Medical University "Prof. Dr. Paraskev Stoyanov" – Varna

Second Department of Internal Medicine

The role of endoscopy in assessing response after neoadjuvant chemoradiotherapy for rectal cancer

Abstract

of a dissertation submitted for award of the educational and scientific degree "Doctor" to

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The dissertation is presented in 134 pages and contains 22 figures and 32 tables.

The bibliography comprises a total of 113 literary sources, of which 4 are in Bulgarian and 109 are in English.

All the research included in the dissertation was carried out at the University Hospital "St. Marina" - Varna

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The official public defense of the dissertation will take place on 08.04.2026 at 12:30 p.m. in Hall 1101 at the University Hospital "St. Marina", fl. 11, Department of Gastroenterology, and online on the Webex platform.

CONTENTS

Abbreviations used

APR Abdominoperineal resection

CBCT cone beam CT – computed tomography with a cone beam

cCR Clinical complete response

CEA Carcinoembryonic antigen

ctDNA Circulating tumor DNA – циркулиращо туморно ДНК

DWI Diffusion-weighted imaging

EMR Endoscopic mucosal resection

EMVI Extramural venous invasion

ERUS Endorectal ultrasound – endorectal ultrasound

eFTR Endoscopic Full Thickness Resection

ESD Endoscopic submucosal dissection

ESMO European Society for Medical Oncology

iCR incomplete response

IMRT Intensity-Modulated Radiation Therapy – Intensively Modulated Radiotherapy

KV-imaging Kilovoltage Imaging

MERCURY Magnetic Resonance Imaging and Rectal Cancer European Equivalence

MRF mesorectal fascia – the mesorectal fascia

mrTRG MRI-based tumor regression grade – степен на регресия по МРТ

MSKCC Memorial Sloan Kettering Cancer Center

NBF neutral buffered formalin

nCR Near-complete response

OPRA Organ Preservation in Rectal Adenocarcinoma – Clinical Trial Name

OR odds ratio – odds ratio

pCR Pathologic complete response

SD standard deviation

SUV Standardized uptake value

TME Total mesorectal excision

TNT Total neoadjuvant therapy

TRG Tumor regression grade

uT stage ultrasound-based T staging

VMAT Volumetric Modulated Arc Therapy – volumetric rotational intensity-modulated radiotherapy

W&W "Watch and wait" strategy

ypN Post-treatment nodal status (ypN) – pathological N-stage after treatment

ypT Post-treatment primary tumor (ypT) – pathological T-stage after treatment

1. INTRODUCTION

Rectal diseases, particularly malignant ones, are a problem of enormous health and social significance. This stems from several facts: first, the large number of people affected worldwide; secondly, the growing proportion of young people of working age among them, and last but not least, the anatomical and physiological characteristics of the area, which make therapeutic interventions a real challenge. The potential impairment in quality of life is so significant that an increasing proportion of patients are even willing to compromise on oncological outcomes in order to preserve the integrity and function of the organ. As American proctologist Walter C. Bornemeier) says in his seminal article on sphincter-preserving hemorrhoidectomy, *"It is said that man has succeeded where animals have failed, thanks to the skillful use of his hands, but compared to the hands, the anal sphincter is far more perfect. If you hold a mixture of liquid, solid matter, and gas in your hands and try to release only the gas through a small opening at the bottom, you will fail. The anal sphincter can do this. It seems to distinguish between solid matter, liquid, and gas. It seems to "know" whether its owner is alone or with someone else, whether he is standing or sitting, whether he is wearing pants or not. No other muscle in the body is such a faithful guardian of human dignity and at the same time so ready to come to the rescue. A muscle like this deserves to be preserved."* (1) This necessitates continuous development in the field, which has led to revolutionary successes and ongoing relentless efforts in the fight against rectal cancer.

Over the past two decades, neoadjuvant chemoradiotherapy (nCRT) and total neoadjuvant therapy (TNT) have led to significant improvements in local control, resectability, and the frequency of organ-preserving treatment.

Accurate assessment of therapeutic response is key to risk stratification, decision-making regarding radical surgery versus organ-preserving strategies

(including "watch and wait") and prognosis. Endoscopy plays a central role in this process—from primary diagnosis and local staging, through assessment of clinical response, to long-term follow-up—but there are methodological limitations that require a multimodal approach combining clinical examination, magnetic resonance imaging (MRI), and other techniques as needed.

2. OBJECTIVE AND TASKS

2.1 Objective

The objective of this dissertation is to conduct a retrospective observational single-center cohort study in patients over 18 years of age with rectal carcinoma undergoing neoadjuvant chemoradiotherapy, aimed at determining the role of endoscopy in assessing the response to treatment.

2.2 Tasks

In order to achieve the set goal, the following tasks are formulated:

1. To analyze the demographic, clinical, imaging, and pathological characteristics of the studied cohort of patients with rectal carcinoma who underwent neoadjuvant chemoradiotherapy (nCRT).

2. To define the prognostic factors associated with achieving a complete clinical response (cCR) after nCRT.

3. To investigate the association between the degree of clinical response determined endoscopically (cCR, nCR, iCR) and imaging and tumor characteristics after nCRT.

4. To perform a comparative analysis between patients with complete or near complete clinical response (cCR+nCR) and those with incomplete clinical response (iCR).

5. To assess the impact of the time interval to the first follow-up endoscopy on pathological tumor response after neoadjuvant chemoradiotherapy.

6. To analyze the association between clinical, endoscopic, and imaging parameters and the likelihood of achieving pathological complete response (pCR).

3. MATERIALS AND METHODS

3.1 Materials

Within the scope of this study, medical record data from a total of 157 patients with malignant neoplasms of the rectum who underwent neoadjuvant chemoradiotherapy at the Radiotherapy Clinic of University Hospital "St. Marina" – Varna between 2019 and 2024 were analyzed. All patients included in the study were over 18 years of age.

3.2 Methods

A retrospective analysis was performed on the data available in the specialized hospital software Gamma CodeMaster and SC DICOM PACS Viewer. The medical written and photographic documentation, as well as the images from the imaging methods performed, were reviewed and subjected to a standardized description.

3.2.1 Study design

A retrospective, observational, single-center cohort study was conducted in patients over 18 years of age with rectal carcinoma treated with neoadjuvant chemoradiotherapy at the Radiotherapy Clinic of the University Hospital "St. Marina" EAD - Varna, for the period 2019-2024.

3.2.2 Inclusion criteria

- Patients diagnosed with malignant neoplasm of the rectum (ICD-10: C20);
- Patients with histologically confirmed adenocarcinoma of the rectum.
- Patients with invasive rectal carcinoma (T2-T4);
- Patients who have undergone neoadjuvant chemoradiotherapy at the Radiotherapy Clinic of St. Marina University Hospital EAD – Varna;
- Patients over 18 years of age;
- Patients with available written documentation, photographs, and images from clinical, endoscopic, and imaging examinations from the follow-up period after treatment.

3.2.3 Exclusion criteria

- Patients with other histological variants of malignant tumors of the rectum (non-epithelial neoplasms, anal carcinoma, etc.);
- Patients with rectal adenocarcinoma in the metastatic stage at diagnosis (M1);
- Patients with synchronous or metachronous malignant disease;

- Patients who have not completed the full course of neoadjuvant chemoradiotherapy;
- Patients under 18 years of age;
- Patients who do not have the medical documentation required for the purposes of the study.

3.2.4. Clinical examination

The clinical evaluation included a digital rectal examination to determine the presence or absence of a palpable tumor formation, its consistency, mobility, and approximate distance from the anal margin. The examination was used as part of the comprehensive assessment of the therapeutic response after neoadjuvant chemoradiotherapy and for classifying the clinical response (cCR, nCR, iCR).

3.2.5. Tumor characteristics

3.2.5.1 Disease stage

Data from the medical records of patients with rectal carcinoma in non-metastatic stage II/III (T2-4;N0-2;M0) according to the TNM classification were analyzed. The stage of the disease was determined by MRI of the small pelvis, CT with intravenous contrast enhancement of the chest and abdomen, and 18F-FDG PET/CT.

3.2.5.2 Tumor location and extent

Based on their distance from the anal margin, rectal carcinomas were classified as low (0-6 cm), intermediate (7-11 cm), and high (12-15 cm) located.

The circumferential extent of the formation was determined, dividing it into four groups: 0-25% of the circumference, 25-50%, 50-75%, and over 75%.

The maximum tumor diameter was also measured in centimeters.

The examinations were performed using flexible colonoscopy with the Olympus Exera III and Olympus Evis X1 systems.

3.2.5.3 MRI characteristics of the tumor

Local tumor characteristics were assessed using T2-weighted MRI (T2-MRI) and DWI-MRI as follows: extramural venous invasion (EMVI), presence of diseased lymph nodes (N), relationship of the formation to the mesorectal fascia (MRF) (free/involved/at risk). A distance between the tumor mass and the fascia of <1 mm was considered at risk. The examinations were performed on a Siemens Magneton Verio 3T magnetic resonance imaging device.

3.2.5.4. Endorectal ultrasound

A prerequisite for a high-quality examination is optimal patient preparation, which we achieved with the help of an osmotic laxative based on macrogol on the day of the endoscopic examination.

After signing an informed consent form for the examination, patients were positioned on their left side. The examination was performed with a radial endorectal transducer with a frequency range of 3-15 MHz. The transducer was covered with a sterile condom, then carefully inserted through the patient's anus above the tumor formation and scanned sequentially from the anal canal to the rectosigmoid.

The ultrasound-based T stage (uT-stage) and the presence of positive lymph nodes in the area—size over 5 mm, irregular contours, and hypoechogenicity—were determined.

The main limitations of the method are the difficult-to-access formations in the upper rectum and post-radiation fibrous changes, which are sometimes impossible to interpret.

3.2.5.5. 18F-FDG PET/CT

Patients undergoing 18F-FDG PET/CT were instructed to refrain from intense physical activity for several days prior to the examination and not to consume food or beverages containing sugar within 6 hours prior to the procedure. Immediately before the injection of the radiopharmaceutical, blood sugar levels were tested due to the impaired accumulation of the drug in tissues in hyperglycemia.

Before the examination, patients removed any metal objects that could cause artifacts and signed an informed consent form.

The radiopharmaceutical 18F-fluorodeoxyglucose (18F-FDG) was injected at a dose of 3–5 MBq/kg body weight. Patients were left at rest for about an hour to allow the drug to distribute throughout the body.

The imaging study itself consisted of two phases: CT for anatomical correlation and PET for imaging metabolic activity, taking approximately 20-40 minutes.

Subsequently, the images were merged and interpreted using the standardized uptake value (SUV). Areas with above-background metabolic activity were considered pathological findings. SUV>2.5–3 in non-

physiological areas such as the brain, heart, and liver were considered potentially pathological.

Primary rectal carcinoma typically demonstrated an SUV of 5-15. Lymph nodes were interpreted as pathologically involved at SUV > 2.5-3, and distant metastases at SUV > 3.

The interpretation of the results was performed in the context of clinical findings and data from other imaging and laboratory tests, due to the risk of false positive findings in inflammatory processes.

The application of PET/CT in the present study was limited to several important indications. Firstly, the detection of metabolically active secondary lesions in distant organs in order to prevent unnecessary surgical intervention. In addition, PET/CT was used as an additional modality in the post-therapeutic assessment of response and restaging.

The reduction in the size of the primary tumor and the negativization of initially metabolically active lymph nodes were considered indicators of a good therapeutic response.

It was noted that in some specific histological subtypes, such as signet ring cell adenocarcinoma, the possibilities for detection by 18F-FDG PET/CT were severely limited due to the low glucose metabolic activity of this type of tumor cells.

3.2.6 Laboratory tests

All enrolled patients underwent serum CEA testing as part of routine clinical assessment prior to initiation of neoadjuvant therapy and during follow-up after completion of therapy.

CEA was determined by a double-antibody sandwich chemiluminescent immunoassay using an ADVIA Centaur automated analytical system (Siemens).

The results were expressed in ng/mL, with a value of ≤5.0 ng/mL accepted as the upper limit of normal according to the reference standards of the laboratory used. In the statistical analysis, CEA values were used as a continuous variable in assessing their association with clinical and pathological response to neoadjuvant chemoradiotherapy.

3.2.7. Neoadjuvant chemoradiotherapy

3.2.7.1. Dose prescription and fractionation

Two standard fractionation regimens were used in patients:

- 28 fractions of 1.8 Gy to a total focal dose of 50.4 Gy
- 25 fractions of 2.0 Gy to a total focal dose of 50 Gy

Irradiation was performed with a Varian Clinac IX linear accelerator (Varian Medical Systems).

Throughout the course of radiotherapy, daily imaging verification of the patient's position and the tumor was performed using:

- cone beam computed tomography (CBCT)
- planar kilovoltage (kV) radiographs for bone verification

3.2.7.2. Dosimetric planning

Dosimetric planning was performed using modern radiotherapy techniques:

- IMRT (Intensity-Modulated Radiation Therapy)

• VMAT (Volume-Modulated Arc Therapy) with the aim of optimal coverage of the target volumes and maximum sparing of the surrounding healthy tissues.

3.2.7.3 Chemotherapy regimen

All patients received concomitant chemotherapy with Capecitabine 500 mg tablets in addition to radiotherapy.

The dosage was according to protocol, 825 mg/m2 twice daily, taken orally on the days of irradiation throughout the course of radiotherapy.

3.2.8. Endoscopic biopsy

During the endoscopic examination, multiple biopsies were taken from the area of interest, and the material was subsequently fixed in 10% neutral buffered formalin (NBF), embedded in paraffin, microtomed, and stained with hematoxylin-eosin.

The permanent preparations thus prepared were subjected to pathomorphological examination for the presence of residual malignant cells after treatment.

3.2.9. Assessment scales

3.2.9.1. Endoscopic classification of clinical response according to the Memorial Sloan Kettering Cancer Center (MSKCC)

Endoscopic assessment of therapeutic response was performed within 6-8 weeks after the end of nCRT using high-resolution Olympus Exera III (HD) and Olympus Evis X1 (4K) equipment. The examination was performed with

optimal patient preparation, defined as Boston Bowel Preparation Scale (BBPS) = 3 in this segment, achieved with macrogol-based osmotic laxatives.

Total colonoscopy was performed in all cases where this was possible. Patients participating in the study were examined both awake and under short-term intravenous anesthesia with Propofol, without this having a significant effect on the diagnostic process.

The endoscopic findings were documented through detailed photographic documentation and a written examination report, stored in digital and paper format.

According to the endoscopic classification introduced by MSKCC for assessing response after neoadjuvant therapy in rectal carcinoma, three groups were identified: clinical complete response (cCR), clinical near complete response (nCR), and clinical incomplete response (iCR).

The criteria for each group are as follows:

cCR—white cicatrix and telangiectasia against a background of normal mucosa, without residual tumor nodules and ulcerations

nCR—minimal residual changes—erythema, fibrin deposits, small ulcerations or nodules, without a formed tumor mass

iCR - ulcer, tumor mass or clearly defined nodule, lumen stenosis, infiltrated dense visible irregular mucosa, clear macroscopic signs of residual tumor

When analyzing the photographic documentation from the endoscopic procedures, the researcher was blinded to the written study protocols.

3.2.9.2. Magnetic resonance assessment of post-therapeutic tumor regression (mrTRG)

Magnetic resonance assessment of tumor regression was performed within 6-8 weeks after completion of nCRT, during hospitalization for the first follow-up endoscopy. No special bowel preparation was required for MRI and mrTRG assessment, as was the case for endoscopy. Magnetic resonance imaging was performed on the day after endoscopy.

T2-weighted MRI images were used to determine the ratio of fibrosis to residual tumor in patients after neoadjuvant chemoradiotherapy. The results were classified on a five-point ordinal scale introduced as a result of the MERCURY (Magnetic Resonance Imaging and Rectal Cancer European Equivalence) study as an MRI analogue of the pathological degree of tumor regression according to Mandard.

T2 images in planes oriented along the tumor axis were evaluated. The results were based on the basic principle that fibrous tissue is characterized by a low-intensity signal (a sign of tumor regression), while intermediate degrees of signal intensity indicate residual neoplasia.

The degrees of tumor response were defined as follows:

mrTRG1- complete response: absence of tumor signal, presence of only low-intensity signal at the topical site of the previous tumor.

mrTRG2- good response: more than 75% of the lesion consists of dense fibrosis with low signal intensity. No distinct mass with intermediate intensity, scattered residual tumor foci may be present.

mrTRG3 – moderate response: the fibrous component prevails, but there are clearly distinguishable areas with intermediate signal intensity

mrTRG4 – poor response: presence of a significant mass with intermediate intensity, prevailing over the low-intensity area of fibrosis

mrTRG5- no response: the signal shows no significant change compared to the image before treatment, there are no areas of hypointense signal indicating fibrosis.

For the purposes of part of the analyses, the mrTRG variable was dichotomized, separating a group with a good response (mrTRG1+mrTRG2) and a group with a poor response (mrTRG3-5), in order to preserve the statistical power of the analysis.

All magnetic resonance imaging studies were performed on a Siemens Magneton Verio 3T device.

3.2.9.3. Pathological evaluation of surgical resection

The material obtained after surgical intervention, whether abdominoperineal resection (APR) or low anterior resection (LAR), was sent for histopathological examination for pathological staging and assessment of tumor regression.

The resected specimens were fixed in 10% neutral buffered formalin (10% NBF) and underwent standard macroscopic description, including size, tumor location, and distance from the proximal, distal, and circumferential resection margins. The mesorectum was dissected for lymph nodes. The area of the macroscopically visible tumor or the site where it had been identified in previous diagnostic procedures was incised through the entire thickness of the intestinal wall, embedded in paraffin, microtomed, and stained with hematoxylin-eosin. All sections of the tumor bed were used simultaneously to assess the degree of tumor regression according to Dworak, ypT, and ypN.

3.2.9.3.1. Determination of ypT

The degree of tumor infiltration after nCRT, assessed pathologically according to TNM criteria, was based on the greatest depth of infiltration of viable malignant cells into the intestinal wall as follows:

ypT0 – no residual primary tumor (corresponds to pCR; Dworak 4);

ypTis – presence of tumor only in the lamina propria without infiltration into the submucosa;

ypT1 – presence of tumor infiltration into the submucosa;

ypT2 – presence of tumor infiltration into the muscularis propria;

ypT3 – tumor infiltration through the muscularis propria into the perirectal adipose tissue;

ypT4a – tumor infiltration to the surface of the visceral peritoneum (applicable to formations in the upper third of the rectum, where there is a peritoneal covering);

ypT4b – tumor invasion into adjacent organs or structures.

The local post-therapeutic pathological stage was determined according to the greatest depth at which viable tumor cells were found, regardless of whether the underlying layers were tumor-involved or occupied by fibrosis.

3.2.9.3.2. Determination of ypN

The mesorectum was systematically and methodically dissected to detect lymph nodes. Each lymph node was individually measured and fixed in a separate paraffin block for subsequent microtomy and staining with hematoxylin-eosin.

It is standard practice to examine more than 12 lymph nodes, but after nCRT they often have dystrophic changes, are small and fibrotic, which makes them difficult to differentiate and examine.

3.2.9.3.3. Determination of the degree of tumor regression according to Dworak

The degree of tumor regression after nCRT was assessed using a five-point ordinal scale according to Dworak (TRG 0-4), which evaluates the ratio between the remaining viable tumor and the fibrous tissue in the tumor bed.

The degrees were determined as follows:

TRG 0 – no regression: tumor mass, no visible fibrous or regressive changes;

TRG 1 – minimal response: tumor mass prevails, fibrosis and post-radiation changes present but limited;

TRG 2 – moderate response: fibrosis and regressive changes are dominant. There are still easily detectable single or grouped tumor cells within the fibrosis;

TRG 3 – almost complete response: fibrosis almost completely replaces the original tumor. Only isolated, difficult-to-detect microscopic foci of tumor cells are present, often scattered in the fibrotic tissue;

TRG 4 – complete response: no viable tumor cells are present in the tumor bed. Only fibrotic tissue is observed.

3.2.10. Surgical techniques

The surgical approach was determined individually based on the location of the tumor, its relationship to the sphincter apparatus, and the possibility of ensuring an adequate resection line (R0 resection) while preserving continence.

3.2.10.1. Low anterior resection (LAR)

This type of surgical technique was used for tumors located more than 5–6 cm from the anal margin, with preserved sphincter and the possibility of a secure distal resection margin of ≥1–2 cm.

The main goal of the technique is to preserve the anal sphincter and restore intestinal patency through colorectal or coloanal anastomosis.

3.2.10.2. Abdominoperineal resection (APR)

Extirpation of the rectum was necessary for tumors located <5 cm from the anal margin, in cases of infiltration of the anal sphincter or musculus levator ani, in formations affecting the anal canal, or in cases where it was impossible to achieve R0 resection while preserving sphincter function. The outcome of the operation is a definitive colostomy.

3.2.11. Statistical methods

The statistical methods in this study were applied to ensure a reliable, scientifically sound, and representative interpretation of the clinical, endoscopic, imaging, and pathological indicators in patients with rectal carcinoma who underwent neoadjuvant chemoradiotherapy. The techniques applied included descriptive, comparative, correlational, and temporal models, which together allowed for a comprehensive quantitative assessment of the study cohort.

The analyses were performed using two specialized statistical software packages – Jamovi version 2.6.3 and IBM SPSS Statistics version 25. Jamovi was used primarily for descriptive and comparative analyses, χ^2 tests, nonparametric comparisons, correlations, and graphical visualizations of

categorical distributions. SPSS was used for Kaplan–Meier survival analyses, time dependence modeling, and graphical representation of survival curves.

3.2.11.1 Descriptive statistics

The descriptive statistics in the study aimed to characterize the main clinical, demographic, and imaging parameters of the patients. Categorical variables, such as the degree of endoscopically assessed clinical response (cCR, nCR, iCR), presence of EMVI, lymph node status assessed by MRI, mrTRG, Dworak, ypT, ypN, as well as the degree of circumferential involvement and tumor location, were presented as absolute and relative frequencies.

Quantitative variables, such as the interval from the end of neoadjuvant chemoradiotherapy to the first follow-up endoscopy and the maximum tumor diameter, were presented as median, interquartile range (IQR), minimum, and maximum values due to the lack of normal distribution. These descriptive characteristics formed the analytical framework for subsequent comparative and correlation analyses.

3.2.11.2 Analysis of associations between categorical variables

The χ^2 test for independence was used to assess statistically significant dependencies between categorical variables. This approach was applied in the analysis of the relationships between endoscopically assessed clinical response and various imaging and pathological indicators, including mrTRG, the presence of EMVI, the degree of circumferential involvement of the rectal wall, and pathologically altered lymph nodes. When the data structure allowed, odds ratios (OR) and 95% confidence intervals were additionally calculated for the χ^2

analysis, which quantitatively described the strength of association between the factors studied.

3.2.11.3 Comparison of quantitative indicators between groups

The comparison of quantitative indicators between independent groups, e.g., the maximum tumor diameter between the different groups of endoscopically assessed clinical response, was performed using the nonparametric Kruskal–Wallis test. This method was chosen because of the asymmetric distribution of the data, the presence of extreme values, and the different sizes of the groups being compared.

3.2.11.4 Correlation analysis

Pearson's linear correlation coefficient was used to assess the relationships between time indicators and pathological characteristics. This method allows the strength and direction of the linear relationship between quantitative variables to be determined, including the relationship between the interval to the first endoscopic control and the Dworak regression gradient.

3.2.11.5 Survival analysis

A key methodological component was the Kaplan–Meier survival analysis, used to determine the optimal interval between the end of neoadjuvant therapy and the first follow-up endoscopy. For the purposes of this analysis, time to event was defined as the number of days from the end of nCRT to the first follow-up assessment. Adverse pathological results (Dworak 0–2, ypT $\geq$ 2, or ypN $\geq$ 1) were considered events, while observations with missing or favorable histological information were treated as censored. Kaplan–Meier

analysis was used because of its ability to include censored observations and describe time dependencies in oncological populations. Since the analysis is univariate, a log-rank test was not used.

3.2.11.6 Graphical visualization

Graphical analysis, performed using Jamovi v.2.6.3 and IBM SPSS v.25, included survival curves, bar charts, boxplot graphs, and visual representations of categorical associations. These graphical methods contributed to a better understanding of the structural dependencies in the data and aided in the interpretation of the results.

3.2.11.7 Level of statistical significance

All statistical tests were two-tailed, and the threshold for statistical significance was set at $\alpha = 0.05$. Values below this threshold were interpreted as statistically significant, while p-values between 0.05 and 0.10 were considered a trend.

3.2.12. Ethical aspects

3.2.12.1. Ethical approval

This study was conducted in accordance with the ethical principles for medical research involving human subjects, as formulated in the Declaration of Helsinki, and current national legislation. The study was approved by the Ethics Committee for Scientific Research at Medical University “Prof. Dr. Paraskev Stoyanov “ – Varna with Protocol No. 23 of 25.11.2025.

Due to the retrospective nature of the study, the lack of direct contact with patients, and the use of existing medical documentation, no additional individual informed consent for participation was required.

3.2.12.2. Protection of personal data

All data used in this retrospective study were processed in compliance with generally accepted ethical principles for the protection of personal information and confidentiality of medical data.

Access to the primary medical records was restricted to the research team. Prior to statistical processing, all direct patient identifiers were removed and replaced with unique codes that did not allow for individual identification.

The data was stored in a secure electronic environment and was used solely for the purposes of this scientific study. The results are presented in summary form, without the possibility of identifying individual participants.

4. RESULTS

4.1 Sample composition

The report from the Medical Statistics Department of University Hospital "St. Marina"– Varna on nosological units for the period 2019-2024 initially included 157 patients. After applying exclusion criteria, 103 people were determined to be suitable for the purposes of the study and were subsequently divided into three groups according to endoscopically assessed clinical response.

The participant selection process is illustrated schematically in Figure 1.

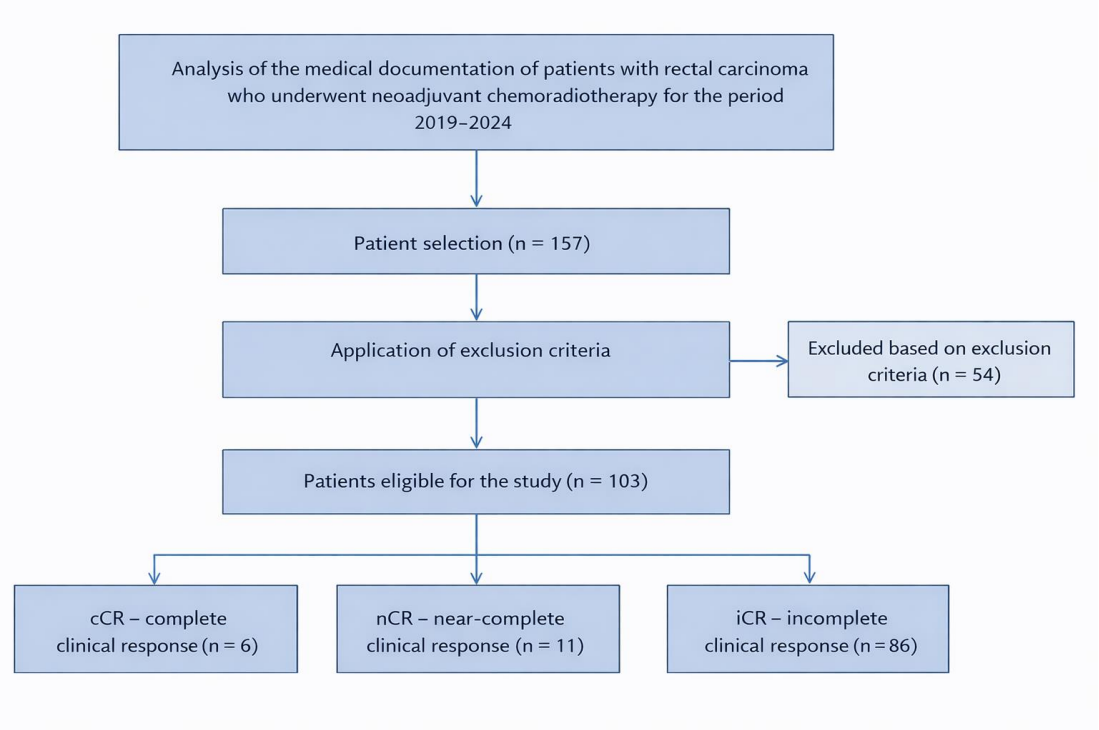


Figure 1. Scheme of patient inclusion and exclusion in the study.

4.2. Descriptive statistics of the sample

The final analysis included 103 patients with rectal carcinoma who underwent neoadjuvant chemoradiotherapy.

The largest proportion of tumors were located in the lower rectum (51.7%), followed by the middle third (34.5%) and the upper rectum (13.8%).

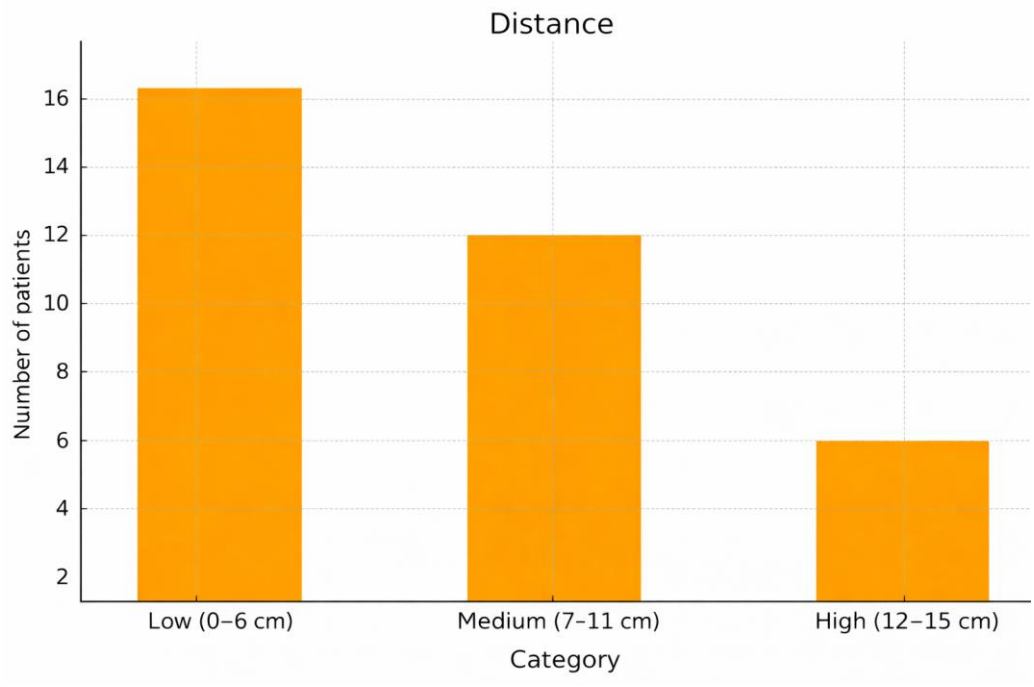


Figure 2. Distance of tumors from the anal margin

In terms of the circumferential extent of the tumor formation, the most common finding was involvement of 75-100% of the rectal wall circumference (43.3%), followed by 50-75% (26.7%) and 25-50% (23.3%). Only 6.7% of patients fell into the group with minimal involvement (0-25%).

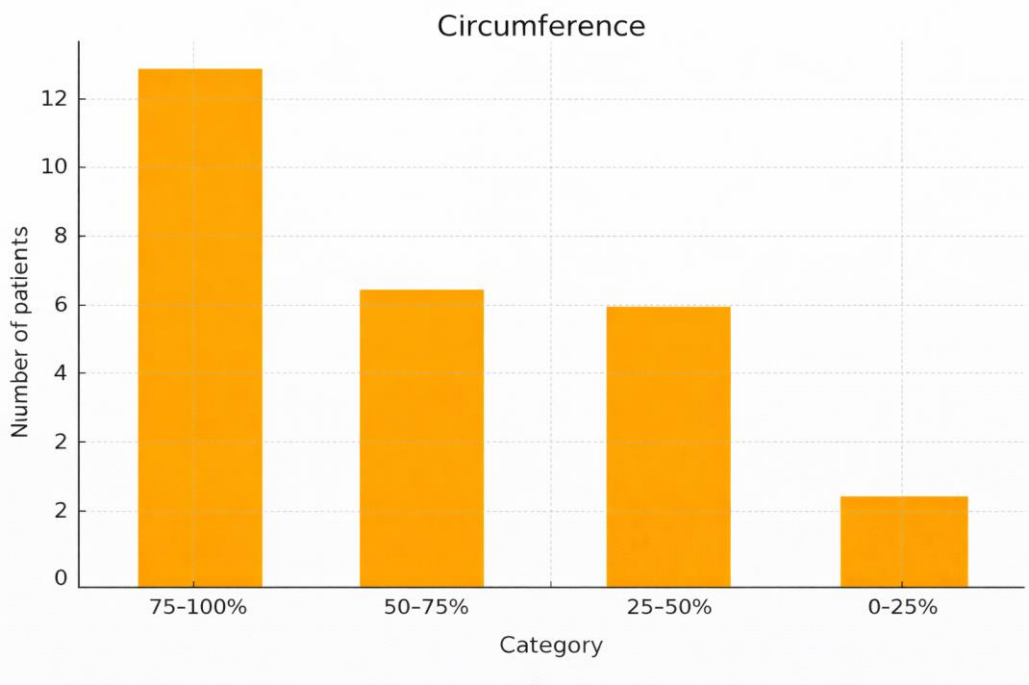


Figure 3. Circumferential spread of tumors

Extramural venous invasion (EMVI) was found in 80% of patients.

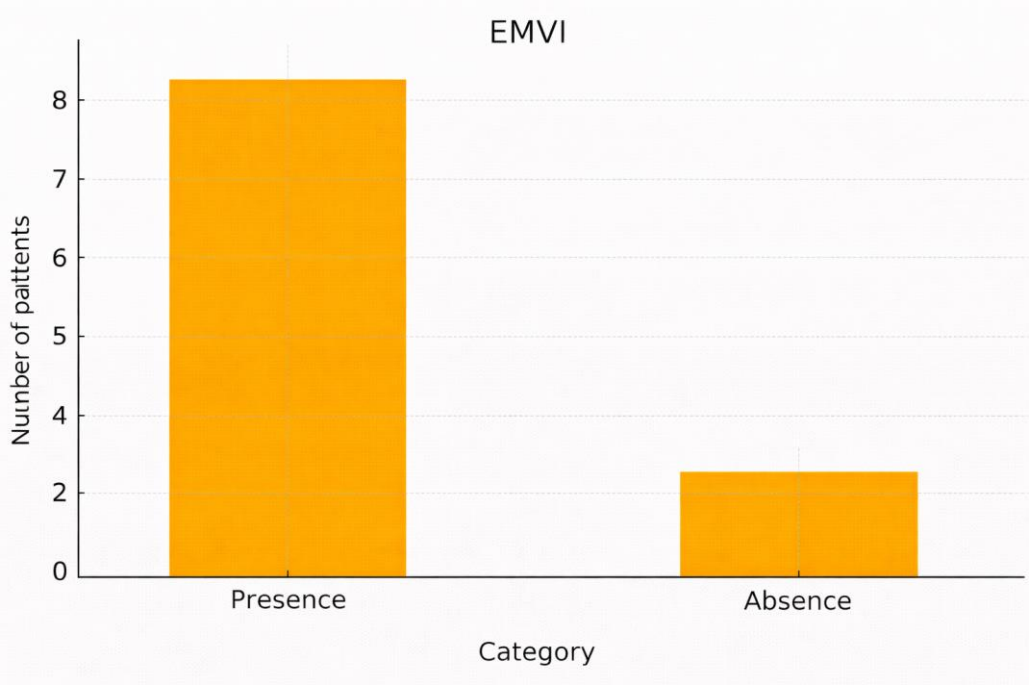


Figure 4. Extramural venous invasion

Pathologically involved lymph nodes, identified by MRI, were present in 81.9% of cases. The mesorectal fascia was free in 57.1% and involved in 42.9% of patients.

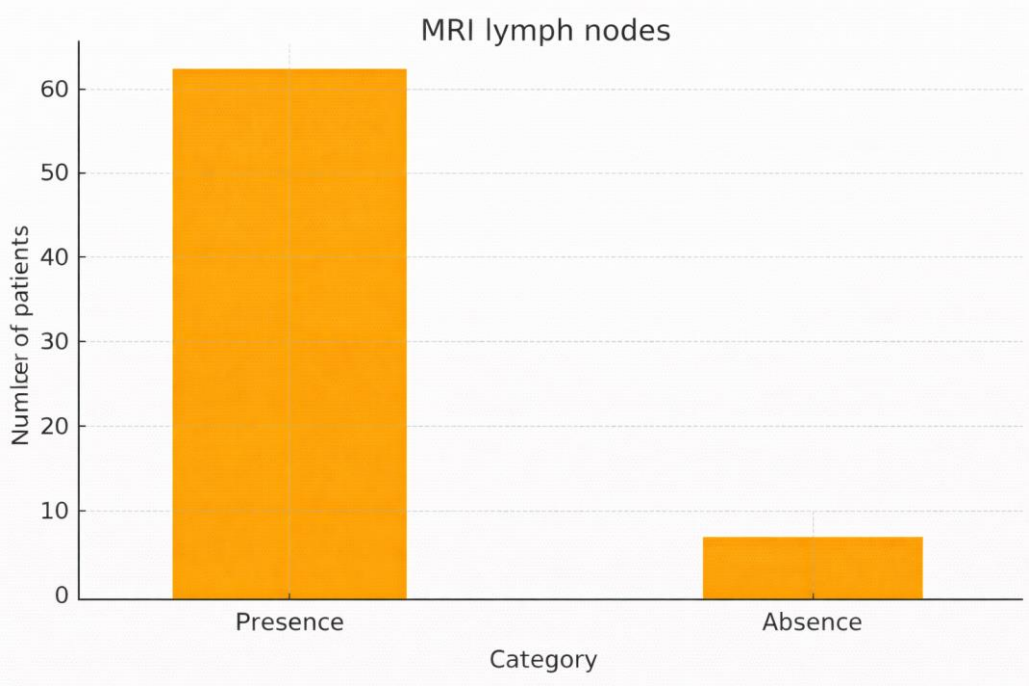


Figure 5. MRI-detected positive lymph nodes

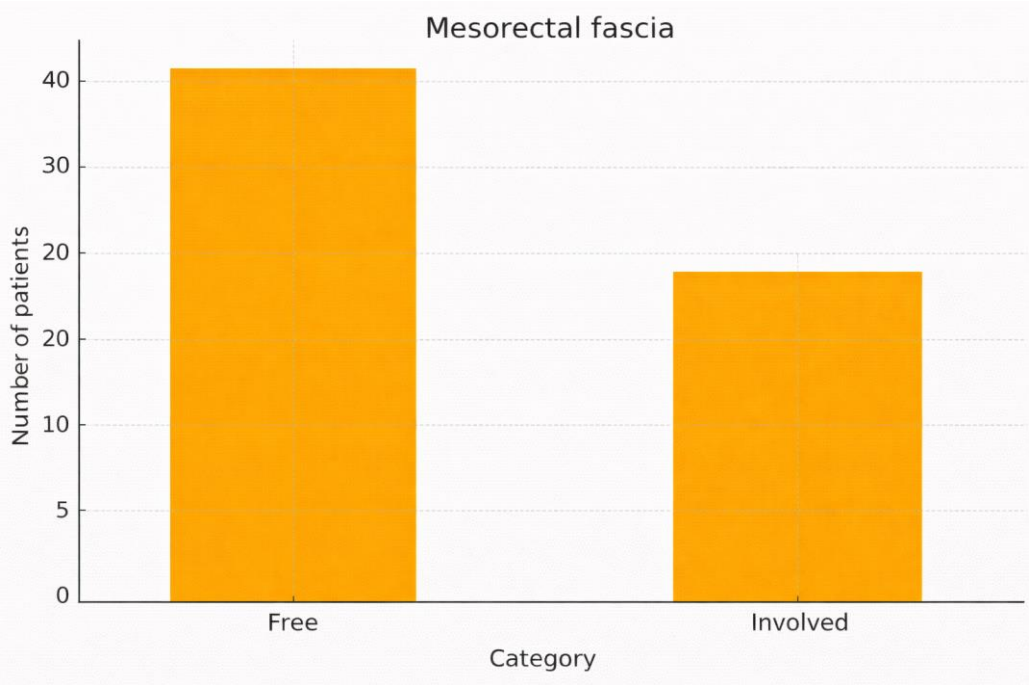


Figure 6. Involvement of the mesorectal fascia

Data on palpable tumor formation in the rectum were found in 93.1% of patients during clinical examination.

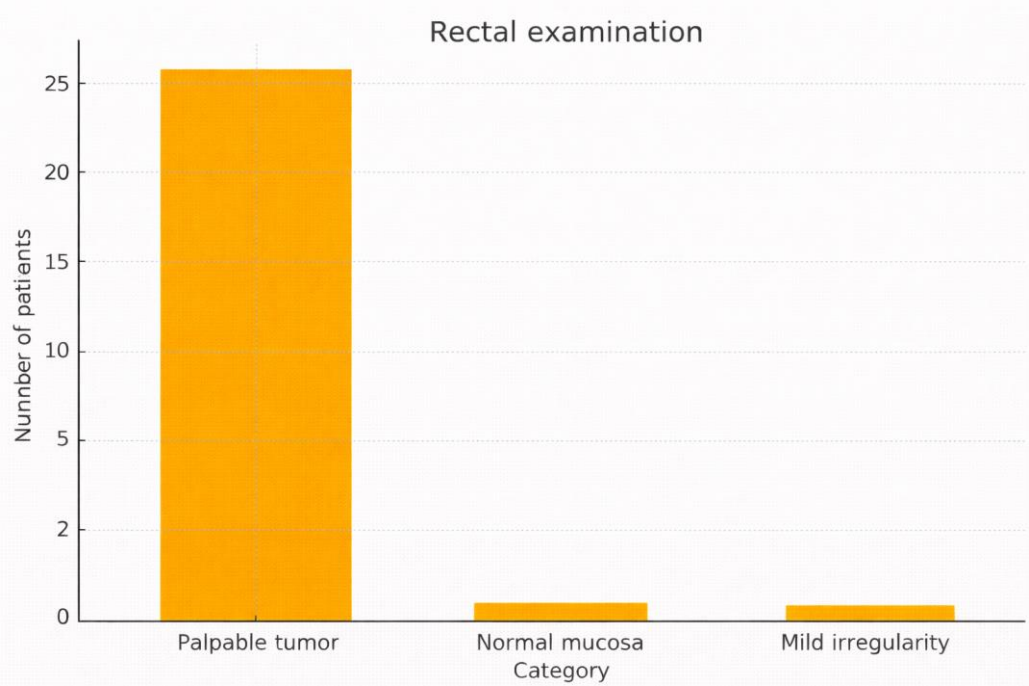


Figure 7. Physical findings during clinical examination

Tumor regression, assessed by MRI, at the first visit after completion of nCRT (mrTRG.1) was classified as good (mrTRG2) in 47.2%, moderate (mrTRG3) in 34.0%, predominantly tumor mass (mrTRG4) in 11.2%, and patients with complete (mrTRG1) or no response (mrTRG5) accounted for 3.8% each.

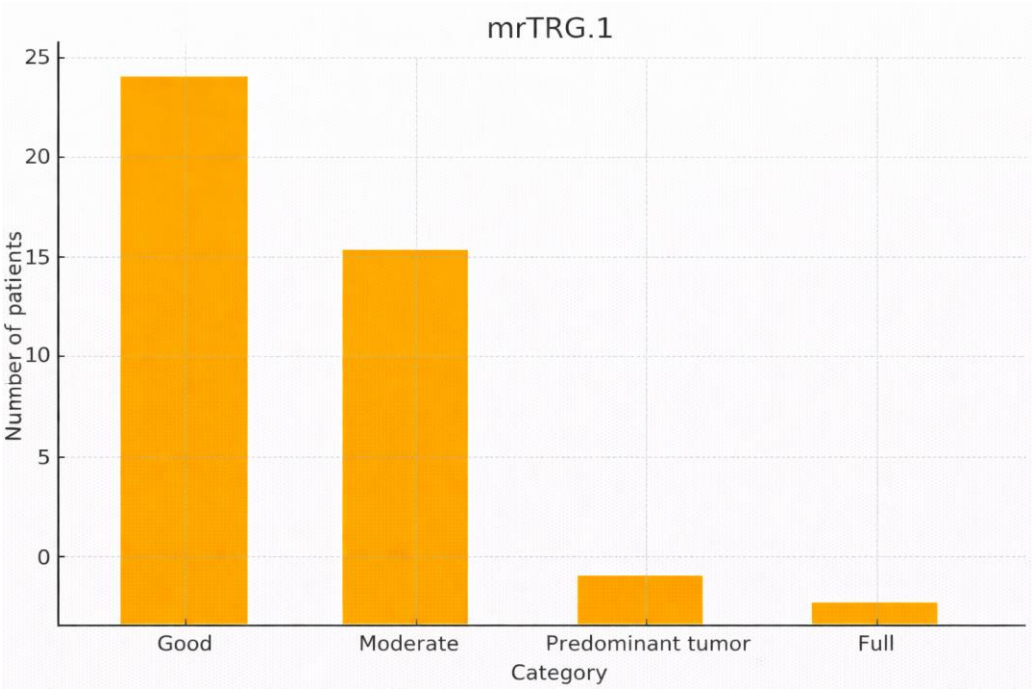


Figure 8. mrTRG

In staging PET/CT, the presence of a metabolically active tumor is observed in 95.6% of patients. At the first follow-up examination after treatment, persistent tumor metabolic activity was recorded in 59%, no evidence of pathological metabolism was found in 23%, 14.8% showed a metabolically active primary tumor and newly developed distant metastases, and 3.3% showed distant metastases only.

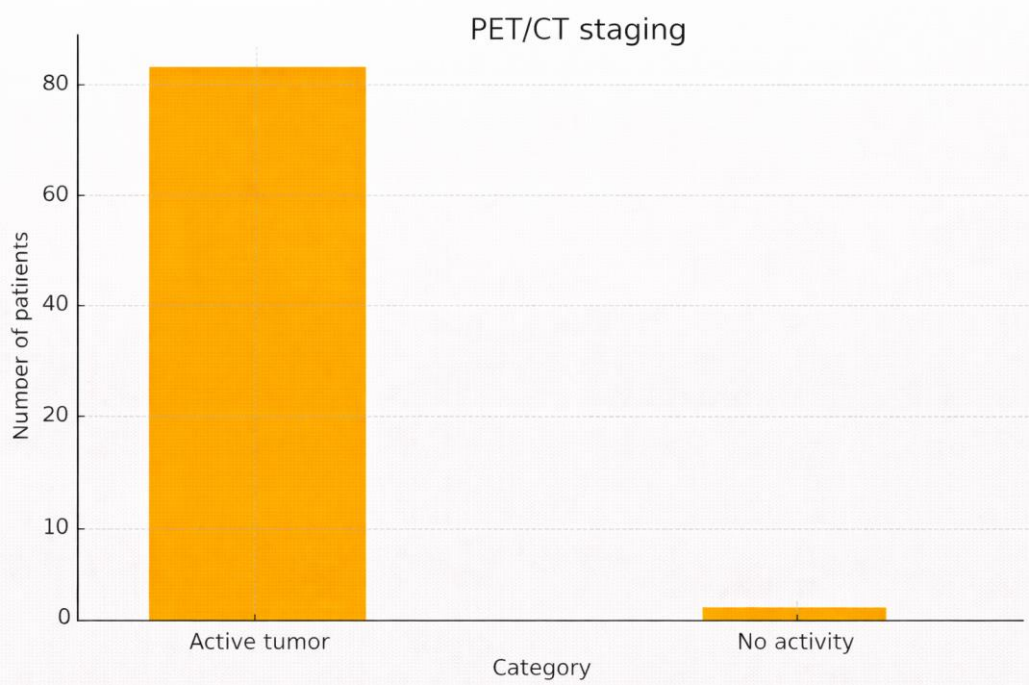


Figure 9. Finding in a staging PET/CT scan

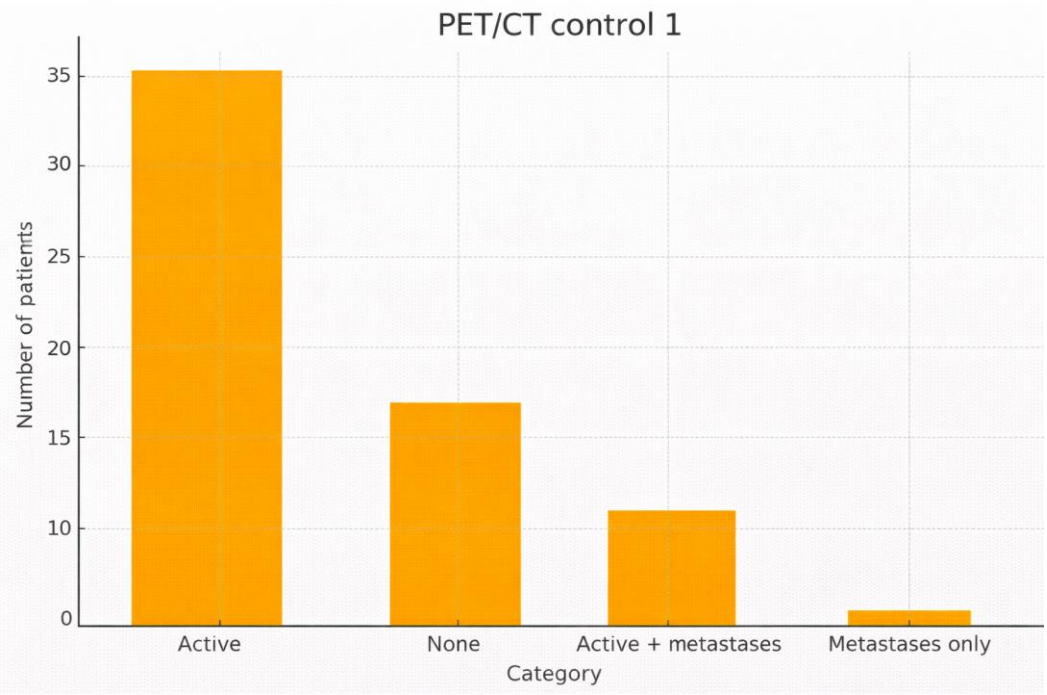


Figure 10. Findings at the first follow-up PET/CT

In the initial endorectal ultrasound, the most commonly defined stage was uT3 (53.8%). After neoadjuvant therapy, the proportion of patients with uT3 and

those with indeterminate stage due to post-radiation changes was the same—31.2%.

There was also an increase in the number of patients with progression in the degree of tumor invasion established by endorectal echography.

Table 1. Endorectal ultrasound at diagnosis and staging

ERUS.1	Count (n)	Percentage (%)
uT3	7,0	53,8
Indeterminate	3,0	23,1
uT1	1,0	7,7
uT2	1,0	7,7
uT4	1,0	7,7

Table 2. Endorectal ultrasound after nCRT

ERUS.2	Count (n)	Percentage (%)
uT3	5,0	31,2
Indeterminate	5,0	31,2
uT4	3,0	18,8
uT2	2,0	12,5
uT1	1,0	6,2

In the histological examination of endoscopic biopsies taken during the first follow-up examination, no malignant cells were found in 51.6% of patients, while in the remaining 48.4% signs of residual viable tumor were detected.

Table 3. Endoscopic biopsy at the first follow-up endoscopy

Biopsy 1	Count (n)	Percentage (%)
Non-malignant	49,0	51,6
Malignant	46,0	48,4

The endoscopically assessed clinical response was incomplete in 62.1% of patients, and data on complete clinical response were found in 5.8% of cases.

Table 4. Endoscopically assessed clinical response at first follow-up

Endoscopically assessed clinical response 1	Count (n)	Percentage (%)
Incomplete (iCR)	64,0	62,1
No Relapse	12,0	11,7
Near-complete (nCR)	11,0	10,7
With Relapse	10,0	9,7
Complete response (cCR)	6,0	5,8

The most commonly detected pathological T stage after treatment was ypT3 (51.5%).

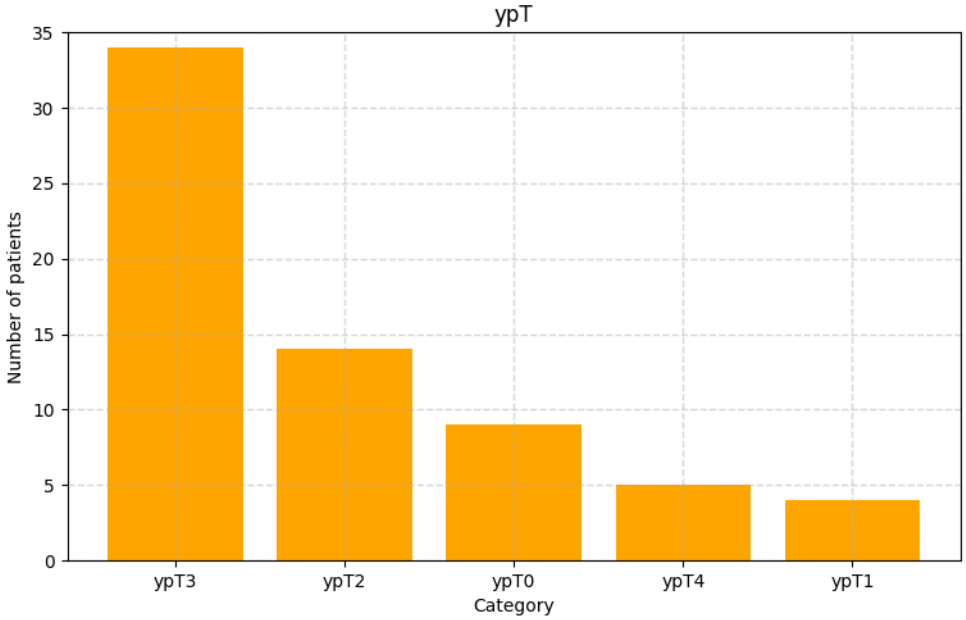


Figure 11. Pathological T-stage after treatment

After treatment, 73% of patients had no evidence of lymph node involvement.

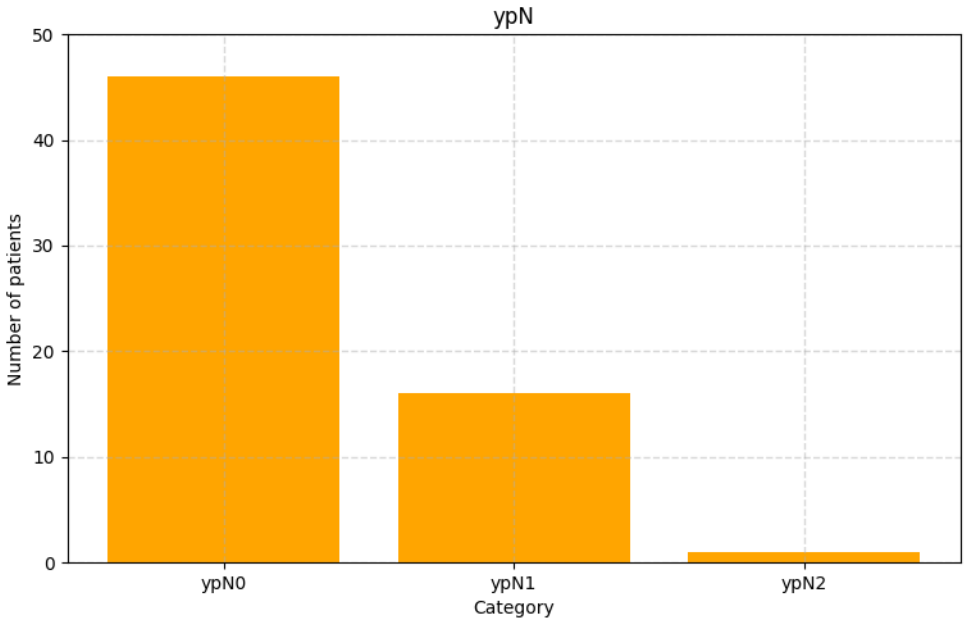


Figure 12. Pathological N stage after treatment

The degree of tumor regression, assessed according to Dworak, in surgical resections after neoadjuvant therapy was distributed as follows: the largest proportion of patients had Dworak 1 (31.7%), followed by Dworak 0 (25%) and Dworak 2 (23.3%).

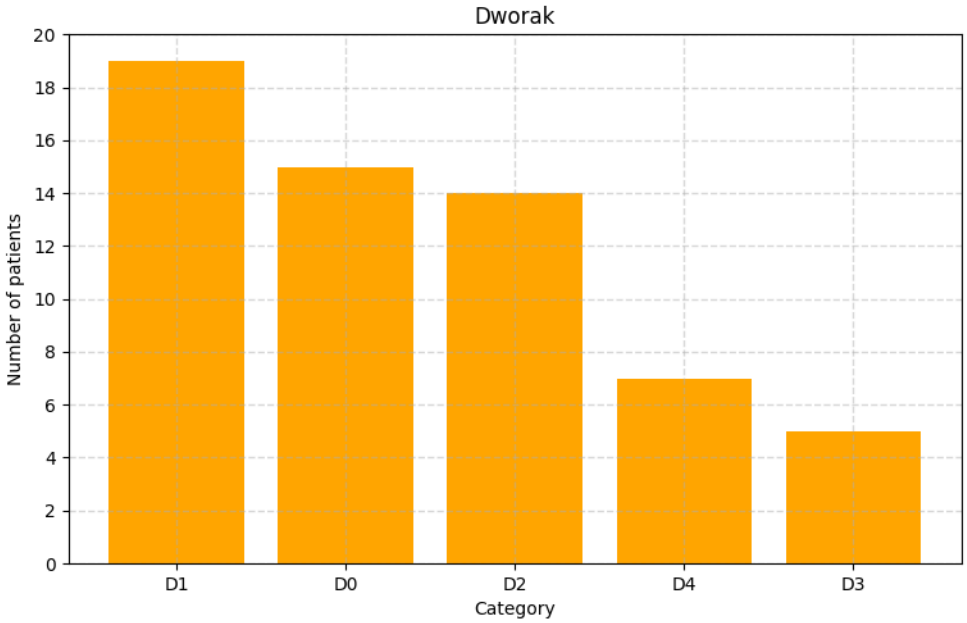


Figure 13. Pathological tumor regression

4.3. Results for task 1: To analyze the demographic, clinical, imaging, and pathological characteristics of the studied cohort of patients with rectal cancer who underwent neoadjuvant chemoradiotherapy (nCRT).

Demographic characteristics

The study cohort showed a predominance of males—60 patients (58.3%) compared to 43 females (41.7%).

Table 5. Distribution of patients in the sample by gender

Gender	Count (n)	Percentage (%)
Male	60	58,3%
Female	43	41,7%

The average age of patients was 67.1 years (standard deviation, SD = 10.8), ranging from 35 to 86 years, with older patients predominating.

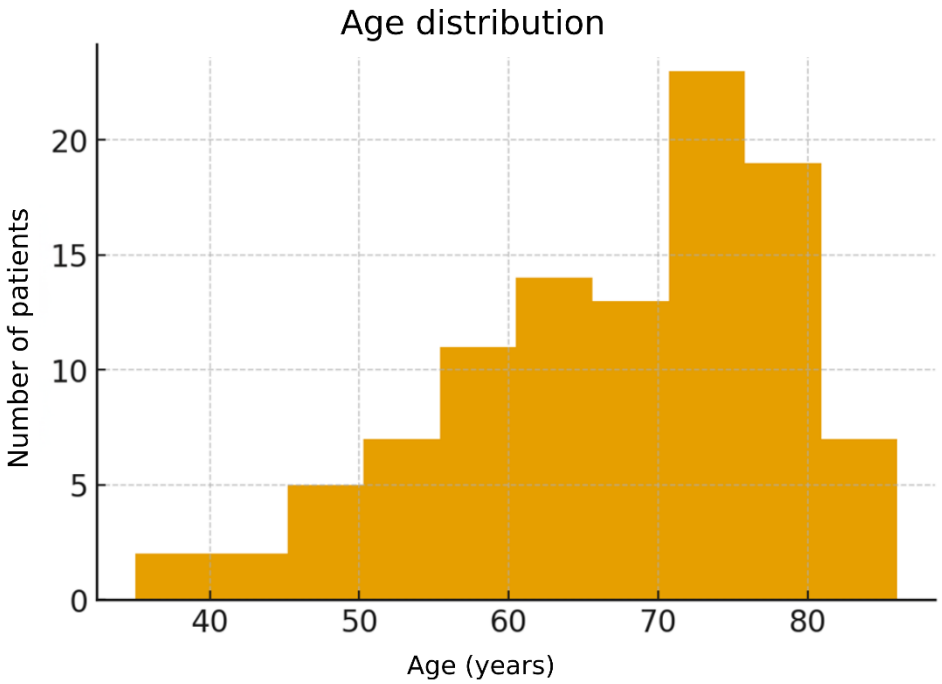


Figure 14. Distribution by ag

Comorbidities were found in 65.0% of patients. The most common were cardiovascular pathologies, followed by metabolic disorders (diabetes mellitus and dyslipidemia) and renal and gastrointestinal diseases. No comorbidities were documented in 35.0% of patients.

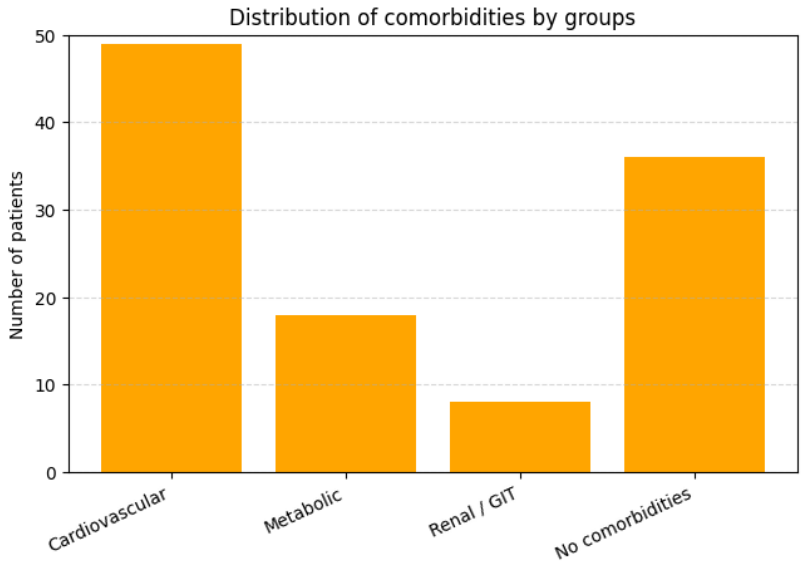


Figure 15. Comorbidities

Clinical and tumor characteristics

Data on the exact tumor location relative to the anal margin were available for 29 patients. Low localization (0–6 cm from the anal margin) was found in 51.7%, medium (7–11 cm) in 34.5%, and high (12–15 cm) in 13.8% of them.

Table 6. Distribution of patients by tumor location (in cm from the anal margin)

Localisation	Count (n)	Percentage (%)
Low (0–6 cm)	15	51,7
Middle (7–11 cm)	10	34,5
High (12–15 cm)	4	13,8

The circumferential tumor coverage (available in 30 patients) was most often between 75–100% (43.3%), followed by 50–75% (26.7%) and 25–50% (23.3%), with involvement below 25% observed in 6.7%.

Table 7. Distribution of patients by circumferential extent of the tumor

Circumferential Extent	Count (n)	Percentage (%)
75–100%	13	43,3
50–75%	8	26,7
25–50%	7	23,3
0–25%	2	6,7

EMVI was found in 80.0% of patients with available MRI assessment (n=75).

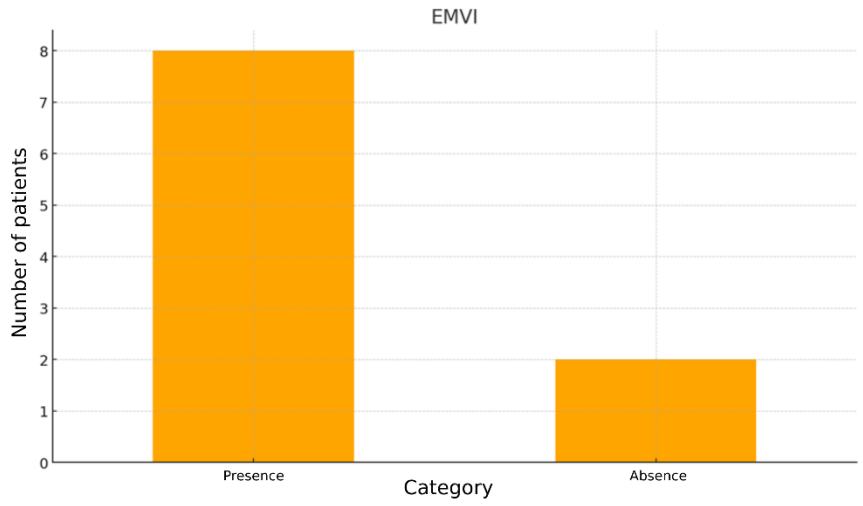


Figure 16. EMVI status

Positive lymph nodes on MRI were found in 81.9% of patients who underwent the examination (n=72).

Table 8. Presence of MRI-detected pathologically involved lymph nodes

Parameter	Category	Count (n)	Percentage (%)
MRI-detected pathologically involved lymph nodes	Present	59	81,9
MRI-detected pathologically involved lymph nodes	Absent	13	18,1

The mesorectal fascia was assessed as free in 57.1% and involved in 42.9% of patients with available data (n=70).

Table 9. Relationship of the tumor to the mesorectal fascia

Mesorectal fascia status	Count (n)	Percentage (%)
Free (not involved)	40,0	57,1
Involved	30,0	42,9

During clinical examination with digital rectal examination (described in 29 patients), a tumor formation was palpated in 93.1% of cases.

Table 10. Physical finding during clinical examination (digital rectal examination)

Digital rectal examination	Count (n)	Percentage (%)
Palpable tumor	27,0	93,1
Normal mucosa	1,0	3,4
Mild irregularity	1,0	3,4

Imaging characteristics after neoadjuvant therapy

The first MRI assessment of tumor regression (mrTRG.1, available in 53 patients) showed a good imaging response (mrTRG2) in 47.2% of patients, moderate (mrTRG3) in 34.0%, predominant tumor mass (mrTRG4) in 11.3%, complete response (mrTRG1) in 3.8%, and no response/relapse (mrTRG5) in 3.8%.

Table 11. Tumor regression grade assessed by MRI (mrTRG)

mrTRG.1	Count (n)	Percentage (%)
Good	25,0	47,2
Moderate	18,0	34,0
Predominant tumor mass	6,0	11,3
Complete response (cCR) response	2,0	3,8
No response/relapse	2,0	3,8

At initial PET/CT staging (n=91), metabolically active primary tumors were found in 95.6% of patients. At the first follow-up PET/CT (n=61), persistent tumor metabolic activity was recorded in 59%, 23% had no evidence of pathological metabolism, 14.8% had an active primary tumor with newly developed distant metastases, and 3.3% had distant metastases only.

Table 12. Findings on staging PET/CT

PET/CT finding	Count (n)	Percentage (%)
Metabolically active primary tumor	87,0	95,6
No metabolic activity detected	4,0	4,4

Table 13. Findings on first follow-up PET/CT

PET/CT control 1	Count (n)	Percentage (%)
Metabolically active primary tumor	36,0	59,0
No metabolic activity detected	14,0	23,0
active primary tumor + distant metastases	9,0	14,8
Distant metastases only	2,0	3,3

Staging endorectal ultrasound (ERUS.1, n=13) most often determined stage uT3 (53.8%). In the follow-up ultrasound after treatment (ERUS.2, n=16), the most common were uT3 and cases defined as indeterminate in stage, against a background of post-radiation changes, 31.2% each.

Table 14. Endorectal ultrasound for diagnosis and staging

ERUS.1	Count (n)	Percentage (%)
uT3	7,0	53,8
Indeterminate	3,0	23,1
uT1	1,0	7,7
uT2	1,0	7,7
uT4	1,0	7,7

Table 15. Endorectal ultrasound after nCRT

ERUS.2	Count (n)	Percentage (%)
uT3	5,0	31,2
Indeterminate	5,0	31,2
uT4	3,0	18,8
uT2	2,0	12,5
uT1	1,0	6,2

Endoscopic and histological findings

The biopsy material obtained during the first endoscopic control (n=95) revealed the presence of malignant cells in 48.4% of cases and the absence of such cells in the remaining 51.6%.

The endoscopically assessed clinical response was rated as incomplete in 62.1% of patients, almost complete in 10.7%, no recurrence in 11.7%, local recurrence in 9.7%, and clinical complete response in 5.8% of cases.

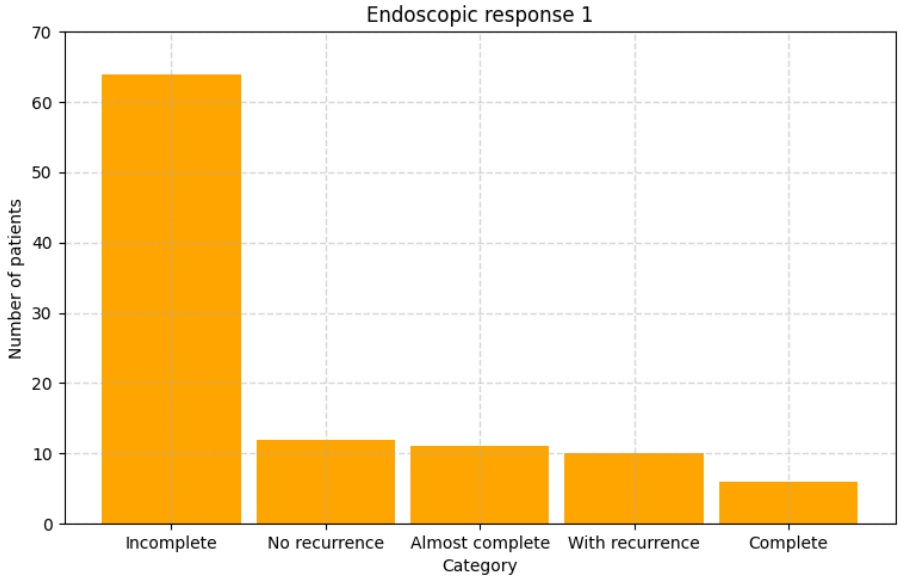


Figure 17. Endoscopic response at first follow-up

Pathological characteristics

Pathological examination of surgical resections after therapy (n=66) showed that ypT3 stage was the most common (51.5%), followed by ypT2 (21.2%) and ypT0 (13.6%). Negative lymph nodes (ypN0) were found in 73.0% of patients.

Table 16. Pathological T-stage after treatment

ypT	Count (n)	Percentage (%)
ypT3	34,0	51,5
ypT2	14,0	21,2
ypT0	9,0	13,6
ypT4	5,0	7,6
ypT1	4,0	6,1

Table 17. Pathological N-stage after treatment

ypN	Count (n)	Percentage (%)
ypN0	46,0	73,0
ypN1	16,0	25,4
ypN2	1,0	1,6

According to the Dworak classification, more than half of the patients had a poor pathological response to the treatment (Dworak 0-1; 56.7%), while a near-complete or complete response (Dworak 3-4) was observed in 20%.

Table 18. Pathological tumor regression after treatment, assessed by Dworak

Dworak	Count (n)	Percentage (%)
D1	19,0	31,7
D0	15,0	25,0
D2	14,0	23,3
D4	7,0	11,7
D3	5,0	8,3

4.4. Results for task 2: Define the prognostic factors associated with achieving a complete clinical response (cCR) after nCRT.

Table 19. Predictive factors associated with achieving clinical complete response (cCR) after nCRT

Variable	cCR (n=6)	non-cCR (n=97)	P
Age (years)	71,0 [68,0–74,0]	68,0 [60,0–76,0]	0,426
Maximum tumor diameter (cm)	4,0 [4,0–4,0]	6.0 [5,0–7,0]	0,218
CEA (ng/mL)	1,2 [0,9–1,5]	2,4 [1,3–5,8]	0,243
Gender (male/female)	3/6 (50,0%)	57/97 (58,8%)	0,692

Low localisation 0–6 sm	1/6 (16,7%)	13/97 (13,4%)	1,000
Circumferential Extent >50%	0/6 (0,0%)	19/97 (19,6%)	0,590
EMVI positive	0/6 (0,0%)	8/97 (8,2%)	1,000
MRI Positive lymph nodes	3/6 (50,0%)	55/97 (56,7%)	1,000
Threatened/involved mesorectal fascia	1/6 (16,7%)	29/97 (29,9%)	0,669
Palpable tumor on digital rectal examination	1/6 (16,7%)	25/97 (25,8%)	1,000
mrTRG 1–2 (complete/good response)	3/6 (50,0%)	22/97 (22,7%)	0,152
Metabolically active tumor (PET/CT staging)	6/6 (100,0%)	80/97 (82,5%)	0,586
uT3–4 on initial ERUS.1	1/6 (16,7%)	5/97 (5,2%)	0,309
Biopsy 1: presence of malignant cells	1/6 (16,7%)	45/97 (46,4%)	0,221

Six patients (5.8%) were included in the group with endoscopic complete clinical response (cCR), and 97 patients were included in the group without complete clinical response (non-cCR = nCR + iCR).

The median age in the cCR group was 71 years [68.0-74.0], and in the non-cCR group – 68 years [60.0-76.0], with the difference not reaching statistical significance ($p = 0.426$). The maximum tumour diameter was smaller

in the cCR group (median 4.0 cm [4.0-4.0]) compared to the non-cCR group (6.0 cm [5.0-7.0]), but without a statistically significant difference (p = 0.218). Similarly, baseline serum CEA values were lower in patients with cCR (1.2 ng/mL [0.9–1.5] vs. 2.4 ng/mL [1.3–5.8]), but also without a significant association (p = 0.243).

The gender distribution was similar between the two groups—men accounted for 50.0% of patients with cCR and 58.8% of those without cCR (p = 0.692). Low tumor location (0–6 cm from the anal margin) was present in 16.7% of patients with cCR and in 13.4% of patients without cCR (p = 1.000).

Involvement of more than 50% of the circumference of the rectal wall was observed only in patients without cCR (19.6% vs. 0.0%) without a statistically significant difference; p = 0.590).

Extramural venous invasion was not found in the cCR group, while in non-cCR patients it was present in 8.2% (p = 1.000).

Positive lymph nodes on MRI were found in 50.0% of patients with cCR and in 56.7% of patients without cCR (p = 1.000).

Compromised or involved mesorectal fascia was reported in 16.7% of patients with cCR and in 29.9% of patients without cCR (p = 0.669). A palpable tumor on rectal examination was found in 16.7% of patients with cCR and in 25.8% of patients without cCR (p = 1.000).

Favorable imaging tumor regression (mrTRG1–2; complete or good imaging response) was observed in 50.0% of patients with cCR and in 22.7% of patients without cCR (p = 0.152). Metabolically active primary tumor on PET/CT staging was observed in 100.0% of patients with cCR and in 82.5% of patients without cCR (p = 0.586). Advanced local stage (uT3–4) at initial endorectal echography was recorded in 16.7% of patients with cCR and in 5.2% of patients without cCR (p = 0.309).

The presence of malignant cells in the biopsy material from the first follow-up endoscopy was found in 16.7% of patients with cCR and in 46.4% of patients without cCR ($p = 0.221$).

4.5. Results for task 3: To investigate the association between the degree of clinical response determined endoscopically (cCR, nCR, iCR) with imaging and tumor characteristics after nCRT.

The degree of clinical response assessed endoscopically was classified into three categories: complete clinical response (cCR), near complete clinical response (nCR), and incomplete clinical response (iCR).

Due to the retrospective design of the study and the incomplete availability of all indicators for each patient, individual analyses were performed on subsamples with available data for the relevant variables.

The association between these categories and imaging parameters after nCRT was analyzed using the χ^2 test and nonparametric methods. Due to the small number of patients in some groups, the results should be interpreted with caution.

Association between endoscopically assessed clinical response and MRI tumor regression gradient

The mrTRG categories were grouped into three levels: good imaging response (mrTRG1-2), moderate response (mrTRG3), and poor response (mrTRG4-5).

Table 20. Endoscopically assessed clinical response × mrTRG.1

Endoscopically assessed clinical response	Good (mrTRG1-2)	Moderate (mrTRG3)	Poor (mrTRG4-5)
cCR	3 (75,0%)	0 (0,0%)	1 (25,0%)
iCR	17 (54,8%)	11 (35,5%)	3 (9,7%)
nCR	3 (50,0%)	3 (50,0%)	0 (0,0%)

No statistically significant correlation was found between endoscopically assessed clinical response (cCR, nCR, iCR) and MRI-based tumor regression gradient at the first follow-up (mrTRG.1) ($\chi^2 = 3.67$, $p = 0.453$).

Association between endoscopically assessed clinical response and extramural venous invasion (EMVI)

Only patients with available MRI assessment for extramural venous invasion (n=57) were included in the analysis of the relationship between endoscopically assessed clinical response and EMVI.

Table 21. Endoscopically assessed clinical response × EMVI

Endoscopically assessed clinical response	EMVI (-)	EMVI (+)	Total
cCR	3 (100%)	0 (0%)	3
iCR	42 (89,4%)	5 (10,6%)	47
nCR	4 (57,1%)	3 (42,9%)	7

A statistically significant correlation was found between the endoscopically assessed clinical response and venous involvement ($\chi^2 = 9.94$, $p = 0.042$). EMVI-positive cases predominated in the incomplete endoscopic

response (iCR) group, while no EMVI-positive patients were observed in the cCR group.

Endoscopically assessed clinical response and circumferential tumor involvement

Table 22. Endoscopic response × circumferential involvement

Endoscopically assessed clinical response	25–50%	50–75%	75–100%
cCR	1 (100%)	0 (0%)	0 (0%)
iCR	4 (18,2%)	6 (27,3%)	10 (45,5%)
nCR	2 (66,7%)	0 (0%)	1 (33,3%)

The relationship between the degree of circumferential involvement of the rectal wall and endoscopic response did not reach statistical significance ($\chi^2 = 5.58$, $p = 0.233$).

Endoscopically assessed clinical response and MRI-assessed lymph node involvement.

Table 23. Endoscopic response × MRI lymph nodes

Endoscopically assessed clinical response	No lymph nodes detected	Positive lymph nodes detected
cCR	0 (0%)	3 (100%)
iCR	6 (13,0%)	40 (87,0%)
nCR	3 (42,9%)	4 (57,1%)

The analysis of the relationship between endoscopically assessed clinical response and the presence of disease-involved lymph nodes on MRI showed a value of $\chi^2 = 4.61$ ($p = 0.100$). Lymph node involvement was more common in patients with iCR.

Endoscopically assessed clinical response and maximum tumor diameter

Table 24. Maximum tumor diameter (cm) by endoscopic response groups

Endoscopically assessed clinical response	n	mean	SD	min	25%	50%	75% / max
cCR	1	4,00	–	4,00	4,00	4,00	4,00
iCR	20	5,85	1,35	3,00	5,00	6,00	7,00 / 8,00
nCR	3	4,67	0,58	4,00	4,50	5,00	5,00

The comparison of the maximum tumor diameter between the three groups, performed using the Kruskal–Wallis test, showed no statistically significant difference ($H = 4.38$, $p = 0.112$).

4.6. Results for task 4: Perform a comparative analysis between patients with good clinical response (cCR+nCR) and those with incomplete clinical response (iCR).

For the purposes of the comparative analysis, patients were divided into two groups according to endoscopically assessed clinical response: a group with good clinical response (cCR + nCR) and a group with incomplete clinical

response (iCR). The relationship between clinical response and tumor location in the rectum was analyzed.

Table 25. Distribution of clinical response by tumor location

Localisation	cCR + nCR	iCR
Low rectum (0–6 cm)	4	9
Middle/Upper rectum (≥7 cm)	0	11

In distally located tumors (0–6 cm from the anal margin), a good clinical response was observed in 4 of 13 patients (30.8%), while in 9 of 13 (69.2%) there was an incomplete clinical response. In contrast, in more proximally located tumors, in the middle and high rectum (≥7 cm), there was not a single case of good clinical response (0 out of 11 patients), with all patients in this group having an incomplete clinical response.

Statistical analysis found a significant correlation between tumor location and clinical response ($\chi^2 = 4.06$, $p = 0.044$). Patients with tumors in the low rectum had a significantly higher chance of achieving a good clinical response compared to those with mid- or high-rectal tumors (OR = 10.89; 95% CI 0.52–229.02). The wide confidence interval reflects the limited number of observations.

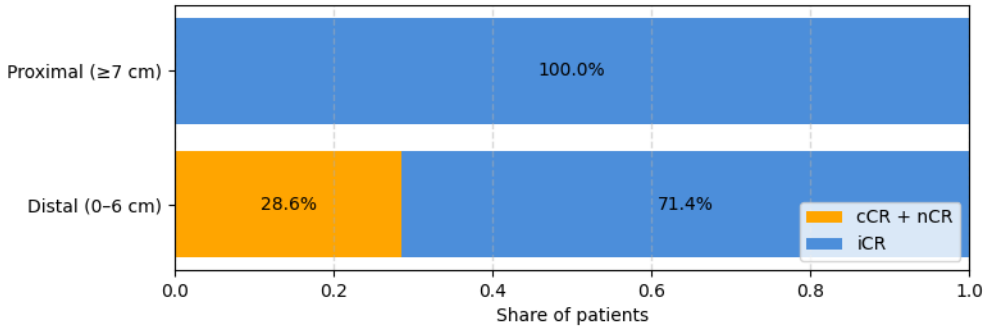


Figure 18. Clinical response rate in distal (0–6 cm) and proximal (≥7 cm) rectal tumors.

4.7. Results for task 5: To assess the impact of the time interval until the first follow-up endoscopy on the pathological tumor response after neoadjuvant chemoradiotherapy.

The median interval between the end of neoadjuvant chemoradiotherapy and the first follow-up endoscopy was 61 days (IQR 42–88 days). The minimum interval was 7 days and the maximum was 1942 days.

Pearson's correlation analysis did not find a statistically significant linear relationship between the interval from the end of nCRT to the first follow-up endoscopy and the degree of pathological tumor regression assessed on the Dworak scale ($r = –0.083$, $p = 0.532$). Within the observed range, the time to the first follow-up assessment did not show a statistically significant relationship with the degree of pathological response.

The time dynamics of the unfavorable pathological outcome (defined as Dworak 0–2) were further investigated using the Kaplan-Meier method. The analysis showed that during the first 60–90 days after completion of therapy, most patients did not develop adverse pathological regression, with the proportion of adverse outcomes gradually increasing after this period.

In the analysis by the ypT indicator (adverse outcome defined as ypT ≥ 2), the first events were observed approximately 50–70 days after the end of nCRT, while for ypN (adverse outcome, ypN ≥ 1), adverse events occurred earlier – around 30–50 days.

Survival without adverse pathological outcome according to the Dworak, ypT, and ypN indicators was presented graphically as Kaplan–Meier curves.

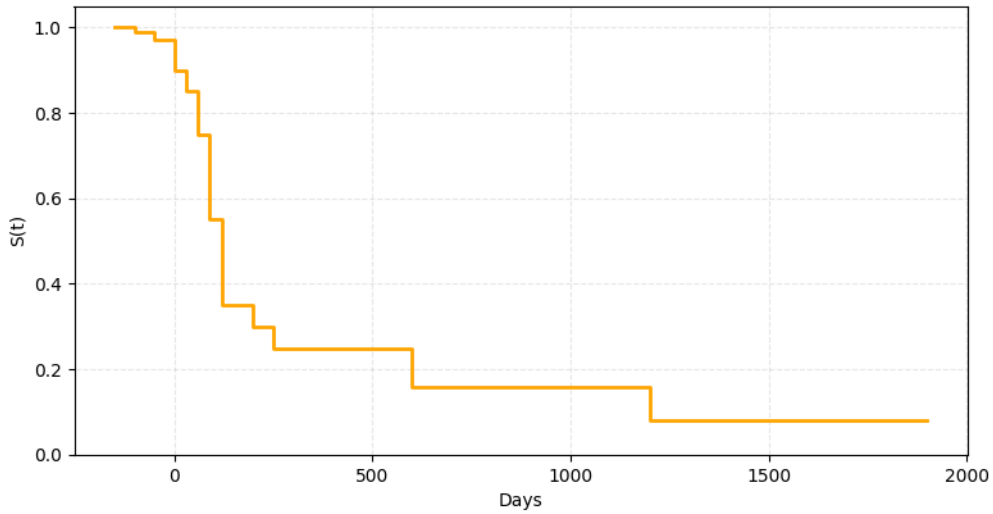


Figure 19. Kaplan–Meier curve for ypT.

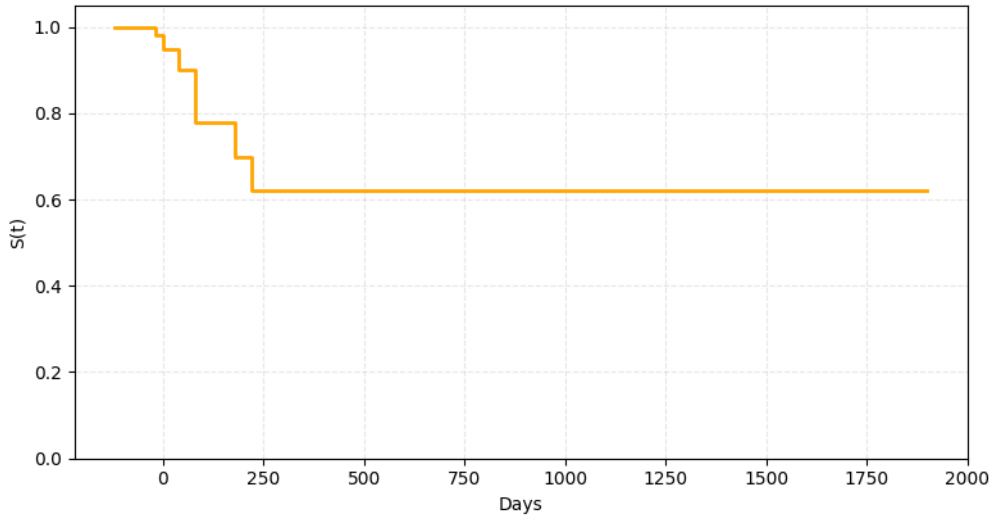


Figure 20. Kaplan–Meier curve for ypN Figure 20. Kaplan–Meier curve for ypN

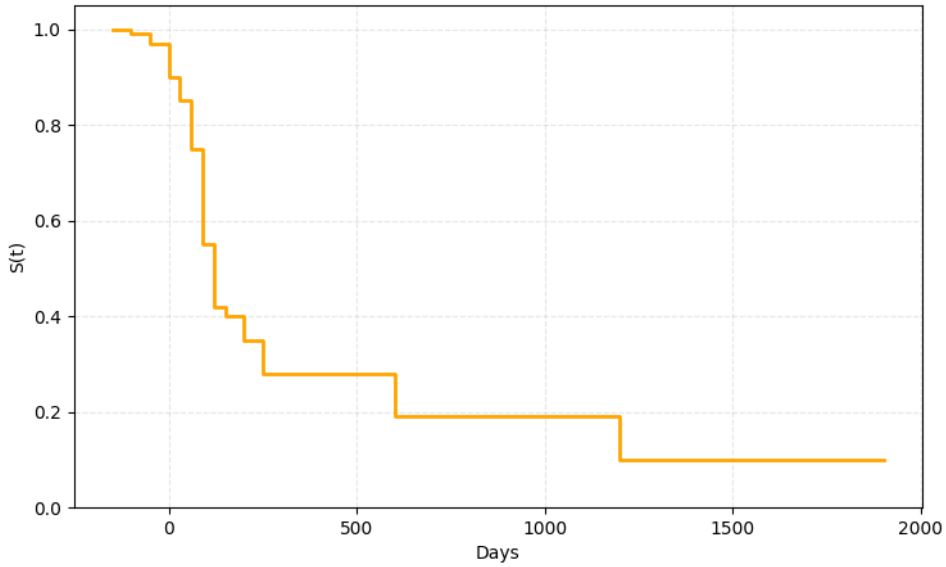


Figure 21. Kaplan–Meier curve for Dworak.

4.8. Results for task 6: To analyze the association between clinical, endoscopic, and imaging indicators and the probability of achieving a pathological complete response (pCR)

Pathological complete response (pCR) was defined as Dworak 4 tumor regression. The prognostic value of clinical, endoscopic, and imaging parameters for pCR was examined using correlation analysis, univariate diagnostic parameters, and a multivariate logistic regression model.

Correlation analysis

Table 26. Correlations between endoscopic, imaging, and pathological parameters (Spearman rho)

Pair of variables	Spearman rho	p

Endoscopically assessed clinical response 1 – Circumferential Extent	0,315	0,117
Endoscopically assessed clinical response 1 – Biopsy 1	0,034	0,743
Endoscopically assessed clinical response 1 – ypT	0,052	0,677
Endoscopically assessed clinical response 1 – ypN	-0,129	0,313
Endoscopically assessed clinical response 1 – Dworak	-0,121	0,357
Circumferential Extent – Biopsy 1	-0,066	0,750
Circumferential Extent – ypT	0,204	0,448
Circumferential Extent – ypN	-0,153	0,572
Circumferential Extent – Dworak	-0,260	0,331
Biopsy 1 – ypT	0,197	0,127
Biopsy 1 – ypN	-0,028	0,832
Biopsy 1 – Dworak	-0,192	0,160
ypT – ypN	0,324	0,010

ypT – Dworak	-0,491	<0,001
ypN – Dworak	-0,205	0,120

Correlation analysis showed that the endoscopically assessed clinical response at the first follow-up (Endoscopic Response 1) was not significantly associated with pathological parameters for tumor regression. No significant associations were found between Endoscopic Response 1 and Dworak, ypT, and ypN ($|rho| < 0.15$, $p > 0.30$).

The strongest inverse correlation was observed between ypT and Dworak ($rho = –0.491$, $p < 0.001$), indicating a strong inverse relationship between the depth of tumor infiltration and the degree of tumor regression. A moderate positive correlation was found between ypT and ypN ($rho = 0.324$, $p = 0.010$), indicating that more advanced local tumor stage is associated with a higher frequency of lymph node involvement.

Univariate analysis of the prognostic value for pCR

Table 27. Prognostic value for pCR – univariate analysis

	Sensitivity (%)	Specificity (%)	Accuracy (%)	p	OR (95% CI)
Endoscopic cCR	28,6	95,8	91,3	0,052	9,20 (1,35–62,83)

Biopsy 1: no malignant cells	71,4	50,0	51,6	0,437	2,50 (0,46–13,58)
CEA ≤5 ng/mL	66,7	31,1	37,5	1,000	0,99 (0,13–5,89)
Follow-up PET/CT: no metabolic activity	20,0	76,9	71,9	1,000	0,83 (0,08–8,18)

The univariate analysis included: endoscopic cCR, absence of malignant cells in the biopsy obtained during the first follow-up endoscopy (Biopsy 1), CEA ≤5 ng/mL, and absence of metabolic activity on PET/CT scan at first follow-up (PET/CT follow-up 1).

Endoscopic cCR demonstrated high specificity (95.8%) and borderline statistical significance as a predictor of pCR (OR= 9.20; 95% CI 1.35-62.83; p= 0.052). The other indicators did not show a statistically significant association with pCR.

Multivariate logistic regression analysis

Table 28. Multivariate logistic regression model for pCR

Parameter	OR	p	95% CI
Endoscopic cCR	15,46	0,013	1,78–134,30
Biopsy 1: no malignant cells	4,94	0,086	0,80–30,64
CEA ≤5 ng/mL	4,63	0,076	0,85–25,11

PET/CT: no metabolic activity	0,35	0,453	0,02–5,52

Endoscopic cCR, absence of malignant cells in Biopsy 1, CEA ≤5 ng/mL, and absence of metabolic activity on PET/CT were included in the multivariate logistic regression analysis.

The only independent statistically significant predictor of pCR was endoscopically determined complete clinical response (OR= 15.46; 95% CI 1.78-134.30; p= 0.013). The absence of malignant cells in Biopsy 1 and low CEA values showed a tendency to be associated with pCR, but without reaching statistical significance, while PET/CT parameters did not demonstrate prognostic value.

5. DISCUSSION

5.1. Summary of main results

This single-center retrospective cohort study evaluates the importance of endoscopy as a component of multimodal assessment of therapeutic response after neoadjuvant chemoradiotherapy in rectal cancer in real-world clinical practice. Patients with non-metastatic rectal adenocarcinoma treated at the medical facility over a five-year period were included.

The analyzed cohort is characterized by predominantly advanced age, a significant frequency of comorbidities, and a high relative proportion of low-lying tumors. Mesorectal and mesorectal fascia involvement is frequently observed, as well as extramural venous invasion and lymph node involvement,

as assessed by MRI. This reflects the profile of patients treated at a large cancer center and differs to some extent from more selective clinical trials.

The frequency of endoscopically confirmed complete clinical response (cCR) in the present study is 5.8%, and that of near complete response (nCR) is about 10%, while the majority of patients show incomplete clinical response (iCR). Pathological complete response (pCR, Dworak 4) was observed in approximately one-tenth of the operated patients. Most patients remain at stage ypT2–3 and ypN0–1, which emphasizes that in a significant proportion of patients, neoadjuvant therapy leads to partial but not complete tumor regression.

With regard to the first task—the description of demographic and tumor characteristics—there is a slight predominance of men, an average age of about 67 years, and a high frequency of cardiovascular and metabolic comorbidities. More than half of the tumors are located low in the rectum, and circumferential involvement is ≥50% in a significant proportion of patients. EMVI positivity and MRI-proven lymph node involvement are observed in a large proportion of patients, reflecting advanced local stage at diagnosis.

When analyzing the results of the second task—defining prognostic factors for endoscopically confirmed complete clinical response—trends toward smaller maximum tumor diameter, lower baseline CEA values, and less frequent presence of EMVI and compromised mesorectal fascia in patients with cCR. Due to the small number of cases with cCR, these trends are not statistically significant, but they outline a profile of a patient with more limited local disease and more favorable tumor characteristics.

The results of the third task show a statistically significant association between endoscopically determined clinical response and the presence of extramural vascular invasion. EMVI-positive tumors are disproportionately represented in the group with incomplete clinical response, while no such cases

are observed in patients with cCR. Post-treatment mrTRG shows a trend toward better imaging regression in patients with cCR.

A comparative analysis between the groups with good (cCR+nCR) and incomplete endoscopically determined clinical response (iCR) demonstrates a higher frequency of favorable response in distally located tumors (0–6 cm) compared to more proximal locations, albeit with a limited number of observations.

Regarding the influence of the interval between the end of neoadjuvant chemoradiotherapy and the first follow-up endoscopy on the pathological response, a median of 61 days was found, with a wide range of variation. Correlation analysis and Kaplan–Meier models did not show a clear statistically significant relationship between the duration of this interval and the degree of pathological tumor regression. The frequency of unfavorable pathological response remained relatively constant during the first 6–8 weeks after completion of therapy.

The sixth task assessed the prognostic value of clinical, endoscopic, and imaging indicators for achieving pathological complete response. In the multivariate logistic regression model, only endoscopically determined cCR remained an independent statistically significant predictor, associated with an approximately 15-fold increase in the probability of pCR. Negative biopsy and CEA ≤5 ng/mL showed a trend toward prognostic value but did not reach statistical significance, while PET/CT parameters did not demonstrate an independent predictive role.

5.2. Comparison with data from the literature

5.2.1. Cohort characteristics and response rate

The demographic profile of the included patients—higher mean age, predominance of males, and high proportion of comorbidities—is consistent with epidemiological data on rectal cancer, but differs from the selection in some randomized clinical trials, which often include younger patients with fewer comorbidities. This probably influences the frequency of complete response achieved and highlights the value of the current results as a reflection of real-world clinical practice.

The pCR rate in the analyzed cohort is at the lower end of the published values for standard long-course neoadjuvant chemoradiotherapy, where pCR typically ranges between 10 and 25% depending on the treatment regimen, stage distribution, and interval to surgery. Similar results have been reported in classic studies of preoperative chemoradiotherapy and in some cohorts treated with conventional regimens without escalation of systemic therapy.

On the other hand, more modern protocols of total neoadjuvant therapy and studies focused on an organ-preserving approach report higher rates of pCR and cCR, often above 20–25%.

The lower cCR rate in the study population probably reflects the more unfavorable initial tumor profile (high proportion of EMVI+, positive lymph nodes, large circumferential extent), as well as the fact that the data are from routine practice rather than a strictly standardized clinical protocol.

In addition, a significant proportion of patients are elderly and have significant comorbidity, which has likely led to more frequent interruptions or modifications of systemic therapy—factors that cannot be fully corrected in a retrospective analysis. These characteristics probably contribute to the lower frequency of complete response compared to the highly selected series reported in the context of organ-preserving treatment.

5.2.2. Prognostic factors for clinical complete response

Many authors report that smaller initial tumor size, lower T-stage, absence of EMVI, and low serum CEA levels are associated with a higher probability of achieving cCR and pCR after neoadjuvant therapy. Similar trends are observed in the cohort we analyzed – patients with endoscopically confirmed cCR had smaller tumors and lower CEA levels, as well as a more favorable local tumor profile in terms of circumferential extent, mesorectal fascia involvement, and the presence of EMVI. The lack of statistical significance of these associations is probably due to the limited number of patients in the cCR group, which limits the statistical power of the analysis.

It is interesting to note that factors associated with more aggressive tumor biology—such as EMVI positivity and more extensive circumferential involvement—are significantly more common in patients without a complete endoscopic response. This corresponds with published data on the role of EMVI as a negative prognostic factor in terms of both local response and long-term outcomes.

In this context, the results obtained support the concept that the initial imaging characteristics of the tumor can be used for risk stratification and for more precise selection of patients who can realistically achieve cCR.

5.2.3. Relationship between endoscopic, imaging, and pathological indicators

One of the main objectives of this dissertation is to evaluate the role of endoscopy in the context of multimodal assessment of therapeutic response—in combination with MRI, histological examination, and serum tumor markers. Post-therapeutic mrTRG demonstrates a tendency towards more frequent favorable categories (1–2) in patients with endoscopically established cCR,

which supports the use of mrTRG as part of the comprehensive post-treatment assessment.

Particularly noteworthy is the observation from the multivariate logistic regression analysis, in which endoscopically confirmed cCR is established as the only independent statistically significant predictor of pCR. This is consistent with published data showing that the endoscopic picture, especially when using standardized criteria (e.g., those of the MSKCC), represents a key factor in the assessment of treatment response.

Although the sensitivity of endoscopy for detecting pCR is not absolute, the presence of typical endoscopically established cCR significantly increases the chances of true pCR and may serve as a basis for discussing an organ-preserving approach in carefully selected patients.

On the other hand, negative endoscopic biopsy and low CEA values demonstrate only a trend toward independent prognostic value and do not reach statistical significance in the multivariate model. This is in line with numerous publications that emphasize the limited sensitivity of standard biopsy after neoadjuvant therapy due to the possible presence of focal residual foci in the submucosa or deeper layers of the intestinal wall, as well as the influence of post-radiation fibrosis on the quality of the samples. The observed trend in CEA is consistent with the literature data that low baseline or post-treatment values are associated with a more favorable response, but cannot be used in isolation as a criterion for watch-and-wait strategies.

The results obtained for PET/CT—lack of independent prognostic value for achieving pCR—are also comparable to the literature, which demonstrates the limited role of this method in accurately distinguishing between complete and incomplete local response in non-metastatic rectal carcinoma. PET/CT remains a valuable tool for detecting distant metastases and ruling out systemic

progression, but its role in selecting patients for organ-preserving treatment is controversial.

5.2.4. Tumor location and clinical response

In the present study, a higher frequency of good clinical response was observed in low-lying tumors (0–6 cm), while in more proximal locations, no cases of cCR or nCR were reported. A similar relationship is described in some series focusing on distal tumors, which report a higher frequency of cCR and broader possibilities for an organ-preserving approach.

At the same time, the data in the literature are not entirely consistent, with a number of authors finding no consistent relationship between tumor location and the degree of therapeutic response. The observed effect may also be influenced by technical factors, including more precise dose planning, differences in tumor biology, and variations in sensitivity to chemoradiotherapy.

The results of the current study should be interpreted with caution due to the limited number of patients in the subgroups and the wide confidence interval of the calculated OR. Nevertheless, the concentration of good clinical response in the distal tumor group is consistent with clinical experience and supports the careful evaluation of these patients as potential candidates for organ-preserving strategies, provided that all other safety criteria are met.

5.2.5. Interval until the first follow-up assessment

The optimal timing of the first follow-up assessment after neoadjuvant therapy remains a subject of active debate. Some authors report that extending the interval to surgical intervention beyond 8–12 weeks may increase the

frequency of pCR, while others emphasize the risk of tumor progression or technical difficulties during surgery due to fibrosis.

The present study evaluates the interval to the first follow-up endoscopy rather than to surgery, which is a different but practically important aspect.

The median of 61 days (approximately 8–9 weeks) corresponds to the interval recommended by many specialized centers for the first comprehensive assessment. The lack of a statistically significant relationship between the length of the interval and the pathological response in the present cohort may be explained by the limited power of the study, the wide range of intervals, and the possibility that other factors (e.g., tumor biology, completeness of therapy) may dominate the effect of time.

The shape of the Kaplan–Meier curves, illustrating a relatively stable risk of adverse pathological regression within the first 6–8 weeks, supports the concept that this interval is a reasonable compromise between the need for maximum tumor regression and the risk of delayed detection of persistent or progressive disease.

5.3. Methodological features and limitations of the study

The interpretation of the results should take into account several important limitations. First, the study is retrospective and single-center, which carries an inherent risk of selection and information bias. The analysis included only patients with complete medical records and a control assessment, which probably led to the exclusion of some of the more complex cases or patients with incomplete follow-up.

Another significant feature is the limited number of patients with cCR and pCR. The small number of events leads to wide confidence intervals in the

subgroup analyses and logistic regression models and increases the risk of both false negative and false positive results. Some of the observed trends—such as the potential association between low CEA values, negative biopsy, and pCR—would likely gain greater statistical clarity in a study of a larger cohort.

In addition, the assessment of imaging parameters, including mrTRG and EMVI, was performed based on available MRI studies conducted in routine clinical practice. Despite the application of standardized criteria in the retrospective evaluation, variability due to different devices, protocols, and interpretation by different imaging specialists cannot be completely ruled out.

By definition, pathological tumor response can only be assessed in patients who have undergone surgical treatment. In patients for whom a decision is made in clinical practice to preserve the organ and continue observation, there is no surgical pathological equivalent to confirm pCR. This is a typical limitation for all studies comparing cCR and pCR, and inevitably makes it difficult to assess the actual frequency of pCR among patients with clinical complete response.

Despite these limitations, the present study has a number of significant advantages: inclusion of a sequential cohort of patients treated by the same multidisciplinary team; use of clearly defined criteria for endoscopic and imaging assessment of response; combined analysis of endoscopic, imaging, histological, and laboratory parameters; and a focus on real-world clinical practice outside the setting of strictly controlled clinical trials.

5.4. Clinical application and significance of endoscopy in multimodal assessment

The results of this study confirm endoscopy as a cornerstone in the assessment of response after neoadjuvant therapy in rectal carcinoma. The

presence of endoscopic cCR, defined by strict morphological criteria, is associated with a significantly higher probability of pCR and may serve as a basis for discussing organ-preserving strategies. At the same time, partial responses (nCR) and especially incomplete responses (iCR) require cautious management—usually surgical treatment or, in certain circumstances, endoscopic or transanal local interventions.

The association between EMVI positivity and incomplete endoscopically determined clinical response highlights the need for these patients to be considered high-risk, with a low probability of true pCR, and aggressive local management (radical resection) remains the preferred standard of care. Similarly, larger circumferential tumor involvement and higher T categories should guide the clinician toward a more conservative assessment of organ preservation options, even with seemingly favorable endoscopic findings.

The lack of independent prognostic value of PET/CT for pCR in the current analysis, as well as the trend but not definitive nature of CEA and biopsy, support the concept that no single method is sufficient on its own. The practical conclusion is the need for an integrated, multimodal assessment in which endoscopy plays a leading role, but always in the context of MRI data, clinical examination, and laboratory parameters.

From the perspective of the follow-up protocol, the data obtained support a first comprehensive assessment (endoscopy, MRI, laboratory tests) approximately 6–8 weeks after completion of chemoradiotherapy, with subsequent follow-up visits at shorter intervals in patients with good but not completely convincing clinical response. In patients with persistent iCR after the first assessment, the probability of subsequent complete regression is low and they should be promptly referred for surgical treatment.

5.5. Prospects for future research

The results obtained provide a basis for future research aimed at more precise selection of patients for organ-preserving strategies and optimization of post-treatment follow-up protocols. First, larger, prospectively collected cohorts are needed to allow reliable assessment of prognostic factors for cCR and pCR, including detailed stratification by stage, systemic therapy regimen, and time interval to first assessment.

The integration of new biomarkers, such as circulating tumor DNA, and advanced imaging techniques (high-resolution MRI, radiomics, functional sequencing) has the potential to significantly improve the accuracy of models for predicting therapeutic response. In this context, endoscopy will likely retain its central role as a method for direct visual assessment, but its role may be complemented by quantitative imaging measures of tumor regression and residual neoplastic tissue.

Future studies could and should focus on specific subgroups—for example, elderly patients, patients with severe comorbidity, or those with EMVI-positive status—in whom the balance between oncological control and quality of life is particularly delicate. For these patients, an optimally structured monitoring protocol based on endoscopy and non-invasive methods could offer a real alternative to standard surgery.

In conclusion, the results of this dissertation support the key role of endoscopy as a major component in the multimodal assessment of response after neoadjuvant chemoradiotherapy in rectal cancer. Endoscopically assessed cCR is established as a strong predictor of pCR, and the integration of endoscopic, imaging, and laboratory parameters allows for more precise patient stratification and rational planning of subsequent management. Further work is needed to validate these findings in larger cohorts and to develop standardized

protocols that minimize oncological risk and maximize the benefits of organ-preserving approaches.

6. CONCLUSIONS

1. The study population is characterized by advanced age, a high frequency of comorbidities, a predominance of low and mid-stage tumors, and a high proportion of unfavorable imaging features, which defines the cohort as high-risk.

2. Classic demographic and clinical indicators—age, sex, tumor location, maximum tumor diameter, and baseline CEA values—do not show statistically significant prognostic value for achieving endoscopic complete clinical response. The presence of extramural venous invasion is associated with a more unfavorable endoscopically assessed clinical response.

3. The three-tiered endoscopic classification of clinical response allows for the identification of patients with a high probability of achieving a complete pathological response, who may be considered candidates for organ-preserving strategies. Post-treatment mrTRG shows a tendency toward more frequent favorable categories in patients with endoscopically assessed complete clinical response.

4. Good clinical response (complete or near complete) is observed mainly in low-lying tumors, while incomplete clinical response predominates in medium- and high-lying lesions.

5. The interval between the end of neoadjuvant chemoradiotherapy and the first follow-up endoscopy shows no statistically significant correlation with the degree of pathological tumor response.

6. Endoscopically confirmed complete clinical response is the only independent predictor of pathological complete response, with an approximately 15-fold increase in the chance of pCR compared to patients without endoscopic cCR. Negative endoscopic biopsy, CEA ≤5 ng/mL, and lack of metabolic activity on PET/CT are associated with a better pathological response but do not demonstrate independent statistically significant prognostic value for pCR.

7. CONCLUSION

Locally advanced rectal cancer remains a significant oncological challenge, with neoadjuvant chemoradiotherapy being a standard element of complex treatment. The introduction of organ-preserving strategies and the "watch and wait" approach requires extremely precise assessment of the therapeutic response in order to achieve an optimal balance between oncological safety, preservation of organ function, and quality of life. In this context, endoscopy plays a key role as a method for direct visualization of the rectal mucosa and assessment of local morphological changes after treatment.

The present study shows that in real-world clinical practice, the frequency of endoscopic and pathological complete response in patients with locally advanced rectal cancer is relatively low, reflecting the high-risk profile of the treated population. Classic clinical characteristics have limited prognostic value for predicting cCR, while imaging features such as extramural venous invasion are associated with more unfavorable tumor evolution.

Endoscopically assessed complete clinical response appears to be the most reliable independent predictor of pathological complete response. This supports the concept that endoscopy should be a leading component in the multimodal algorithm for assessing response after neoadjuvant therapy. At the same time, the limited sensitivity and imperfect overlap between cCR and pCR

require that endoscopic assessment always be interpreted in the context of MRI, clinical examination, and, if necessary, PET/CT and laboratory parameters. The interval until the first follow-up endoscopy within approximately 6–8 weeks after completion of neoadjuvant therapy appears to be a reasonable compromise between the need for maximum tumor regression and the risk of missing persistent or progressive cancer, although no optimal time window is clearly demonstrated in the present study. The results obtained emphasize the need for prospective studies to validate the optimal time and combination of methods for assessing response.

In conclusion, endoscopy plays a central role in assessing response after neoadjuvant chemoradiotherapy in rectal cancer. Endoscopically determined complete clinical response, defined by clear morphological criteria and interpreted in a multimodal context, can aid in the selection of patients for organ-preserving strategies. The integration of endoscopic, imaging, pathological, and laboratory indicators is a prerequisite for more precise personalization of treatment and for achieving an optimal balance between oncological safety and quality of life.

8. CONTRIBUTIONS

8.1. Scientific contributions

1. For the first time in Bulgaria, a systematic analysis of endoscopically determined clinical response (complete, near complete, and incomplete) after neoadjuvant chemoradiotherapy in locally advanced rectal cancer in real clinical conditions was performed, with parallel assessment of MRI, ERUS, PET/CT, endoscopic biopsy, serum CEA, and pathological indicators (ypT, ypN, Dworak).

2. The independent prognostic value of endoscopically determined complete clinical response for pathological complete response has been determined, demonstrating a statistically significant increase in the chance of pCR in patients with cCR in a multivariate logistic model.

3. A statistically significant association was identified between extramural venous invasion and the degree of endoscopically determined clinical response, which emphasizes the influence of the vascular-invasive tumor profile on local regression after neoadjuvant therapy.

4. The diagnostic capabilities and limitations of standard endoscopic biopsy and PET/CT in predicting pathological complete response in the context of organ-preserving strategies in rectal cancer were quantitatively determined.

5. The influence of the interval from the end of neoadjuvant therapy to the first follow-up endoscopy on the degree of pathological response was assessed, and time frames were outlined in which the risk of adverse regression remains relatively stable.

8.2. Scientific and applied contributions

1. Based on the results obtained, practical criteria were formulated for interpreting the endoscopically established complete clinical response and its place in the multimodal assessment of response after neoadjuvant chemoradiotherapy in rectal cancer.

2. Principles are proposed for selecting patients with low-lying tumors and favorable endoscopic and imaging profiles as potential candidates for organ-preserving therapeutic strategies (watch and wait or local interventions) under strict monitoring.

3. The results obtained support the standardization of an in-hospital protocol for comprehensive assessment and follow-up after neoadjuvant chemoradiotherapy, including a first endoscopic and imaging assessment around 6–8 weeks and subsequent follow-up visits.

4. A structured database has been created for patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy and followed up endoscopically, which can serve as a basis for future prospective and multicenter studies.

5. The observations obtained can be used in the training of residents and specialists in gastroenterology, medical oncology, and surgery in the interpretation of endoscopic and imaging response and in the planning of multidisciplinary management of locally advanced rectal cancer.

9. APPENDICES

Appendix 1. Classification of tumor regression according to Dworak

Grade (Dworak) Description of tumor regression

0 No regression – tumor tissue shows no visible signs of response, no fibrotic changes.

1 Mild regression – dominant tumor mass with fibrosis and/or vascular changes (vasculopathy), but with clearly recognizable invasive carcinoma.

2 Moderate regression – fibrous tissue predominates with rare residual tumor cells or small tumor nests; tumor structures are difficult to recognize.

3 Marked regression – predominantly fibrosis with isolated or highly sparse residual tumor cells that are difficult to detect by microscopic examination, with or without residual mucinous component.

4 Complete regression – absence of residual viable tumor cells; only fibrous or fibrous-mucinous tissue is present in the area of the primary tumor.

Appendix 2. MRI tumor regression gradient (mrTRG)

Grade (mrTRG) Description of MRI tumor regression

1 Complete radiological response – low-signal fibrosis or linear/semicircular scar at the tumor site with no visible intermediate tumor signal or mass.

2 Good response – dense fibrosis occupying the site of the primary tumor with no clearly demarcated residual tumor; minimal residual tumor tissue is possible.

3 Moderate response – more than 50% of the volume is occupied by fibrosis or mucin, but with an intermediate tumor signal present in part of the lesion.

4 Poor response – limited areas of fibrosis or mucin with a predominant intermediate tumor signal, suggesting significant residual disease.

5 No response – the tumor on MRI appears similar to the baseline (predominantly intermediate tumor signal) or there is evidence of growth/recurrence in the tumor bed.

Appendix 3. Endoscopic criteria for clinical response (cCR, nCR, iCR)

Category Endoscopic criteria

Complete clinical response (cCR)

Flat, white fibrous scar at the site of the primary tumor, often with telangiectasia; no visible tumor mass; no ulceration, infiltration, or nodularity; normal or near-normal lumen without stricture.

Near complete clinical response (nCR) Scar with minimal residual mucosal changes: irregular or slightly granular mucosa, small mucosal nodules, superficial ulceration or erosions, mild erythema in the scar area; no clearly defined tumor mass, but the finding does not fully meet the criteria for cCR.

Incomplete clinical response (iCR)

Obvious residual tumor – visible polypoid, nodular, or infiltrating mass; deep ulcer with infiltrated edges; narrowing of the lumen due to tumor infiltration; finding incompatible with clinical complete or near complete response.

Appendix 4. Main demographic, clinical, imaging, and pathological characteristics of the study cohort

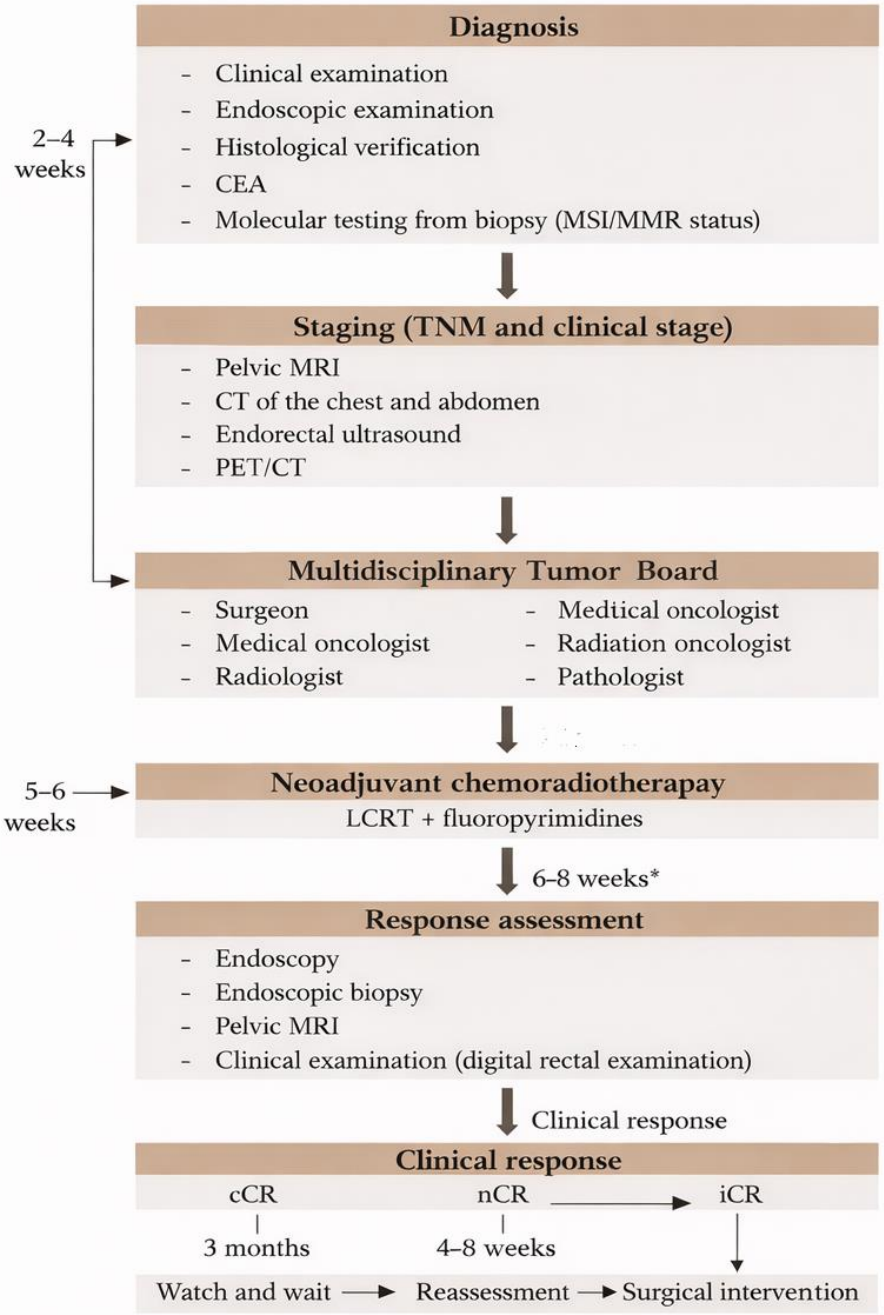
Parameter	Category	n	%
Sex	Male	60	58,3
	Female	43	41,7
Age (years)	Mean ± SD	67,1 ± 10,8	–
Comorbidities	Yes	67	65,0
	No	36	35,0
Tumor Localisation (n=29)	Low	15	51,7
	Middle	10	34,5
	High	4	13,8
Circumferential Extent (n=30)	75–100%	13	43,3
	50–75%	8	26,7
	25–50%	7	23,3

Parameter	Category	n	%
	0–25%	2	6,7
EMVI (MRI, n=75)	Positive	60	80,0
	Negative	15	20,0
MRI Lymph nodes (n=72)	Positive	59	81,9
	Negative	13	18,1
Mesorectal fascia status (n=70)	Free	40	57,1
	Involved	30	42,9
mrTRG.1 (n=53)	1	2	3,8
	2	25	47,2
	3	18	34,0
	4	6	11,3
	5	2	3,8
PET/CT follow-up (n=61)	Metabolically active tumor	36	59,0
	No metabolic activity	14	23,0
	Metabolically active tumor + distant metastases	9	14,8
	Distant metastases	2	3,3
Endoscopically assessed clinical response	cCR	6	5,8
	nCR	11	10,7

Parameter	Category	n	%
	iCR	64	62,1
ypT (n=66)	ypT0	9	13,6
	ypT1	4	6,1
	ypT2	14	21,2
	ypT3	34	51,5
	ypT4	5	7,6
ypN (n=63)	ypN0	46	73,0
	ypN1–2	17	27,0
Dworak (n=60)	0–1	34	56,7
	2	14	23,3
	3–4	12	20,0

Appendix 5. Diagnostic and therapeutic algorithm for locally advanced rectal carcinoma (adapted from ESMO)

Management of Locally Advanced Rectal Cancer



*6–8 weeks after completion of neoadjuvant chemoradiotherapy.

** Follow-up every 3 months during the first 2 years, then ever every 6 months up to the 5th year.

cCR – complete clinical response
nCR – near-complete clinical response
iCR – incomplete clinical response

Publications related to the dissertation

1. Trifonov AD. Neoadjuvant chemoradiotherapy and total neoadjuvant therapy in locally advanced rectal cancer: Current data and guidelines. Varna Med. Forum. 2025;14. doi:10.14748/vmf.v14i2.10496