed by 5FU 2400mg/m2 in 46 hours infusion, every 2 weeks, for 6 cycles
   2.2. CAPOX: Oxaliplatin 130mg/m2 on a 2 hours infusion. Capecitabine 1000mg/m2 bid daily, for 14 days, starting on the evening of the oxaliplatin infusion. Repeat every 3 weeks, for 4 cycles

Toxicities

Chemotherapy toxicity and dose adjustment:

Dose reduction is planned in case of severe haematological and/or non haematological toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTC, version 5.0. Treatment will be delayed until: neutrophils ≥1.5 x 109 /L and platelets ≥75 x 109 /L.

1) 5FU dose-modification:

Recovery from mucositis, diarrhea If 5-FU treatment is delayed, then the associated oxaliplatin dose should also be delayed. If 5-FU is discontinued permanently, oxaliplatin should also be discontinued. If toxicity requires a dosing delay of more than four weeks, the subject will be permanently withdrawn from the study treatment for toxicity. Dose modifications for hematologic or GI toxicity will be based on the worst toxicity observed during the previous cycle. After recovery, standard dose adjustments for 5-FU toxicity should be applied. The dose of 5-FU should be reduced by 20% in subsequent cycles for the following toxicities: febrile neutropenia,

grade 4 thrombocytopenia, or failure of hematological recovery to neutrophils ≥1500 /μL and platelets ≥75000/μL within 2 weeks of the scheduled start of the next treatment cycle; grade 3-4 mucositis, diarrhea, or nausea or vomiting in spite of optimal antiemetic prophylaxis. In the mFOLFOX6 protocol, the bolus 5FU should be interrupted before the aforementioned reduction of the continuos infusion 5FU. A second dose reduction of 5-FU of 20% from the original dose may be made if the above toxicities recur. After reductions of doses, they should not be increased again and must be carried on to the rest of the treatment.

2) Capecitabine:

Patients with a creatinine clearance of 30-50 mL (min must commence treatment with CAPE at 75% of the full dose. Dose modifications for hematologic, skin or GI toxicity will be based on the worst toxicity observed during the previous cycle. After recovery, standard dose adjustments for capecitabine toxicity should be applied. The dose of capecitabine should be reduced by 25% in subsequent cycles for the following toxicities: febrile neutropenia, grade 4 thrombocytopenia, or failure of hematological recovery to neutrophils ≥1500 /μL and platelets ≥75000/μL within 2 weeks of the scheduled start of the next treatment cycle; grade 3-4 mucositis, hand-foot syndrome, diarrhea, or nausea or vomiting in spite of optimal antiemetic prophylaxis.

3) Oxaliplatin;

If a second dose reduction of 5FU is performed, oxaliplatin dose must also be reduced by 25%. Oxaliplatin neurotoxicity should be assessed before every oxaliplatin dose. If neurotoxicity is grade 3, oxaliplatin dose should be reduced by 25%. If toxicity is grade 4, oxaliplatin should be discontinued permanently. For oxaliplatin infusion reactions grade 2 or less occur, oxaliplatin can have its infusion time extended until 6 hours and the patient must receive pre medications such as H1 antagonists, H2 antagonists and corticosteroids. If it recurs or is graded 3 or more, oxaliplatin administration must be suspended. Where it is available, desensitization protocols can be applied, 5FU may continue even if oxaliplatin is discontinued.

RT Toxicity and Stopping Rules

Toxicity will be assessed and recorded according to the CTCAE v4.0 acute radiation morbidity scoring criteria.

Table: Stopping rules for radiotherapy during chemoradiation

Adverse event	Definition	Action
Diarrhea	Grade 4	should be interrupted until the treatment-related symptoms have been reduced and parental support is no longer necessary
Other gastro-Intestinal toxicity	Grade 4	should be interrupted and restarted according to the patients' condition

CTC v 4.0
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40

Assessment of Response

Assessment of response will be performed at 12 weeks (and 18 weeks from last date of radiation therapy if cCR or near-complete response is detected at 12 weeks). All patients will undergo endoscopic reassessment, DRE and high-resolution MR. Endoscopic biopsies will be at the discretion of the attending surgeon/endoscopist.
Patients with complete or near-complete clinical response at 12 weeks will be recommended reassessment at 18 weeks from RT. Patients with clinically overt incomplete clinical response at 12 or 18 weeks will be referred to immediate radical surgery.

Randomization

Individuals will be randomized and allocated at a 1:1 ratio to the two groups (control and experimental) using a permuted block design with a random block size of 4, 6, and 8. (1-3)
A randomization list will be generated electronically using appropriate software immediately after being considered eligible.

Protocol Blinding

Patients and attending phisicians will not be blinded to the treatment arm randomized for each patient. However, as a strategy to reduce investigator's expectations and reduce inherent bias, the central committee will be blinded to the treatment arm. It is expected that blinding the central committee, who will be responsible for assessing the primary endpoint, any bias related to the investigator's expectation about the treatment arm and the chances of Watch and Wait will be nulled.

Sample size calculation

The primary endpoint (decision to WW due to cCR/near CR) was observed in 55% and 85% at 12 weeks (in contrast to the 18 weeks used in the present trial) among patients with early cT3 and cT2 rectal cancer respectively.[29] In this study, there was a distribution of 66% of cT3 and 33% cT2. Therefore, response rates appear to be highly dependent on exact T-stage distribution. Considering the expected inclusion of more advanced disease (late mrT3 or even mrT4 rectal cancers) we expect 40% cCR/near-CR in the control arm. A similar difference 60% versus 40% was achieved in the preliminary report of the outcomes of the OPRA trial. This difference in TME-free survival at 3 years was statistically significant favoring patients undergoing nCRT with cCT in comparison to nCRT preceeded by induction chemotherapy (both regimens incorporating oxaliplatin). In this setting, if experimental results in ≥60% cCR/near-CR, the study will be considered POSITIVE. The incorporation of oxaliplatin to a consolidation CRT regimen that results in ≥20% increase in cCR/near-CR exceeds the potential disadvantages of treatment-related toxicity.

The investigators will assume that the primary outcome will occur in 40% of individuals in control group and 60% in the experimental group, which corresponds to an absolute difference in proportions of 20%. It is estimated that a sample of 194 (97 per group) provides 80% statistical power to detect this difference at a significance level of 5% using the Chi-square test and assuming a two-sided significance hypothesis and considering a 1:1 allocation. The estimated dropout rate is 10% in each group, so it is expected to include 216 individuals (108 per group). The sample size calculation was performed using SAS 9.4 (PROC POWER procedure).

Time-table

Patient accrual: 2 years and 6 months
Patient/institution/year: 5-6 (20 institutions: 100-120/year – 2 years n=200-240)

Interim analysis:

If the arm of two drugs during consolidation shows ≥25% response rate after 72 patients, study will be interrupted (efficacy). If the arm of two drugs shows less than 5% response rate after 72 patients, the study will be interrupted.

Discussion

Complete primary tumor regression has become a relevant endpoint in rectal cancer management. Achievement of a complete clinical response to neoadjuvant treatment strategies has provided the opportunity to avoid major abdominal surgery, its associated morbidity and the requirement for temporary or definitive stomas. Long-term data suggests that nearly 70% of patients who achieve a cCR will never require radical surgery.[5,8,9] In addition, in 30% of these patients that develop local regrowth salvage resection is successful in the vast majority of patients leading to excellent local disease control and survival.[7,30]

In this setting, changes in neoadjuvant treatment regimens may now be driven by the attempt to increase response rates. Most studies at this point, presented nearly 25% cCR rates among centers practicing WW and using standard CRT regimens similar to the experimental arm of the German trial (2 cycles of 5FU-based chemotherapy).[9] In this setting, several treatment alternatives have been investigated in order to improve response rates to allow for organ-preservation. Initial retrospective studies (before introduction of total neoadjuvant therapy concept - TNT) suggested that the inclusion of additional chemotherapy agents (in addition to 5FU/fluoropyrimidines and concomitant to RT) to nCRT regimens would significantly increase pCR rates.[17] Oxaliplatin was the most common additional chemotherapy agent added to 5FU. Unfortunately, subsequent randomized clinical trials failed to demonstrate significant increases in pCR rates when oxaliplatin was added to standard nCRT regimens. Instead, a significant increase in treatment related toxicity was observed.[22]

A single phase 2 study was performed using additional cycles of bolus 5FU aimed at improving cCR (instead of pCR) rates.[16,21,29] This study incorporated 4 additional cycles of bolus 5FU infusion (to the usual 2 cycles) to be delivered during RT but also during the "resting" period. Surprisingly, cCR rates were nearly 50% of all patients treated including tumors with baseline T2/T3 rectal cancer. While the increase in cCR rates could have been attributed to the increase in number of cycles of chemotherapy delivered during and after RT completion ("consolidation" chemotherapy even though not named as such at the time), one additional change in the regimen could have also contributed to the increase in cCR rates: RT dose escalation was also incorporated to this nCRT regimen (50.4Gy to 54Gy). Therefore, it became impossible to establish a direct cause-effect relationship between cCR rates and consolidation chemotherapy or RT dose-escalation.

Another prospective non-randomized study also suggested the potential effects of consolidation chemotherapy to response in rectal cancer. The "timing" trial included patients with locally advanced disease into 4 different arms (sequentially, not randomized).[20,31,32] The primary objective of the study was to investigate progressive longer interval periods between RT completion and surgery in response: 6, 12, 18 and 24 weeks. However, patients included in the 12, 18 and 24 received consolidation chemotherapy with mFOLFOX (2,4 and 6 cycles respectively) resulting in significant increases in pCR rates (pCR 25%, 30% and 38% respectively) compared to no consolidation chemotherapy (pCR 18%). Again, while the increase in pCR rates could have

been attributed to the increase number of chemotherapy cycles (consolidation), the effect of prolonged intervals in time could also have contributed to this observation.

Finally, with the introduction of the TNT concept – providing adjuvant chemotherapy immediately before nCRT (induction) or after nCRT (consolidation), initial experiences (using FOLFOX as consolidation) suggested an increase in complete response and in the chances of organ preservation among these patients.[33] One prospective randomized study (OPRA) presented the preliminary outcomes of the comparison between induction and consolidation chemotherapy (FOLFOX). While there was no difference in 3-yr disease free survival rates between arms, organ-preservation rates was significantly better for consolidation chemotherapy when compared to induction chemotherapy.

In summary, there is evidence to support that consolidation chemotherapy may contribute to improve response rates in rectal cancer following nCRT. Both 5FU-only and 5FU/Oxaliplatin-based chemotherapy consolidation regimens have shown promising results.[20,34] However, no study addressed the benefit of oxaliplatin during consolidation to improve response rates. While previous studies incorporating oxaliplatin were negative and associated with increased toxicity, all of these studies used oxaliplatin in concomitance to RT.

For these reasons, we decided to design a study to address the impact of 2 different consolidation chemotherapy regimens in complete primary tumor response to treatment in rectal cancer.[35] The findings of the present study may allow for a definitive recommendation of specific consolidation regimens, particularly when the primary purpose of the use of neoadjuvant therapy is to achieve a complete clinical response and offer organ-preservation to these patients.

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