REVIEW

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Regarding:
Defense of the dissertation "The Role of Endoscopy in Assessing Response After Neoadjuvant Chemoradiotherapy in Rectal Cancer"
Scientific supervisor: Assoc. Prof. Aleksandar Kamenov Zlatarov, MD, PhD
Educational and scientific degree: PhD
Field of Higher Education: 7. Healthcare and Sports; Professional field 7.1. Medicine
Scientific specialty: Gastroenterology
Author: Dr. Aleksandar Dimitrov Trifonov
Scientific organization: Medical University "Prof. Dr. Paraskev Stoyanov" – Varna
Form of doctoral training: Individual preparation

I was provided with the full set of documents related to the official defense of the dissertation for the acquisition of the educational and scientific degree "Doctor." The procedure fully complies with the Law on the Development of the Academic Staff in the Republic of Bulgaria, the Regulations for its implementation at MU–Varna, and the Rules for the Acquisition of Scientific Degrees and Academic Positions at MU–Varna.

By Order No. R-109-42/16.01.2026 of the Rector of Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, I was appointed as a member of the scientific jury. During the first remote meeting of the jury, I was elected to prepare this review.

Dr. Aleksandar Dimitrov Trifonov was born on 18.08.1994. He graduated in Medicine from the Medical University – Varna in 2019. During 2019–2020 he worked as a physician in the Emergency Department of St. Marina University Hospital, Varna. In 2020 he won a competitive position as an Assistant Professor in the Second Department of Internal Medicine at MU–Varna. He specialized in gastroenterology at the Clinic of Gastroenterology, Hepatology and Nutrition at St. Marina University Hospital during 2020–2024 and obtained his specialty in 2024. Since 2025 he has been working in the Department of Gastroenterology for Endoscopic Diagnostics at St. Marina University Hospital, Varna.

The PhD candidate is a well-trained gastroenterologist and university lecturer, having completed specialization at a leading national university hospital. He is proficient in English, demonstrates a clear interest in interventional endoscopy, presents certificates from prestigious international gastroenterology forums, and shows strong potential for an outstanding career in interventional endoscopy and academic gastroenterology.

Rectal cancer is becoming an increasingly significant clinical problem—on the one hand due to its rising incidence and the progressively younger age at diagnosis, and on the other due to the expanding efforts toward organ preservation. When choosing a treatment strategy, the

goal is to balance oncological safety with maintaining quality of life and social functioning. We are witnessing broader indications for endoscopic therapy in rectal cancer, increasing use of endoscopic submucosal dissection, and the introduction and validation of intermuscular dissection, which provides a radical treatment option for T1B carcinomas. Strategies incorporating additional chemoradiotherapy following extensive endoscopic therapy are also gaining traction in support of organ preservation.

Given the shift toward younger and more socially active patient populations, organ preservation is becoming a leading priority. Although abdominoperineal resection is oncologically justified, it can be devastating for patients' quality of life and social integration. Moreover, even expertly performed anterior resection is associated with persistent symptoms in over half of patients. These realities further reinforce the growing importance of endoscopic therapy as part of organ-preserving approaches. Additional chemoradiotherapy is also being increasingly utilized. At the same time, because of advancements in oncological treatment, a complete response to chemoradiotherapy is being observed in more patients with locally advanced tumors, and optimal management for such cases remains a matter of debate. For these reasons, the topic chosen by the PhD candidate is highly relevant.

Structure of the Dissertation

The dissertation consists of 139 standard typed pages and includes 32 tables and 22 figures. The bibliography comprises 113 sources, 109 in English and 4 in Bulgarian.

Literature Review

The literature review is well organized. Special attention is given to the epidemiology and global burden of rectal cancer, particularly the rising incidence, younger age at diagnosis, and persistently high mortality. A notable concern is the increasing incidence among individuals aged 20 to 49, contrasting with declining rates in populations over 50 in countries with established colorectal cancer screening programs.

The review also covers the role of neoadjuvant chemoradiotherapy and total mesorectal excision in reducing local recurrence and potentially mortality. It addresses the anatomy and physiology of the rectum, molecular pathogenesis, histological characteristics, risk factors, and etiology. Inherited syndromes and modifiable risk factors are both highlighted. Screening strategies and the need for earlier initiation are discussed.

The diagnostic algorithm is presented in detail, including lower endoscopy, endoscopic ultrasound, MRI, and PET/CT. The roles of surgical treatment and neoadjuvant strategies are also examined, as well as total neoadjuvant therapy, in which all systemic treatment is delivered preoperatively.

Particular emphasis is placed on patients who achieve a complete clinical response, for whom the "watch and wait" strategy is increasingly applied. Challenges include confirming complete response and establishing appropriate selection and follow-up protocols. Novel therapies, including immunotherapy, early detection strategies, and the importance of

multidisciplinary management, are explored. Local recurrence and distant metastases are also reviewed as key determinants of survival.

The author underscores the significant impact of surgical treatment on quality of life, particularly in relation to permanent or temporary colostomy, the high incidence of Low Anterior Resection Syndrome, and the beneficial effect of the "watch and wait" strategy on quality of life among those with complete clinical response.

The review addresses the need for standardized criteria for defining complete clinical response, optimal follow-up protocols, and reliable predictors of response — key motivations for this dissertation.

The "watch and wait" strategy appears to be a suitable option for patients who achieve complete response and represents a viable alternative to surgery, offering real potential for organ preservation. However, it remains insufficiently established, requiring strict adherence to protocols, high levels of expertise, and substantial institutional resources—factors that currently limit its widespread implementation. Most importantly, correct patient selection is crucial.

Aim

The aim is clearly formulated:
To conduct a retrospective observational single-center study of patients with rectal cancer who underwent neoadjuvant chemoradiotherapy, with a primary focus on investigating the role of endoscopy in assessing treatment response.

Tasks

There are six tasks, all directly aligned with achieving the aim. Notably, the study seeks to analyze prognostic factors associated with complete clinical response to neoadjuvant therapy and to explore correlations between clinical response and tumor characteristics.

Material and Methods

The study is retrospective, observational, and single-center, including 157 patients with rectal cancer treated with neoadjuvant chemoradiotherapy over a five-year period (2019–2024). Inclusion criteria are clearly defined. All patients had rectal carcinomas staged T2–T4, without distant metastases, and all underwent MRI, CT, and FDG-PET/CT. Endorectal ultrasound was performed in part of the cohort.

Endoscopic assessment of response was performed in all patients 6–8 weeks after therapy, using a unified classification system, and biopsy samples were obtained from all visible lesions. Post-treatment MRI was performed, and histological evaluation of surgical specimens was conducted using validated tumor regression grading systems. All patients underwent surgery, with surgical technique tailored to tumor height and relationship to the sphincter apparatus. Appropriate statistical methods were applied.

Results

A total of 157 patients were included in the study, of whom 101 met all criteria and remained in the final analysis. The PhD candidate presents an exceptionally thorough follow-up and analysis of this cohort.

Most tumors were distally located. Only 6 patients demonstrated complete response; 86 had incomplete response and 11—near-complete response, according to the author's definitions. A striking finding is the late stage at diagnosis: over 40% of patients presented with tumors involving more than 75% of the rectal circumference, and more than 80% had lymphatic dissemination confirmed by MRI and PET/CT. Palpable, advanced tumor masses were identified in over 90% of patients, and initial endorectal ultrasound revealed T3 or higher staging in more than half of the cases.

An interesting observation is that in 51.6% of patients, post-treatment endoscopic biopsies showed no tumor cells, which allows for various interpretations. Endoscopic evaluation confirmed complete clinical response in 5.8%, incomplete response in 62.1%, and near-complete response in 10.7%—a distribution that differs from the histopathological findings. Tumor regression was classified as good in 47.2% of patients.

Follow-up PET/CT revealed newly emerged distant metastases accompanied by persistent metabolic activity of the primary tumor in 14.8% of patients, and in 3.3% PET/CT identified distant metastases that had not been detected at initial diagnosis. According to the Dworak classification, more than half of the patients exhibited poor pathological response to therapy.

Practically no strong prognostic factors indicating complete clinical response were identified. Overall, complete clinical response was seen more often in patients diagnosed earlier and in tumors with distal localization. The PhD candidate found that extramural venous invasion was more common in patients with incomplete endoscopic response, who also demonstrated persistently positive lymphatic dissemination on follow-up MRI. Endoscopic signs of incomplete response may therefore serve as predictors of a more aggressive tumor phenotype with extramural venous invasion and persistent lymphatic spread after neoadjuvant therapy.

Correlation analysis revealed a strong inverse relationship between tumor invasion depth and the degree of tumor regression. The well-known correlation between invasion depth and risk of lymphatic metastasis was statistically confirmed. Complete endoscopic response proved to be the strongest predictor of complete pathological response. Absence of tumor cells in post-treatment biopsy and low CEA levels showed a tendency toward predicting complete pathological response, though without reaching statistical significance.

Summarizing the findings: complete endoscopic response is the only reliable predictor of complete pathological response. Tumors diagnosed at an earlier stage and those with distal location demonstrate better response to neoadjuvant therapy. Another key finding is that PET/CT, despite its usefulness in detecting distant metastases, has no predictive value for complete pathological response and therefore does not play a leading role in selecting patients for organ-preserving strategies.

The PhD candidate also analyzed the optimal timing of the first comprehensive post-treatment assessment, including endoscopy, identifying an interval of 61 days as optimal—balancing maximal tumor regression with the risk of delayed detection of persistent or progressive disease.

A particular strength of the dissertation is the author's explicit discussion of methodological limitations. Identified weaknesses include the retrospective design and the relatively small number of patients with complete response, which necessitate caution in interpreting the results. Nevertheless, the study presents multiple valuable insights, highlighting the importance of early diagnosis, multidisciplinary management, and the complexity and heterogeneity of rectal cancer. It underscores the critical role of endoscopy not only in initial diagnosis but also in evaluating therapeutic response.

The use of a validated classification system for endoscopic assessment of treatment response is essential, and this study reinforces its value. Demonstrating that complete endoscopic response predicts complete pathological response confirms its future role in selecting patients for "watch and wait" or other organ-preserving approaches. Conversely, incomplete endoscopic response correlates with aggressive tumor biology and identifies patients who require radical, high-volume surgical intervention.

Conclusions

The PhD candidate formulates six conclusions. Of greatest practical significance is the following: performing follow-up endoscopy after neoadjuvant therapy in rectal cancer has important prognostic value. Using a three-tier endoscopic classification allows identification of patients in whom a "watch and wait" or other organ-preserving strategy can be safely applied when complete clinical response is established. Patients with low rectal cancer diagnosed at an earlier stage, normal CEA levels, negative biopsy at follow-up endoscopy, and lack of metabolic activity on follow-up PET/CT have a higher likelihood of favorable pathological response.

Contributions

The PhD candidate outlines ten contributions, five scientific and five practical-scientific. For the first time in Bulgaria, a comparatively large cohort of patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy has been studied in detail with imaging, laboratory, and histological methods. The leading role of lower endoscopy in both diagnosis and assessment of treatment response and prognosis is emphasized.

The study demonstrates that endoscopically confirmed complete response correlates with complete pathological response. Of practical importance is also the finding that incomplete clinical response is associated with extramural venous invasion. Endoscopic detection of residual viable tumor correlates with aggressive tumor biology and indicates the need for extensive radical surgery. The optimal interval for performing follow-up endoscopy is also defined. Criteria for interpreting complete endoscopic response and its implications for clinical decision-making are formulated. The study introduces, for the first time in Bulgaria,

the pathway toward a "watch and wait" strategy or other organ-preserving approaches for carefully selected patients, and proposes criteria for their appropriate selection.

Discussion

The dissertation is comprehensive, well-structured, and of substantial clinical relevance. The author presents an in-depth analysis of a relatively large cohort of patients with newly diagnosed locally advanced rectal cancer who were optimally assessed with modern imaging and laboratory modalities. Although many findings confirm already known data, the dissertation has undeniable merits and contributes meaningfully to the Bulgarian medical community.

The retrospective design, the limited number of patients with documented complete clinical and subsequent pathological response, and the absence of a standardized endoscopic protocol for both initial and follow-up evaluations do not diminish the scientific value of the work.

Unfortunately, the dissertation also reinforces the concerning trend of late diagnosis of rectal cancer in Bulgaria, when therapeutic options and chances for cure are severely restricted. It reveals once again the paradox that, despite the large and continuously growing number of medical institutions in the country—many of which heavily advertise advanced medical capabilities—rectal cancer continues to be diagnosed at advanced stages, limiting the feasibility of contemporary organ-preserving strategies. One of the primary reasons for this is the absence of a national colorectal cancer screening program.

Conclusion

Considering the well-chosen and highly relevant topic, the clearly formulated aim and tasks, the extensive and current literature review, the large number of patients analyzed and followed, the practically valuable conclusions, and the undeniable contributions of the research, I recommend that the esteemed Scientific Jury vote **in favor** of awarding Dr. Aleksandar Trifonov the educational and scientific degree **"Doctor of Medicine."**

22.02.2026, Sofia
Respectfully,

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