

REVIEW

ON DISSERTATION PAPER

By D-r Alexander Dimitrov Trifonov, on the topic: "The role of endoscopy for assessment of response after neoadjuvant chemoradiation therapy for rectal carcinoma" for awarding the educational and scientific degree "doctor" in the field of higher education 7 "Health care and sport", professional direction 7.1 "Medicine" by scientific specialty 01.03.14. "Gastroenterology".

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REVIEWER

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By decision of the order of the Rector of the Medical University - Varna No. P-109-42/16.01.2026 and protocol 1 of the meeting of the scientific jury on 29.1.2026, I am determined to present this review.

1. Brief biographical and professional data of the PhD student

Dr. Alexander Trifonov is a graduate of MU - Varna, where he finished his study with honors in 2019. He then started working at UMHAL St. Marina in Varna as a doctor in a multidisciplinary emergency department, in the Gastroenterology Clinic and in the Unit of Gastroenterology for Endoscopic Diagnostics /after 2025/. Since 2020, he has been an assistant professor at the Second Department of Internal Medicine of MU-Varna. Dr. Trifonov completed his doctoral studies in full-time form at this structure. In 2024, he acquired the specialty "Gastroenterology". In a short period of training and specialization, Dr. Trifonov emerged as a competent physician with broad interests in diagnostic and therapeutic endoscopy, metabolic dysfunction associated diseases, rare gastrointestinal tract conditions, and as a young scientist with annual participation in scientific conferences in Bulgaria and abroad.

2. Relevance of the dissertation topic

In recent decades, the standard of care for non-metastatic locally advanced rectal adenocarcinoma has been neoadjuvant chemoradiotherapy (nCRT). With the increasing incidence of rectal carcinomas, including in patients of active, young age, the decision for the next step of the algorithm - surgical treatment with low anterior resection or abdominoperineal resection of the rectum or active observation and waiting - is difficult. Therefore, methods for assessing the response to nCRT are of extremely important clinical importance. After the initial diagnosis of rectal carcinoma, patients are referred back to the gastroenterology unit for

restaging after nCRT by examination, including rectal examination, colonoscopy with biopsy and magnetic resonance imaging assessment of post-therapeutic tumor regression. None of the mentioned modalities has an independent and completely accurate role in this process. Biopsy examination has well-described limitations for proving local tumor response /with a false negative result when the biopsy does not cover the entire wall, i.e. to include the muscularis propria/. There are no established markers for predicting the biological behavior of carcinoma. Thus, the clinical decision requires careful deliberation, high competence and the use of high-tech methods and equipment. Therefore, this dissertation is relevant and necessary for scientific knowledge and clinical practice.

3. Characteristics, volume, structure, and evaluation of the dissertation work

The dissertation of Dr. Alexander Trifonov consists of 139 pages and follows the traditional structure: introduction - 1 page; literature review - 53 pages; goal and objectives - 1 page; clinical material and methods of the study - 13 pages; results - 23 pages; discussion - 7 pages; conclusions, conclusion and contributions - 1 page each; literature review of 113 sources. Of the cited sources, 5 are publications by Bulgarian teams, most of the references are current, from the last 5 years. The author's own results and their generalization allow the PhD student to propose an algorithm for guiding management in advanced rectal carcinoma, adapted and consistent with the recommendations of ESMO. The dissertation has a relatively balanced content; it is written in clear, correct Bulgarian and has a good and comprehensive style.

The literature review competently presents both the main and the most current publications, in consideration of the topic. The excellent arrangement of the information is impressive, but on the other hand - the frequent lack of correspondence with the expected reference literature /under the number in the list/. The review provides a contemporary overview of the alarming data on survival and mortality of rectal carcinoma, the accepted knowledge on diagnosis, staging and therapeutic procedures. The issue of nCRT is discussed in depth in terms of regimen, treatment response and follow-up. The strategy for active surveillance "Watch and Wait" in the different clinical stages of rectal cancer, balancing oncological and functional outcomes, is critically discussed. Each main part of the review ends with adequate conclusions. The key conclusion is that the combined assessment of clinical response after nCRT with endoscopy and MRI provides suboptimal information about histopathological tumor regression, which is a basis for future studies. In the future, it is indicated that the management will be more successful and individualized through the hope of new biomarkers and algorithms based on artificial intelligence data processing. The review would benefit from a tabular presentation of data from retrospective and prospective randomized trials evaluating the role of endoscopy and MRI in assessing therapeutic response after initial chemoradiotherapy, as well as from a more complete systematization of all current publications in the field.

The aim of the dissertation is to address the role of endoscopic examination in the evaluation and restaging of patients with rectal carcinoma after nCRT in a University referral

center. To achieve this aim, 6 tasks are formulated: characterization of the patients included in the retrospective analysis; search for factors – predictors of complete clinical response (cCR) after nCRT; comparative evaluation of the definitions from the control endoscopy (in the categories cCR, nCR, iCR) with other imaging methods and tumor characteristics; differences in the categories of complete, almost complete and incomplete clinical response; study of the period between the completion of nCRT and follow-up endoscopy and the last, most important task is directed at the correspondence between the assessment with clinical methods and the final histopathological staging after surgical intervention. Task 3 is reasonable, but with a not very clear formulation. The section “Materials and Methods” successfully and in a logical sequence describes the design of the study and the specific aspects of classifying patients according to the presence of clinical and histopathological response to nCRT. For the correct selection of the cohort, inclusion and exclusion criteria are well formulated. An important inclusion criterion is the availability of written, photo documentation and images from the endoscopic examination after treatment. It would be good to indicate the specific number of patients in whom data from each imaging method are available. For example, in the “Results” section it is clear that baseline and follow-up endorectal ultrasound were performed in 13 and 16 patients, respectively. Analysis of surgical resections was performed in 55 patients. Statistical methods were applied in accordance with the objectives of the protocol.

In a retrospective study, Dr. Trifonov analyzed 103 patients who underwent nCRT for invasive, histologically proven non-metastatic rectal carcinoma /T2-T4/ at the Radiotherapy Clinic of St. Marina University Hospital for a period of 5 years /from 2019 to 2024/. The study was conducted in a referral center with traditions and with high-quality and comprehensive care for this pathology. The main baseline characteristics of the group of patients with rectal carcinoma are listed in a table in Appendix No. 1, broken down in the first part of the "Results" section and with some repetition in the analysis under task 1. Since information was collected retrospectively from the hospital database, clinical and tumor characteristics are not fully available for all included patients. The presentation quickly moves to an analysis of the post-nCRT cohort, with restaging shown graphically and tabularly in terms of the proportion of cases according to the respective method: “rectal digital exam”; MRI response in 5 groups; follow-up PET/CT finding in 4 groups; endorectal ultrasound data in 5 categories; endoscopic biopsy at follow-up in the groups with and without malignant cells on morphological examination. Endoscopically assessed clinical response was classified as incomplete in 62.1%, almost complete in 10.7% and complete in 5.8%. The small proportion of patients with complete clinical response is probably the main reason for not defining statistically significant predictors of the success of nCRT /by task 2/. In about half of those treated with nCRT, no malignant cells were detected in a control endoscopic biopsy. There is no statistically significant coincidence in the categories of endoscopically assessed clinical response and clinical response with MRI-established regression gradient /by task 3/. A factor associated with incomplete clinical response, although analyzed in a small proportion of the included patients, is the initial localization of the neoplastic process, because no patient with carcinoma in the middle and

high rectum achieved a good clinical response /by task 4/. The time interval to the first control endoscopy does not show an association with the degree of histopathological response /by task 5/. In its final stage, the protocol analyzes important indicators from restaging studies, such as the presence of endoscopic data for complete response (cCR), the absence of tumor cells in the control biopsy, a normal level of the tumor marker CEA and the absence of activity on PET/CT to predict the presence of histopathological complete response (pCR), respectively TRG 4 (according to Dworak). Thus, the presence of endoscopic cCR has low sensitivity but optimal specificity for predicting pCR, with an overall diagnostic accuracy of 91.3% at a statistical significance level of 0.052. The author's own results are illustrated by 21 figures and 28 tables. The discussion summarizes, without unnecessarily repeating, the data provided in the "Results" section. The presentation critically shows the good and limiting aspects of the study. The PhD student competently analyzes and compares the obtained results with the data from the published literature in a clear and easy-to-understand format. However, the opinions should be supported by a quote from the reference list listed below. Thus, Dr. Trifonov performs a useful analysis, albeit based on retrospective data, but valuable in its intelligent and honest presentation.

A logical consequence of the above results and discussion are six clearly formulated and informative conclusions. I confirm that the conclusions are supported by the conducted study. The dissertation work of Dr. Alexander Trifonov has undeniable contributions, such as the first systematic analysis of the endoscopic response after nCRT in our country and a comprehensive assessment of the advantages and disadvantages of the methods for restaging patients with rectal cancer from real clinical practice.

In connection with the dissertation work, Dr. Alexander Trifonov offers a published full-text review on the topic.

Evaluation of the contributions of the dissertation work

I fully accept the stated conclusions and contributions of the dissertation work. The significance of the work is supported by the competent analysis, combined with the intelligence and knowledge of the dissertation author in the field of GIT diseases.

4. Critical remarks

There are no grounds for important critical remarks. I would like to recommend expanding the publication activity of Dr. Trifonov, based on the results described in this study.

5. Conclusion

The dissertation work of Dr. Alexander Dimitrov Trifonov on the topic: "Role of endoscopy in assessing the response after neoadjuvant chemoradiotherapy in rectal carcinoma" presents results and conclusions with an original contribution to science and meets the requirements of the Law for the Development of the academic staff of the Republic of Bulgaria and its Regulations for the implementation.

The dissertation shows that Dr. Trifonov has the qualities and skills to independently conduct scientific research based on in-depth theoretical knowledge and professional skills in the scientific specialty "Gastroenterology."

In connection with this, I convincingly give my positive assessment of the work of Dr. Alexander Trifonov and propose to the Scientific Jury to award Dr. Alexander Dimitrov Trifonov an educational and scientific degree "Doctor".

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