COVER PAGE

Study Protocol

OFFICIAL TITLE: Neoadjuvant Chemoradiotherapy and Consolidation Chemotherapy for Rectal Cancer: A Randomized Controlled Trial

BRIEF TITLE: Neoadjuvant Chemoradiotherapy and Consolidation Chemotherapy for Rectal Cancer

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1. INTRODUCTION

1.1 Literature Review

Colorectal cancer is the second leading cause of cancer-related deaths worldwide. It is estimated that 10% of cancer mortality is attributed to malignant neoplasms of the colon and rectum [1]. More specifically, in the United States alone, 53,200 colorectal cancer deaths were reported [2].

The current treatment of choice for locally advanced rectal cancer (Stage II/ III) is the combination of neoadjuvant chemoradiation followed by radical surgical resection based on the principles of total mesorectal excision (TME) after a 8-12 weeks period [3]. Therapy is usually completed with the administration of adjuvant chemotherapy based on oxaliplatin and fluoropyrimidines. This combined approach allowed the reduction of local recurrence at levels around 5%. Despite the impressive results in local control, the same was not confirmed for the long-term, overall survival. Possible explanations to that are: a) the compliance and completion of the treatment schemes during the postoperative period were low and b) there was a delay in the administration of adjuvant chemotherapy; both could lead to subclinical metastatic disease progression [4].

On the basis of achieving both goals, (i.e., local control through neoadjuvant radiotherapy and metastatic disease control through systemic chemotherapy) the administration of the two therapies in the preoperative period was proposed, in the form of combined or total neoadjuvant therapy [1, 5–8].

Additional theoretical benefits of total neoadjuvant therapy are faster defunctioning stoma reversal, as well as the possibility of a more accurate evaluation of the tumor biological behavior, thus enabling a safer staging for patients who would be candidates for a watch and wait protocol [1–3, 5–12]. Furthermore, for patients who will eventually undergo surgery, total neoadjuvant therapy could probably increase R0 resection and sphincter-preservation rates [3, 5, 8– 10, 12].

However, many researchers question the safety and efficacy of total neoadjuvant therapy [7, 13]. First, the administration of neoadjuvant chemotherapy significantly increases the risk of

severe toxicity from cytotoxic agents [14]. At the same time, according to the results of one of the largest prospective randomized trials, the addition of neoadjuvant chemotherapy into the treatment algorithm did not offer any advantage in the pathological response, 5-year overall and disease-free survival rates [15]. Finally, there is considerable heterogeneity in the current literature, most likely reflecting the different schemes used in different trials regarding the radiotherapy regimen, the chemotherapy regimen as well as the sequence of each one in each protocol [16].

We believe it is difficult to interpret any differences in results when multiple parameters have been changed in a comparative trial [17]. For this reason, when testing our current standard neoadjuvant protocol to the new trend of total neoadjuvant therapy we decided to keep the same scheme and timing for the experimental group also, and the only parameter which is different is the use of the classic chemotherapy scheme during the waiting period following chemoradiation and before surgery [18].

2. OBJECTIVE

2.1 Description of the proposed project

The purpose of this protocol is to compare neoadjuvant chemoradiation plus consolidation chemotherapy before surgical resection with the standard neoadjuvant chemoradiation followed by surgical resection and adjuvant chemotherapy in patients with rectal cancer.

3. MATERIAL AND METHODS

3.1 Population

The sample will consist of males and females aged 18 to 80 years.

3.2 Diseases

The study will include patients with rectal cancer that will meet the current criteria for neoadjuvant chemoradiotherapy, and surgical resection based on the principles of total mesorectal excision (TME).

3.3 Inclusion / Exclusion Criteria

Inclusion criteria are the following [10]:

- Histologically confirmed rectal adenocarcinoma
- cT3, cT4, threatened CRM / MRF, EMVI (+), ≥N1
- Multidisciplinary tumor board decision for neoadjuvant treatment
- Tumor distance from the anal verge ≤15 cm based on endoscopy or magnetic resonance imaging
- Patient 18 to 80 years old
- General health condition status WHO 0-1
- Absence of co-morbidities that may affect treatment
- Neutrophils >1,500 / mm3, platelets >100,000 / mm3, hemoglobin> 10 g / dL, normal creatinine, and creatinine clearance> 50 mL / min
- Signed informed consent of the patient

Exclusion criteria are the following:

- Distant metastases
- Non-resectable cancer
- Contraindications for the administration of chemotherapy
- Previous pelvic radiotherapy or chemotherapy

- History of inflammatory bowel disorders
- History of angina, acute myocardial infarction or heart failure
- Active sepsis or systemic infection
- Untreated physical and mental disability
- Synchronous malignancy
- Pregnancy or breast-feeding
- Lack of compliance with the protocol process
- Non-granting of signed informed consent

3.4 Study Arms

In this study there will be two arms [5, 10]. Patients that are randomized in the first arm will receive neoadjuvant chemoradiotherapy and consolidation chemotherapy and then undergo surgical resection of the tumor. In the second arm, patients will receive the standard long-course neoadjuvant chemoradiotherapy regimen and then undergo tumor resection. The treatment will be completed with adjuvant chemotherapy. In both groups, surgery will follow the principles of total mesorectal excision (TME).

The control group will receive the standard 5-week neoadjuvant chemoradiotherapy regimen. Six weeks after completion the patient will be re-staged with rectal MRI and depending on the response will be operated (TME): immediately in case of non-response (mrTRG 5) or after an additional 6-week delay (overall 12 weeks after the end of chemoradiotherapy) in case of partial response (mrTRG 2-4). Adjuvant chemotherapy will be, also, administered.

The experimental group will receive the standard 5-week neoadjuvant chemoradiotherapy (CRT). Thereafter, all patients will commence consolidation chemotherapy. At the 6th week after the end of CRT, patients will undergo MRI re-staging: In case of non-response (mrTRG 5) they will be submitted immediately to surgery, and, subsequently, excluded from the trial. In case of response (mrTRG 2-4) they will receive consolidation chemotherapy for the whole waiting period between the end of CRT and surgery - 12 weeks.

The following interventions will be introduced:

Neoadjuvant Chemoradiotherapy. 5-week neoadjuvant radiotherapy regimen (28 x 1.8 Gy) combined with Capecitabine (bid 800 mg/m2, twice daily, on days 1-33-38)

Consolidation Chemotherapy. CAPOX (Capecitabine bid1000 mg/m2 and Oxaliplatin 130 mg/m2, day 1, every 3 weeks) or alternatively FOLFOX

Adjuvant Chemotherapy. 8 cycles of CAPOX (Capecitabine bid 1000 mg/m2, twice daily, day 1-14, every 3 weeks and Oxaliplatin 130 mg/m2, day 1, every 3 weeks) or alternatively, 12 cycles of folinate, fluorouracil and oxaliplatin (FOLFOX)

3.5 Anesthesia

Patients will receive general anesthesia.

3.7 Primary endpoint

Disease Free Survival. Occurence of Disease Free Survival. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 3 years postoperatively]

3.8 Secondary endpoints

Secondary endpoints of the present study are:

Complete Pathological Response. Occurence of Complete Pathological Response. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 1 month postoperatively]

Postoperative Complications. Occurence of postoperative complications based on the Clavien Dindo Classification [20]. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 1 month postoperatively]

Length of Hospital Stay. Postoperative time that the patient can be safely discharged. Measurement unit: days. The patient will be discharged, when it is ensured that is medically safe

to be released. In particular, as the exit time of the patient, will be regarded the time that the patient will fulfil the Clinical Discharge Criteria. [Time Frame: Maximum time frame 39 days postoperatively]

Readmission. Occurence of postoperative readmission. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 1 month postoperatively]

Negative Resection Margin. Occurence of Negative Resection Margin. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 1 month postoperatively]

Overall Survival. Occurence of Overall Survival. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 3 years postoperatively]

Chemotherapy Toxicity. Occurence of Chemotherapy Toxicity. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 3 years postoperatively]

Local Recurrence. Occurence of Local Recurrence. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 3 years postoperatively]

Treatment Compliance. Occurence of Treatment Compliance. If such an episode occurs, then it will be defined as=1 'YES' If such an episode does not occur, then it will be defined as=0 'NO'. [Time Frame: 3 years postoperatively]

3.9 Calculation of the sample size

The sample size calculation was based on the primary endpoint. According to the literature, the disease-free survival Hazard Ratio between standard practice and combined neoadjuvant therapy is 0.23 [21]. Therefore, for a prospective randomized study with alpha: 5%, power: 90% and dropout

rate: 15%, the estimated number of patients in each group is 42. A total of 84 patients will be required.

3.10 Randomization

The randomization of the patients will be performed using a dedicated software with a 1:1 allocation ratio. The allocation group will be concealed with opaque envelopes.

3.11 Blindness

There will be no blindness at the level of the patient, the treating physicians (surgeon, oncologist, radiotherapist) and the researcher who will record the data.

3.12 Exit criteria

The patient will be discharged when it is ensured that is medically safe to be released. The exit time will be regarded as the time that the patient will fulfill the Clinical Discharge Criteria. More specifically, the patient should display the following: steady vital signs, fully oriented, without nausea or vomiting, mobilized with a steady gait and without a notable bleeding [22].

3.13 Monitoring

Following hospital discharge, the patient will be called for reassessment at one month after the operation. Patients will be included in the standard monitoring protocol (CT, MRI, cancer markers), unless otherwise required. At the same time, the pathological assessment of the specimen will be recorded. In addition, at 3 and 5 years postoperatively, overall, disease-free survival and recurrence rates will be recorded.

3.14 Medication

Both preoperative and postoperative patient treatment will be standardized. The principles of the ERAS protocols will be applied to patients [23]. More specifically, antimicrobial prophylaxis will include the administration of intravenous antibiotics within 60 minutes prior to the onset of operation. Patients will receive preoperative, mechanical bowel preparation and per-os antimicrobial prophylaxis. Prior to surgery, patients will abstain from solid and liquid foods for 6 and 2 hours, respectively. The nasogastric tube will be removed postoperatively and repositioned only in case of ileus. Postoperative analgesia will include a multidisciplinary approach using analgesics (paracetamol, lornoxicam) in combination with dorsal or epidural analgesia. Opioid administration will be avoided. Postoperative nausea and vomiting prophylaxis will include granisetron 3mg / 3ml IV. Mechanical and pharmaceutical thromboprophylaxis will be used. A zero-balance approach to fluid losses will be applied. Mobilization will be initiated from the first postoperative day. Feeding will be initiated on the basis of the intestinal function recovery.

3.15 Study Group

All participating members have years of experience in their field and have, therefore, completed the learning curve for the required techniques. Data collection and recording will be carried out by an independent, third party, researcher.

3.16 Conducting a Study

The study will be conducted in the Department of Surgery of University Hospital of Larissa in collaboration with the Oncology and Radiation Oncology Department of University Hospital. Patient data will be recorded both in the patient charts and in an electronic database. The required laboratory examinations will be defrayed by the patient insurance funds.

4. LITERATURE

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