COVER PAGE

Study Protocol

OFFICIAL TITLE: Evaluation of computed tomography and magnetic diffusion resonance imaging in the preoperative staging of colon cancer

BRIEF TITLE: CT and MRI in Preoperative Colon Cancer Staging
UNIQUE PROTOCOL ID: CTMR
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1. INTRODUCTION

1.1 Literature Review

Over the last years a significant improvement in the treatment of patients with colon cancer has been reported. This has been attributed to the improvement of the staging techniques, as well as the optimization of the surgical management. However, the current five-year survival rates of colon cancer patients in European countries ranges from 32% to 64%. [1]. This variation could be due to treatment discrepancies and the lack of adherence to the international guidelines [2].

Surgical treatment of colon cancer includes the radical resection of the tumour (colectomy). Following resection, the specimen is histopathologically examined, the disease is staged and further treatment is determined. Neoadjuvant treatment (radiotherapy or/and chemotherapy) for colon cancer has not been yet approved, unlike rectal cancer, where neoadjuvant treatment is recommended for specific disease stages [3].

Preoperative staging of colon cancer aims to identify those patients with remote metastatic disease, who will, more likely, not benefit from upward surgery. Recent developments in colon cancer management, demanding more precise local disease staging, to identify those patients who will likely benefit from neoadjuvant chemotherapy, are still at a clinical trial stage [4].

Preoperative treatment depends on the disease stage, which is defined by the tumour's invasion in the colonic wall, the dissemination in nearby organs or lymph nodes, and the presence of distal metastases. The stage is first evaluated radiologically and then confirmed via histopathological examination of the specimen. Imaging is an already approved tool for the staging of colonic cancer, while in some studies the combination of different imaging methods has been reported to improve the initial evaluation [5, 6, 7, 8, 9, 10].

Over the last years, evaluation of the circumferential resection margin (CRM) is also recommended in the preoperative staging of patients with colon cancer. This assessment is particularly important for tumours located at the cecum, right, or left colon, since these areas lack of mobile mesocolon and therefore it is possible to infiltrate the retroperitoneal resection margin.

Nevertheless, the retroperitoneal invasion of these tumours has not been evaluated adequately as a preoperative marker for both local recurrence and for the selection of patients who may benefit from neoadjuvant treatment. In various studies the percentage of retroperitoneal resection margin's infiltration was between 7-10% for cecum and right colon adenocarcinomas, while its presence was identified as a risk factor for local recurrence. The retroperitoneal surface infiltration was preoperatively evaluated with the combination of imaging methods and the findings were postoperatively compared with the histopathological features of the specimen [11, 12].

A more precise, imaging based, preoperative staging, could lead to a more targeted neoadjuvant treatment for patients with advanced disease, with the introduction of chemo- and/or radiotherapy. This approach could result to the downstaging of the tumour, with better short and long term oncological results.

2. OBJECTIVE

2.1 Description of the proposed project

The objective of this study is the evaluation of different imaging methods for the optimal preoperative staging of colon cancer patients. Imaging findings will be compared with the histopathologic results of the specimen following surgical resection.

3. MATERIAL AND METHODS

3.1 Population

The sample will consist of males and females aged 18 to 90 years.

3.2 Diseases

The study will include patients with colon cancer that will meet the current criteria surgical resection based on the principles of complete mesocolic excision (CME).

3.3 Inclusion / Exclusion Criteria

Inclusion criteria are the following:

- Histologically confirmed colonic adenocarcinoma
- Patient 18 to 90 years old
- Abscence of comorbidities that may affect treatment
- Signed informed consent of the patient

Exclusion criteria are the following:

- Inability to receive or contraindication for intravenous contrast
- Renal impairment
- Previous allergies to intravenous contrasts
- Incompatible implants with magnetic resonance imaging
- Claustrophobia
- Active sepsis or systemic infection
- Untreated physical and mental disability
- Lack of compliance with the protocol process
- Non-granting of signed informed consent

3.4 Study Arms

In this study there will be one arm. All prospectively included patients with colon cancer will be preoperatively submitted to MRI for staging. The evaluation of the diagnostic accuracy will be based on the cross-examination with the CT scan and the pathology results.

The MRI protocol will include the following imaging series: T1 and T2 in axial and coronal plane before the administration of intravenous contrast, diffuse weight imaging in axial plane and T1 after the administration of intravenous contrast.

The CT scan protocol will include the following: per os and intravenous administration of contrast, axial slices of 0.3mm thickness and reconstruction per 1mm, multi-planar reformation and three-dimensional volume rendering.

3.5 Anesthesia

Patients will receive general anesthesia.

3.7 Primary endpoint

Diagnostic accuracy in T stage. Evaluation of diagnostic accuracy in the T stage assessment

[Time Frame: 1 month postoperatively]

3.8 Secondary endpoints

Secondary endpoints of the present study are:

Diagnostic accuracy in N stage. Evaluation of diagnostic accuracy in the presence of local or distant metastatic lymph nodes

[Time Frame: 1 month postoperatively]

Diagnostic accuracy in the retroperitoneal resection margin. Evaluation of diagnostic accuracy in the retroperitoneal resection margin

[Time Frame: 1 month postoperatively]

Diagnostic accuracy in peritoneal or nearby organ infiltration. Evaluation of diagnostic accuracy in the peritoneal or nearby organ infiltration

[Time Frame: 1 month postoperatively]

3.9 Calculation of the sample size

The sample size calculation was based on the primary endpoint. According to the literature, the specificity of MRI of the T1/T2 vs T3/T4 differentiation is 84%. Therefore, for a prospective study with alpha: 5%, power: 80%, d=10% and dropout rate: 30%, the estimated number of patients is 120.

3.10 Randomization

There will be no randomization or allocation concealment.

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.

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.

3.14 Medication

Both preoperative and postoperative patient treatment will be standardized. The principles of the ERAS protocols will be applied to patients. 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 Radiology 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

1. Xynos E., Gouvas N., et al. Clinical practice guidelines for the surgical management of colon cancer: a consensus statement of the Hellenic and Cypriot Colorectal Cancer Study Group by the HeSMO. Annals of Gastroenterology (2016) 29, 3-17

2. Nelson H, Petrelli N, Carlin A, et al.: Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001;93:583– 596.

3. Jhaveri KS, Hooman HN, MRI of Rectal Cancer: An Overview and Update on Recent Advances. AJR 2015; 205:W42–W55

4. FOxTROT Trial, Lancet Oncol. 2012 Nov;13(11):1152-60. doi: 10.1016/S1470-2045(12) 70348-0. Epub 2012 Sep 25.

5. Nerad E, Lambregts D et al, MRI for Local Staging of Colon Cancer: Can MRI Become the Optimal Staging Modality for Patients With Colon Cancer? Diseases of the Colon & Rectum, 2017: 60; 4: 385–392,

6. Jakobs MA, Macura KJ. Et al, Multiparametric Whole-body MRI with Diffusion-weighted Imaging and ADC Mapping for the Identification of Visceral and Osseous Metastases From Solid Tumors. Academic Radiology 2018

7. Kijima S, Sasaki T, Nagata K et al, Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT World J Gastroenterol 2014;20(45): 16964-16975.

8. Antosh G, Vogt F, Freudenberg L et al, Whole body dual modality PET/CT and whole body MRI for tumor staging in oncology. JAMA 2003: 290, 24: 3199-3206,

9. Hunter C, Blake H, Jeyadevan N, et al. Local staging and assessment of colon cancer with 1.5-T magnetic resonance imaging. Br J Radiol 2016; 89: 0257.

10. Ellebæk SB, Fristrup CW, Bau Mortensen M. Intraoperative Ultrasound as a Screening Modality for the Detection of Liver Metastases during Resection of Primary Colorectal

Cancer - A Systematic Review. Ultrasound International Open 2017; 3: E60–E68.

11. Παπασταματίου Μ, Νικολόπουλος Δ. Σταδιοποίηση καρκίνου του παχέος εντέρου. Ανακοίνωση στο Παγκύπριο Συνέδριο Χειρουργικής 2010.http://www.medtime.gr

12. ElibolFD, ObuzF,SökmenS,Terzi C, CandaAE,Sağol Ö, Sarıoğlu S. The role of multidetector CT in local staging and evaluation of retroperitoneal surgical margin involvement in colon cancer. DiagnIntervRadiol 2016; 22:5–12

13. Bateman AC, Carr NJ, Warren BF. The retroperitoneal surface in distal caecal and proximalascending colon carcinoma: the Cinderella surgicalmargin?J ClinPathol2005;58:426–428.

14. Hajian-Tilaki K,J Biomed Inform. 2014 Apr; 48:193-204. doi : 10.1016/j.jbi.2014.02.013. Epub 2014 Feb 26.

15. Heald RJ, Husband EM, Ryall RD,1988 Sep; 81(9): 503–50

16. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. JClinOncol. 2010;28:272–278.