



**TITLE: TIMING TO MINIMALLY INVASIVE SURGERY AFTER NEOADJUVANT CHEMORADIOTHERAPY FOR RECTAL CANCER: A MULTICENTER RANDOMIZED CONTROLLED TRIAL**

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# MULTICENTER RANDOMIZED CONTROLLED TRIAL (TiMiSNAR)

## TIMING TO MINIMALLY INVASIVE SURGERY AFTER NEOADJUVANT CHEMORADIOTHERAPY FOR RECTAL CANCER: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

### 1. BACKGROUND AND RATIONALE OF THE STUDY

Chemoradiotherapy is a well-known risk reducing treatment of local recurrence in the treatment of rectal cancer, followed by total mesorectal excision (TME). In low rectal tumors, surgery alone has the 30% overall survival and a local recurrence rate of about 55-65%, with a disease-free survival of 30%-35% [1]. Preoperative administration of fluorouracil-based chemotherapy improved local recurrence rates to 7% [2]. The optimal timing of surgery in relation to chemoradiation is still controversial. Retrospective analysis has demonstrated in the recent decades that the regression of adenocarcinoma can be slow and not complete until after several months [3]. More recently, increasing pCR rates have been demonstrated to be correlated with longer time interval [4] [5] [6]. Conversely, several reports have shown no impact of the interval after chemoradiation on pCR and technical performance [7] [8]. In the Lyon trial the rate of pCR or near pCR increased from 10.3% to 26% [9] and in retrospective studies the increase rate was about 23%-30%. These results may be explained on the relationship between radiation therapy and tumor regression: DNA damage occurs during irradiation, but cellular lysis occurs within the next weeks [10]. A recent pilot study on comparison of resonance imaging and histopathological responses at two times, has suggested that volume reduction and down-staging occur between week 9 and week 14 after neoadjuvant treatment, with a 23% pCR rate at longer time [11]. In the Stockholm III trial, a significantly lower frequency of postoperative complications was reported, even though not described in the other studies where morbidity and complications were the same. All of these studies, however, presented some biases, such as absence of randomization, the choice of surgical timing made arguably by the surgeon, tumor size and response to RCT, different cut-off period and a limited number of recruited patients, that may have negatively or positively influenced these results [12] [13]. Delaying surgery with the aim to detect excellent responders for organ preservation, eventually, may be legitimate, even though the start of adjuvant therapy, whose advantage in pretreated rectal cancer patients is still controversial, would be delayed, and this may negatively affect survival [14] [15]. A recent meta-analysis on thirteen reports has been published, showing rates of 14% and 20% in the shorter and longer group, respectively. This meta-analysis has some biases: the pCR correlation with surgical delay could not be adjusted in a multivariate analysis with other clinico-pathological variables, the outcome (DFS and OS) of pCR, even if likely better than those without pCR as literature demonstrates, could not be directly assessed due to lack of individual patient data, the number of patients operated on in the delayed group could have been chosen using a surgical decision, different time intervals were grouped all together, no randomized trial were included in the meta-analysis, and the relevance of the reports included in was assessed by NOS scale, that is quite arbitrary, several reports on observation, demonstrating a higher percentage of pCR, were not included, but it is quite relevant to consider also these studies.

## 2. PURPOSE

To demonstrate if delayed timing of surgery after neoadjuvant chemoradiotherapy actually affects pCR and reflects on DFS and OS rather than standard timing. This prospective trial will take place at SS Antonio e Biagio e Cesare Arrigo Hospital in Alessandria.

## 3. STUDY DESIGN

### 3.1. Study Type

The trial is a multicenter, prospective, randomized controlled, unblinded, parallel-group trial comparing standard and delayed surgery after neoadjuvant chemoradiotherapy for the curative treatment of rectal cancer. Three-hundred and forty patients will be randomized on an equal basis to either robotic-assisted/standard laparoscopic rectal cancer surgery after 8 weeks or robotic-assisted/standard laparoscopic rectal cancer surgery after 12 weeks. Eight weeks are the current standard interval to surgery after neoadjuvant treatment, while 12 weeks represent the “minimum” longer time interval to determine further tumor modifications and the “a priori” choice to avoid hypothetical surgical detrimental effect (postoperative complications related to radiation therapy). The recruiting interval will be of 5 years and the follow-up period will end 5 years after the last patient is randomized.

### 3.2. Primary Endpoint

- pCR

### 3.3. Secondary Endpoints

- DFS
- OS
- postoperative complications (Clavien-Dindo classification)
- reintervention
- late complications (Clavien-Dindo classification)
- radiation toxicity
- chemotherapy toxicity
- QoL
- Functional status

## 4. ELIGIBILITY

### 4.1. Inclusion Criteria

- Age >18 years
- cT3/4N0/+M0 confirmed on CT-scan, MRI (stratification for T3a-b-c-d)
- Tumor starting from the distal or medium rectum (even those crossing the peritoneal reflection at distal margin, within 15 cm from the anal margin)

- Histologically-proven adenocarcinoma of the rectum
- Eligible for a resective surgery with TME (low anterior resection, intersphincteric resection, abdominoperineal resection)
- Eligible for resection by minimally-invasive surgery (standard or robotic-assisted laparoscopic procedure, all robotic systems will be accepted)
- Eligible for chemoradiation treatment
- Able to give written informed consent
- Capable of completing required questionnaires at time of consent (provided questionnaires are available in a language spoke fluently by the participant)

#### 4.2. Exclusion Criteria

- Metastatic disease
- Squamous carcinoma of the anal canal
- Synchronous colorectal tumors requiring multi-segment surgical resection (n.b. a benign lesion within the resection field in addition to the main cancer would not exclude a patient)
- History of psychiatric or addictive disorder or other medical condition that, in the opinion of the investigator, would preclude the patient from meeting the trial requirements
- Pregnancy
- Unable to complete neoadjuvant treatment
- Unable to give free informed consent
- Previous radiation treatment on the pelvis
- Inflammatory bowel disease
- Hereditary colorectal disease
- Previous tumors other than non-melanoma skin cancer, papillary or follicular thyroid cancer
- Participation in another rectal cancer clinical trial relating to the topic of this trial

#### 4.3. Study Population

Patients will be identified after endoscopy and screened for inclusion into the study once referred to the colorectal surgeon.

##### 4.3.1. Recruitment of Patients

A total of 340 patients, 170 in each arm, will be enrolled in the trial. In arm A, surgery will be performed after 8 weeks; in arm B, surgery will be performed after 12 weeks. (See Table 1). Eligibility of participants should be established prior to start neoadjuvant therapy.

Table 1	
STANDARD INTERVAL TIME ARM	DELAYED INTERVAL TIME ARM
170 pts	170 pts
surgery will be performed after 8 weeks (non-extended timing)	surgery will be performed after 12 weeks (extended timing)

#### 4.3.2. Informed Consent

Patients will be approached for possible recruitment following diagnosis and radiological staging (see section 6), provided they fulfil the inclusion/exclusion criteria (see section 5.1 and 5.2). Patients will be provided with verbal and written details. A verbal explanation of the trial will be provided by a medically qualified member of the healthcare team for the patient to consider.

Patients will be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. Patients will be allowed 24 hours as a minimum and one week as a maximum, to consider their participation in the trial. Patient can refuse to participate in the trial without giving any reasons.

Patients who accept to participate in, will then be formally assessed for eligibility and invited to provide informed, written consent (see appendix 1) for their participation in the trial, including explicit consent for the transfer of a copy of their signed consent form to the Coordinator Center (CC).

Informed consent may be obtained by the Principal Investigator (PI) or another clinically qualified member of each participating trial center, indicated by the Principal Investigator to take informed consent.

A copy of the signed consent form will be given to the patient.

Patients will remain free to withdraw from the trial at any time by revoking consent without giving reasons and without prejudicing any further treatment.

#### 4.3.3. Loss of Capacity Following Informed Consent

Loss of mental capacity of a patient after giving informed consent for the trial is expected to be a rare occurrence. In the event of incapacity, patients will not receive any further trial-specific interventions, without prejudicing any further treatment.

#### 4.3.4. Site Eligibility

The trial is a multicenter collaboration, involving all those centers able to provide the standard of cure for locally advanced rectal cancer. All the involved centers have to respect the following criteria:

- Site able to perform robotic-assisted and standard laparoscopic rectal cancer surgery and TaTME (transanal total mesorectal excision)
- Site able to provide a preoperative work up according to the work up criteria specified in this trial (see section 6)

- Site able to provide standard neoadjuvant treatment, both chemo and radiation therapy, according to the criteria specified in this trial (see section 7.1)
- Predicted capability to recruit a minimum of 15 patients per year to the trial.

#### 4.4. Randomization

Randomization should take place as soon as possible after consent is obtained and after patients have completed their baseline patient reported questionnaires. Patient consent and randomization must take place as close to the date of start of the neoadjuvant treatment as possible and must be no more than 30 days prior to planned treatment.

##### 4.4.1. Process of Randomization

Following confirmation of written informed consent and eligibility, patients will be randomized into the trial by an authorized member of the staff at each trial center. Randomization will be performed centrally by data managers, using the software specified in the next section (4.4.2). Randomization form have to be sent via email completed in all the specified fields. It will be returned with the indication of the time interval by email, as well. The following information will be required at randomization:

- Patient details, including initials, height, weight, gender and date of birth
- Date of diagnosis
- Pre-operative investigations performed
- Planned operation (anterior resection/intersphincteric resection/APR)
- Name and code of the trial center
- Name of the person making the randomization
- Name and code of the coordinator of the trial center
- Confirmation of eligibility
- Confirmation of written informed consent and date obtained
- Date of randomization

##### 4.4.2. Arm Allocation

Patients will be randomized on a 1:1 basis to receive minimally-invasive rectal cancer surgery 8 or 12 weeks after neoadjuvant treatment and will be allocated a unique trial number. A computer-generated software with block randomization criteria will be used to ensure treatment groups are well-balanced for the following patient characteristics, details of which will be required for randomization (see appendix 2):

- Intended surgical technique (robotic/laparoscopic/transanal)
- Intended RT with or without boost



## 5. PREOPERATIVE WORK UP

Preoperative investigation and preparation will be as per institutional protocol (see appendix 3 – DVA 19 Colorectal cancer Rev. 05 18/02/2016, section 5). In summary, blood test, endoscopy, CT scan and MRI are compulsory exams, endoscopic rectal ultrasound is required but not compulsory and only for tumors localized within 10 cm from the anal verge. Physical examination and digital rectal exploration should precede all instrumental examinations.

### 5.1. Blood Test

Blood test is mandatory and should include the following markers:

- Complete cell blood count (CBC)
- Serum level of:
  - Creatinine
  - alanine aminotransferase
  - aspartate aminotransferase
  - Gamma glutamiltransferase
  - Bilirubin
  - Alkaline phosphatase
  - Pseudocholinesterase
  - Prothrombin Time (PT)
  - Partial thromboplastin time (activated) (PTT or aPTT)
  - Antithrombin III
  - Fibrinogen
  - Albumin
  - Total protein count
  - Sodium, Calcium, Potassium, Chlorum, Phosphorus, Magnesium
- HCV, HBV test
- Carcinoembryonic antigen level (CEA)
- Carbohydrate antigen 125 (Ca 125)

### 5.2. Endoscopy

A complete colonoscopy with biopsies is mandatory. In case of stenotic tumor or low patient's compliance to perform a complete colonoscopy, a rectoscopy with biopsies is required, completed by CT Colonography. At least 9 biopsies (3 anterior, 3 lateral, 3 posterior circumferentially) are required for a complete and more precise pathological report, including immunohistochemical and biological features. All trial centers have to send the endoscopic report to the coordinator center.

### 5.3. CT Scan

Thoraco-abdominal CT scan with and without contrast medium is required for staging of disseminated disease, if any. The presence of diffuse disease (lung, liver, extraregional lymph nodal disease) is an exclusion criterion (see section 5.2). CT Colonography is performed in case

of stenotic tumors or low patient's compliance to the endoscopic exam. All trial centers have to send the CT scan report to the coordinator center.

#### 5.4. MRI

Pelvic MRI is mandatory and the technique of first choice for both primary staging and restaging of rectal cancer, according to the recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting [16]; MRI is the most accurate test to define locoregional clinical staging. By detecting extramural vascular invasion (EMVI), and determining the T substage and circumferential resection margin (CRM), MRI can also predict the risks of local recurrence and synchronous/metachronous distant metastases. Another important addition to the 2012 guidelines is a recommendation for structured reporting; European Society of Gastrointestinal and Abdominal Radiology (ESGAR) has recently presented an alternative template (both for primary staging and for restaging after neoadjuvant treatment) based on the specific recommendations arising from 2016 updated consensus meeting. Studies have shown that implementation of structured report templates can improve the quality of MRI reporting for rectal cancer staging compared to free-text formats, and leads to higher satisfaction levels from referring surgeons [17] [18]. Accordingly, structured reporting is now recommended by the panel unanimously and it will be a mandatory item for this trial (see appendix 4). No MRI reports without this template will be accepted. All trial centers have to send the structured template to the coordinator center.

High quality MRI allows further subclassification of cT3, which is recommended by ESMO guidelines and it is useful in stratifying and selecting patients with indication to neoadjuvant treatment before surgery (table 1) [19].

Table 1. Subclassification of T3 rectal cancer	
	Depth of invasion beyond the muscularis propria (mm)
T3a	<1
T3b	1-5
T3c	6-15
T3d	>15

#### 5.5. ERUS (Endoscopic rectal ultrasound)

ERUS has indication in earliest tumor (T1-T2), which can be selected for transanal endoscopic microsurgery (TEM); ERUS provides less value in locally advanced rectal cancer and it may be indicated in those patients who refuses undergo MRI or with contraindications.

## 6. NEOADJUVANT TREATMENT

### 6.1. Chemoradiation Therapy

Several phase II studies have indicated the use of concomitant chemotherapy for better efficacy from such combination. The studies showed downstaging with pCR of more than 15% after preoperative CRT compared with approximately 5% after RT alone [20] [21].

Two recent randomized trials, comparing preoperative RT with CRT, in resectable cases, demonstrated that local control is significantly better in the combined modality groups, but with no significant gain in OS. The trials do not give an answer to whether the addition of chemotherapy mainly works as a radiosensitizer, improving local control, or if it has an effect of its own [22] [23]. In the European Organization for Research and Treatment of Cancer (EORTC) study, a favorable effect on local control was seen with concomitant chemotherapy, even though no conclusive results were demonstrated [24]. The addition of chemotherapy resulted in the Locally Advanced Rectal Cancer Study (LARCS) in more sphincter-preserving procedures although this was not an end point in the study.

Concomitant chemotherapy advantages can be summarized as follows:

- Improved sensitivity to radiation therapy on neoplastic cells
- Higher systemic control of the disease (micrometastases eradication)
- Increased complete pathological response and sphincter preservation

The initial trials of trimodality therapy in rectal cancer utilized a fluoropyrimidine bolus (5FU – 5-fluorouracil) has been recently overcome by continuous infusion of 5FU that improves local control, distant metastases and survival.

Recent data have shown that capecitabine can replace 5FU in chemoradiotherapy with equivalent efficacy and comparable toxicity profile, also avoiding the insertion of a central venous catheter [25].

Concomitant chemotherapy treatment associated to long course radiation therapy with IMRT (Intensity Modulated RadioTherapy – 50-54 Gy in 25-28 fractions; an optional boost is suggested) consists of Capecitabine 825 mg /m<sup>2</sup>/ twice daily during radiation therapy.

When one or more side effects are experienced, a specified form must be completed, if neoadjuvant treatment is not completed, informing the patient being excluded from this trial (see neoadjuvant exclusion form).

## 6.2. Restaging and treatment-efficacy assessment after Neoadjuvant Therapy

Assessment of treatment efficacy has principally relied on histopathologic findings on the specimen after surgery. Qualitative evaluation of the degree of fibrosis in the pathologic specimen can be used to derive a tumor regression grading (TRG) system. Accurate preoperative assessment of response to therapy (restaging) may permit to better define the final treatment strategies. Morphological MRI evaluation is considered the best available tool for locally advanced rectal cancer staging after neoadjuvant treatment, allowing an accurate evaluation of the disease extent and of the lymph node involvement. The MERCURY study group has developed an MRI-based tumor regression grading (ymrTRG) system by applying the principles of histopathological ypTRG [26].

Recently, a pilot study from UK has defined two groups of patients divided into favourable vs unfavourable responders based on the following three factors:

- ymrT
- ymrTRG
- Change in volume

ymrT is based on the interpretation of local extent of persistent tumor signal intensity relative to the layers of bowel wall on T2-weighted images. Tumor response is evaluated as either

replacement of tumor signal by low signal intensity fibrosis (dark stroma) or the development of high signal intensity mucin pools, that are not considered to be tumor.

ymrTRG is based on principles similar to the pathological ypTRG system described by Dworak and subsequently modified by Mandard.

Change in volume, better defined as percentage volume reduction is calculated multiplying tumor length, width and height, using the following formula:

$$100 * \frac{(\text{Volume at baseline}) - (\text{Volume post-CRT})}{(\text{Volume at baseline})}$$

Restaging is worked out generally between week 4 and 6 after neoadjuvant treatment (mean 90 days). Further volume reduction and down staging have been investigated to occur up to week 14 after radiation therapy. Time interval to surgery in this trial are 8 weeks and 12 weeks after treatment, that are the standard and the expected “minimum” longer time interval to determine further tumor modifications. Post-treatment staging for evaluation of postneoadjuvant treatment response, eventually, will depend on MRI evaluation at week 7 for patients in both the two arms; a MRI evaluation will be repeated at week 11 for patients randomized in the delayed arm.

A Thoraco-abdominal CT-Scan with and without contrast enhancement will be performed at week 6 after neoadjuvant surgery, for restaging of potential disseminated disease.

## 7. SURGERY

Minimally-invasive mesorectal resection is required: both robotic or standard laparoscopic approach or Robotic TaTME will be accepted, in accordance with each surgeon’s usual practice. The specifics of each operation will be at the discretion of the operating surgeon (e.g. port-site placement, mobilization of the splenic flexure, inferior mesenteric artery/vein division, high versus low vascular division etc.), as well as the decision to convert to an open operation. Conversion to open operation is defined as the use of a laparotomy wound for any part of the mesorectal dissection. All participating centers are allowed and encouraged to use Indocyanine Green test (ICG), wherever available, but it is not mandatory. Indocyanine green is a sterile, water-soluble protein-binding dye with low toxicity and fast biliary excretion [27]. Dose and utilization information have to be sent to the CC.

### 7.1. Robotic Surgery

Robotic surgery is intended as a surgical technique that utilizes a computer-assisted aid to perform surgical procedures. All devices who respects the identification of “computer-based” or “robot” system are allowed. An operation is intended to be performed by robotic technique if TME is carried out by robotic assistance. All other steps of the procedure can be performed either by standard laparoscopy or by robotic technique. Participating centers with at least 20 Robotic TME performed before starting the trial are allowed to use robotic assistance for TME.

## 7.2. Standard Laparoscopic Surgery

Either Standard or 3D-laparoscopy are allowed to be performed for TME. Centers have to provide documentation of at least 50 laparoscopic procedures performed before starting the trial.

## 7.3. Robotic TaTME (or TAMIS or Robotic Transanal Surgery (RTS))

Robotic transanal surgery (RTS) is a newer approach to rectal dissection whose purpose is to overcome the limits of the traditional transabdominal approach, improving accuracy of distal dissection and preservation of hypogastric innervation. Although there are few published cases in literature, an increasing interest on this new technique has raised, thanks to the excellent pathological and acceptable short-term clinical outcomes reported [28] [29] [30]. The purpose of this trial is not to value the efficacy of TaTME, which is intended to be performed only by those centers with high specialization on robotic surgery, with at least 5 TaTME procedures performed before starting the trial.

## 7.4. Operative Assessment

An operative clinical case report (CRF) will be completed and will include the following items (see appendix 5):

- Surgeon
- ASA status
- Surgical (robotic-assisted/standard laparoscopy/TaTME)
- Details of previous abdominal operations
- Type of operation performed (anterior resection/intersphincteric resection/APR)
- Duration of operation (docking time, robotic time, total operation time)
- In case of robotic approach, conversion to laparoscopic or open technique and reasons
- In case of TaTME approach, conversion to either transabdominal robotic or laparoscopic or open technique and reasons
- Any intra-operative complications

## 8. PATHOLOGY

Histopathological analysis of the rectal resection specimens is recommended according to internationally agreed criteria.

A complete and correct histopathology report have to include:

- Gross description including site, maximum tumor size, distance from distal and proximal resection margins, evidence and site of perforation (if any), plane of surgical excision (mesorectal, intramesorectal or muscularis propria for mesorectum and extralevator, sphincteric or intrasphincteric/submucosal/perforation for APR only) and distance from dentate line (for APR). Hystopathological examination should include a photographic

record of the surgical specimen and assessment of TME quality [III, B], which is a strong quality control measure.

- Histology including type and differentiation, local invasion (including depth of extramural invasion), margin involvement, proximal and distal cut ends, and distance to the non-peritonealized circumferential resection margin (CRM) and whether complete (R0) resection. If CRM involved then maximal length of involved margin, mode of involvement at CRM. All measures have to be in millimeters. A proforma report such as the one by the Royal College of Pathologists is recommended (see appendix 6).
- Any evidence of response to neoadjuvant therapy (Dworak score [31] – see appendix 7)
- Locoregional spread including lymph nodes<sup>1</sup> (number retrieved and number involved), lymphatic or extramural vascular invasion, perineural invasion (EMVI, EMLI, PNI), presence of tumor deposits (ENE)
- Tumor budding
- MSI (N-RAS, B-RAF, K-RAS) investigation
- Co-existent conditions including ulcerative colitis or Crohn's disease
- TNM (v.8, 2013 – see appendix 8)

All participating centers are required to submit the histopathological report to the coordinator center with the following patient information:

- Unique trial number
- Initials
- Date of birth
- Local histopathology report number

## 9. POST-OPERATIVE CARE AND FOLLOW UP

Post-operative care and follow up will be as per institutional protocol, but patients must be reviewed at 30 days, and 6 months post-operatively at a minimum (see appendix 9). Any further visits will be according to local standard clinical practice. All patients will be followed up as per protocol until 5 years after the last patient has been randomized.

### 9.1. Post-Operative Report

Data collected will include (see appendix 10):

- Duration of post-operative hospital stay
- Post-operative complications and severity (any correlated discharge delay must be reported)
- Details of any reoperation required and reason
- Patient status (alive or dead)

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<sup>1</sup> Although a minimum number of 12 lymph nodes are accordingly sufficient to be examined for a good pathological staging, all centers are encouraged to retrieve as more lymph nodes as possible. The more lymph nodes examined, the more correct p-staging is achieved.

## 9.2. Follow Up Report

Data collected will include (see appendix 11):

- Detail of any further therapy
- Details of any local or distant recurrence, including:
  - Date of recurrence
  - Site of recurrence
  - Method of diagnosis
- Details of any new primary cancer diagnosis
- A medical history, physical examination, Karnofsky and toxicity score (if any ongoing medical treatment)
- CT, MRI, PET (if required) report
- Quality of life questionnaires
- Blood test as previously specified (see section 6.1)

## 9.3. Death

All deaths must be recorded on the Notification of Death CRF, complete of date of death and cause of death (see appendix 12).

# 10.SAFETY REPORTING

## 10.1. Reporting of Serious Adverse Events (SAE)

### 10.1.1. Definitions

**AE:** An Adverse Event is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

**AR:** An Adverse reaction of an investigational medicinal product is any untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

**UAR:** An Unexpected Adverse Reaction is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). When the outcome of the adverse

reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

**Severity:** The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

**SAE:** A Serious Adverse Event is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment.

**SAR:** A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a Serious Adverse Reaction.

An Adverse Event or Adverse Reaction which is considered as serious:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires hospitalization or prolongation of existing inpatients’ hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

**SUSAR:** Suspected Unexpected Serious Adverse Reactions

## 10.2. Reporting Procedure

### 10.2.1. Non-Serious Adverse Events And/Or Non-Serious Adverse Drug Reactions

Adverse Events (AE) and /or Adverse Reactions (AR) must be recorded as indicated in the trial.

### 10.2.2. Serious Adverse Events Or Serious Adverse Drug Reactions

All Serious Adverse Events (SAE) occurring from the time a subject is registered until 30 days after last trial treatment, must be reported within 24 hours.

All SAEs that are simply signs and symptoms of the disease being studied do not need to be collected, unless more severe than expected for the subject’s condition.

### 10.2.3. Examples of SAES that Do Not Need to Be Reported

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.



- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.

Any SAE that occurs outside of the SAE detection period (after the 30-days period), considered to be reasonably related to the investigational treatment or study participation, have to be promptly notified.

This must be done by fax within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the trial treatment (i.e. unrelated, likely related, and not assessable) and the decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator. The investigator is obligated to assess the relationship between investigational treatment and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

For the causality assessment, the following definitions must be used:

<b>Relationship to the trial treatment description</b>	<b>Description</b>
UNRELATED	There is no evidence of any causal relationship to the protocol treatment
LIKELY RELATED	There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.

Details should be documented on the specified Serious Adverse Event Form (see appendix 13).

### 10.3. Reporting of Complications

Information on all complications will be collected for this trial whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other investigation.

For each complication, the following data will be collected (see appendix 14):

- Start and end dates of event, if resolved (and times, if known/applicable)
- Full details of complication in medical terms with a diagnosis (if possible)
- Action/intervention
- Outcome

#### 10.4. Responsibilities for Safety Reporting

**Principal Investigator** (i.e. Lead trial clinician at each recruiting site or appropriate clinical individual identified in trial delegation log)

- Checking for complications during admission and follow-up, including judgment in assigning:
  - causality i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
  - seriousness
  - expectedness

**Chief Investigator** (or nominated individual in PI's absence)

- Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment
- Undertake review of Unexpected Serious Complications (USCs) (see section 11.1)

#### Data Monitoring

A Data and Safety Monitoring Board (DSMB) will monitor the recruitment, the reported adverse events and the data quality at least one a year. Arising problems will be discussed with the Coordinator Center who will take appropriate measures. Relevant information (including relevant safety data) will be included in the study status reports serving as a basis of discussion during the group meetings. These reports will be made available to investigators participating to the study. (see section 15.3).

## 11. QUALITY OF LIFE ASSESSMENT

Patients will also be asked to complete the baseline generic health-related QoL and fatigue questionnaires (SF-36v2 and MFI-20) and patient reported bladder and sexual function questionnaires (I-PSS and IIEF/FSFI) following informed consent and prior to randomization (see appendix 15).

## 12. END OF THE STUDY

The end of the study is defined as 5 years after the date that the last patient has been randomized to the trial.

## 13.COSTS EVALUATION

The present trial is a no profit clinical study and does not require additional costs, i.e. in terms of laboratory tests, imaging, surgical treatment, compared to similar cases of standard rectal cancer treatment.

### 13.1. Trial Insurance

This is a No-Profit multicenter, prospectively-structured study Trial, in which no “experimental” drug or technique will be utilized for the treatment of the specified disease. Both robotic and laparoscopic techniques are commonly used in Our Hospital and worldwide, respecting the definition of “Good Clinical Practice” (section 2.4 of the MoH’s decree of December 17, 2004) and covered by the insurance policy in force in Our Hospital and in the other participating centers.

## 14.STATISTICAL EVALUATION

### 14.1. Sample Size

The primary endpoint is the pCR rate. Based on the published results from prospective studies on delayed time interval or observation only and on retrospective study for standard time interval, we assume that the mean rate of pCR in the standard treatment is about 15%, while the mean pCR rate in the observation treatment or longer time interval is 30%. To determine this difference, 270 patients are required, using a two-group continuity corrected  $\chi^2$  test of equal proportions, assuming an  $\alpha$  error of 4.9% and a power of 80% (MedCalc Version 17.9.7); an interim analysis on efficacy will be performed when half of events will be observed. The conservative Haybittle-Peto [32] boundary will be used as a stopping guidance in order to perform the final analysis at the significance level of 4.9%, two sides. Considering results from the pilot study reported on section 1, the percentage of unfavourable patients is 20% (favourable MRI tumor regression grade is defined as grades 1, 2 and 3; unfavourable MRI regression as grades 4 and 5). In addition, a meta-analysis on results from five randomized European clinical trials for locally advanced rectal cancer, has confirmed this rate of “poor” responders subgroup, identified by having no pCR and no DFS within 2 years [33]. In computing the sample size, we assume that the percentage of missing data will be 5%. A total of 340 patients, 170 for each arm, is intended to be enrolled, eventually. Patients will be randomized on a 1:1 basis to receive minimally-invasive rectal cancer surgery 8 or 12 weeks after neoadjuvant treatment and will be allocated a unique trial number. A computer-generated software with block randomization criteria will be used to ensure treatment groups are well-balanced for the specified patient characteristics (see section 5.4.1). All enrolled patients’ data will be registered in a prospective electronic database (ACCESS, MICROSOFT OFFICE Professional Plus 2010, regular licensed).

## 14.2. Statistical Analysis

All efficacy outcomes will be assessed in the intention-to-treat population, which includes all enrolled patients who did not violate the eligibility criteria. pCR, OS and DFS will be assessed from the time of treatment allocation to local progression, death or disease progression. Patients who will not die and will not experience local or distant disease progression at the date of study cutoff will be censored at the last available information on status.

Time-to-event data will be analyzed by the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards model will be used to adjust the treatment effect for baseline prognostic factors.

## 15. ETHICAL CONSIDERATIONS, CONFIDENTIALITY AND QUALITY ASSURANCE

### 15.1. Ethical Considerations and Patient Protection

The PI will ensure that the study will be performed in accordance with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The trial has been written, and the study will be conducted according to the Guidelines for Good Clinical Practice. The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee (IEC).

### 15.2. Confidentiality: Subject Identification – Personal Data Protection

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not to be made publicly available. A sequential identification number (number of randomization - RND) will be automatically attributed to each patient registered in the study, any other personal identity information (name, surname, etc.) will not be registered to the Data Center. RND will identify the patient and must be included on all CRFs. In order to avoid identification errors, patient initials and date of birth will also be reported on the CRFs.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a “key” kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection (privacy) regulations. Breach of such regulations may result in administrative or even criminal sanctions.

The informed consent form for treatment must be accompanied by an information sheet prepared according to the regulations described above and a separate patient consent form indicating that the patient consents to the processing of such data (see appendix 16). Such information must:

- Identify the roles of the holder and processor (appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research)

- Adequately describe the flows of communication involving them, particularly if third parties should become involved
- Seek patient's prior and specific consent to such processing.

Patient information or documentation may be considered anonymous, and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer available.

Particular attention should therefore be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed, or biological samples/materials are taken and kept for future research purposes, associated or not with the pathology considered in the study.

The Principal Investigator (Dott. Igor Monsellato) and the Local Principal Investigators of all Participating Centers are also responsible for data management, from collection to processing, processing and transfer to the data collection or Case report forms (CRFs).

## 16.PUBLICATION POLICY

The trial will be registered with an authorized registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

Credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (<http://www.icmje.org>):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

Main Investigators, and relevant senior trial staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators (surgeons and pathologists) will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission.

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