JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205

Volume 15 Issue 05, May 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

CHOICE OF THE OPTIMAL METHOD OF TREATMENT OF LOCALLY ADVANCED RECTAL CANCER.

Almuradova D.M. [1] ***, Yusupov A.A.*** [1] ***, Ismoilov Zh.Kh.*** [1]
[1] Tashkent State Medical University . Tashkent. Uzbekistan .
Email: almuradovadilbar@gmail.com ORCID : 0009-0002-4147-9460
adham_yusupov96@mail.ru ORCID: 0009-0004-7088-3344
jamshid.6788684@gmail.com ORCID: 0009-0000-5523-2114

Abstract: Rectal cancer is one of the most common forms of malignant neoplasms both in the world oncological practice and in Uzbekistan. About 600,000 new cases of this disease are diagnosed annually in the world. Over the past few decades, there has been a steady increase in the incidence of rectal cancer. The data on the relative incidence of this nosology are comparable among Russian and foreign authors according to Siegel R., Miller K., rectal cancer, including anal canal cancer, accounts for about 50% of all colon tumors. In recent years, there has been a tendency towards an increase in the incidence of rectal cancer worldwide, so its share in the structure of oncological morbidity in men is 5.3% and in women 4.4%. Locally advanced rectal cancer is a tumor of limited mobility or immobile with involvement or destruction of its own fascia, without obvious signs of distant metastasis in patients who, due to its spread beyond the organ, cannot undergo radical surgery without a high risk of local relapse in the near future after surgery. One of the urgent tasks of modern oncoproctology is to improve the long-term results of treatment of patients with locally advanced rectal cancer (LARC).

Key words: locally advanced rectal cancer, chemoradiation therapy, neoadjuvant chemotherapy, consolidation chemotherapy, induction chemotherapy, SANDWICH therapy, pathomorphism. capecitabine; ox aliplatin.

Relevance. In recent years, against the background of an increase in the overall incidence of rectal cancer both in the world and in Russia, the proportion of patients with a locally advanced tumor process at primary treatment is more than 30% [8]. The use of preoperative prolonged chemoradiotherapy (CRT) in combination with fluoropyrimidine drugs, followed by total mesorectumectomy and adjuvant chemotherapy (CT) is the standard of treatment for this group of patients and is included in national recommendations of the USA (NCCN), Western European countries (ESMO) and Russia (AOR). Colorectal cancer accounts for 15% of all cancer cases, and rectal cancer (RC) accounts for 30%. More than 1 million cases of colorectal cancer are registered worldwide every year. In most countries, mortality from RC ranks 5th or 6th [5]. Unfortunately, this goal is not always achievable in the treatment of RC, since the radicalism of the operation is often achieved through extensive resections with the loss of the locking apparatus of the rectum [7]. At the same time, expanding the scope of surgical intervention does not prevent the risk of relapse, which requires combined treatment in various modes.

Epidemiology . The highest incidence of rectal cancer is recorded in Japan (Hiroshima: men - 23.3, women - 10.0), the Czech Republic (men - 18, women - 7). High incidence is recorded in New Zealand, North America, Northern and Western Europe. Low **incidence** is noted in Africa, South and Central America. In Russia, the incidence of rectal cancer is quite high (St. Petersburg: men -13, women -8) [12]. The share of rectal cancer in the structure of morbidity

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 15 Issue 05, May 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

from 13 malignant neoplasms in the male population is 5.2%, in women - 4.7%. Among the CIS countries, it was minimal in Armenia, Uzbekistan and Kyrgyzstan (2-3%), and maximal in Moldova (8% in men and 5.2 in women). Rectal cancer in Russia, Belarus, Uzbekistan is in fifth place. On average, in men, rectal cancer in these countries is from 4 to 5%. The increase in standardized incidence rates was 12–50% for both sexes in Azerbaijan and Armenia, and for men in Kazakhstan and Belarus. The lowest increase was observed in Uzbekistan (3.3% for men and 4.2% for women). A decrease in standardized incidence rates of rectal cancer was noted in Kyrgyzstan (15.9% and -25%).

Etiology. Most malignant neoplasms of the rectum develop against the background of adenomatous polyps or adenoma. Polyps are histologically classified as tubular (5% malignancy), villous (40% malignancy), or mixed (20% malignancy)[39]. The degree of intestinal epithelial dysplasia also plays an important role in the etiology of rectal cancer and ranges from 5% malignancy (low grade) to 35% (high grade). The risk of malignancy of benign neoplasms also correlates with the size of adenomas: 90% are less than 1 cm in size (1% risk), 10% are more than 1 cm (10% risk). Despite advances in radiation and drug therapy, as well as recent advances in molecular biology of cancer, the leading

The surgical method remains the treatment of this pathology [1]. However, despite the abundance of modern surgical techniques, many fundamentally new designs of suturing devices and modern high-tech equipment for operating rooms, the improvement of the surgical method from an oncological standpoint has to a certain extent reached its limit, as evidenced by the lack of significant improvements in the long-term results of surgical treatment in recent decades [1].
Complicated course of cancer often does not allow preoperative RT, bringing to the forefront the need for urgent surgical intervention. In this case, when metastases are detected in regional lymph nodes, it is necessary to limit oneself to postoperative radiation therapy only. To enhance the effectiveness of preoperative RT, local microwave hyperthermia began to be used as a radiomodifier [15]. However, to develop an individualized approach, it is necessary to develop a rational strategy that would facilitate the optimal choice of the combined treatment method and the volume of surgical intervention to achieve the best oncological results. Oncological and functional adequacy of treatment follows from the preference for a particular volume of surgical intervention compared to other operations, depending on the combined treatment method used, and consists in achieving, with minimal functional damage, a decrease in not only the frequency of locoregional cancer recurrences, but also, if possible, distant metastases.[5] Modern diagnostic methods (transrectal ultrasound, MRI of the pelvic organs) make it possible to obtain information about the degree of local tumor spread and the state of regional lymph nodes even before the start of treatment, which allows for advance planning of the latter[17].
In recent years , a number of studies have been conducted on optimizing the choice of combined treatment methods depending on the cancer localization [4], expanding the indications for sphincter-preserving surgery in the context of combined treatment using radio-modification.
In the past 20–30 years, the incidence of local recurrences and distant metastases in patients with rectal cancer remains high, especially in cases where the tumor has spread beyond the rectal wall and there is metastatic involvement of regional lymph nodes[30]. However, rectal

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 15 Issue 05, May 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

cancer (histologically, it is usually adenocarcinoma) is a relatively radioresistant tumor, which makes it advisable to search for effective radiomodifiers to increase the overall effectiveness of treatment measures carried out at the neoadjuvant stage of complex treatment. [14].

In cases where complete tumor regression is achieved after neoadjuvant treatment, it is possible to use the tactics of dynamic observation, without the surgical stage of therapy. This tactic is very important in patients with tumor localization in the lower ampullar region, who require extirpation of the rectum according to oncological principles [18]. Maximum sphincter-preserving treatment, provided that adequate oncological results are achieved, is the ultimate goal of the complex of treatment measures [12].

Adjuvant chemotherapy is one of the most important components of the complex treatment of patients with locally advanced rectal cancer. First of all, this is due to the frequency of distant metastases, which remains high in this category of patients [15]. The results showed that a longer interval increases the frequency of complete morphological response (pCR) and does not increase the frequency of surgical complications [10–14].

In a number of studies, local hyperthermia is used to increase the radiosensitivity of the tumor. This method has received scientific justification in domestic and foreign studies both in the study of fundamental radiobiological aspects of hyperthermic effects on normal and tumor tissues, and in the analysis of the results of including a thermal component in the scheme of treatment measures for tumors of various localizations [13]. The use of neoadjuvant thermochemoradiotherapy is aimed at achieving maximum regression of the primary tumor, and with a high initial probability of non-radical surgical intervention in prognostically unfavorable areas, it increases the chance of performing R-0 resections and sphincter-preserving operations when the tumor is localized in the lower ampullar region of the rectum [13]. In cases where complete regression of the tumor is achieved after neoadjuvant treatment, it is possible to use the tactics of dynamic observation, without the surgical stage of therapy. This tactic is very important in patients with tumor localization in the lower ampullar region, who require extirpation of the rectum according to oncological principles. Maximum sphincter-preserving direction of treatment, provided that adequate oncological results are achieved, is the ultimate goal of the complex of therapeutic measures [6].

Drug therapy for colorectal tumors is usually considered in one section; the general strategy of therapeutic approaches to these tumors differs [32]. Radiation therapy has been an important part of rectal cancer (RC) treatment for many decades, and the study of the optimal combination and sequence of surgical , radiation, and drug treatment methods for tumors in this location continues to this day [15]. At the first stage, it was established that adjuvant chemotherapy based on 5-fluorouracil in combination with radiation therapy significantly improves both relapse-free (RFS) and overall (OS) survival in patients with rectal cancer. Unlike colon cancer, in RRC, the addition of leucovorin to 5-fluorouracil does not increase the effectiveness of treatment [18]. In addition, it has been shown that radiation therapy combined with continuous infusion of 5-FU is more effective than radiation therapy combined with jet injection of fluorouracil [22,23]. In recent years, neoadjuvant chemoradiotherapy has attracted the attention of researchers.

A significant advantage of neoadjuvant chemoradiotherapy compared to adjuvant chemotherapy in terms of locoregional control and toxicity has been demonstrated[7]. According to the results of the study, preoperative chemoradiation therapy at stage II–III of the

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 15 Issue 05, May 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

disease was recognized as preferable, although there were no differences in overall survival [3,17]. One of the important indicators of the effectiveness of neoadjuvant chemoradiation therapy for RCC is the frequency of complete pathologically confirmed tumor regressions, the frequency of which, according to different authors, fluctuates within 10–25% [15,19, 20].

The absence of differences in overall survival in the German CAO/ARO/AIO-94 study, which was confirmed by updated long-term results with a median follow-up of 11 years reported at ASCO 2011 [26], is explained by the fact that neoadjuvant chemoradiation therapy regimens use doses of cytostatics that are adequate only to achieve the radiosensitization effect and insufficient to achieve systemic control and eradication of micrometastases [2]. That is why neoadjuvant chemotherapy followed by chemoradiation therapy, then surgery and adjuvant chemotherapy was recognized as the most optimal strategy for treating stage II–III rectal cancer [2,5,7].

A further direction of clinical research was the search for more effective regimens of preoperative and adjuvant chemotherapy based on the introduction of new drugs into treatment regimens [20].

The basis for these programs was the results of clinical trials of capecitabine and oxaliplatin in colon cancer. Thus, the X-ACT study demonstrated the advantages of adjuvant chemotherapy with capecitabine compared with the combination of 5-fluorouracil / leucovorin in patients with stage III colon cancer [4], and concluded that capecitabine is a justified alternative.

In addition, the MOSAIC (Multicenter International Study of Oxaliplatin, Fluorouracil and Leucovorin in the Adjuvant Treatment of Colon Cancer) study assessed the efficacy of oxaliplatin in adjuvant therapy for stage II–III colon cancer (n = 2246), comparing the FOLFOX-4 and 5-FU/LV (De Gramon regimen) regimens[8 As early as 2006, a pilot phase I study was presented in which, after 4 courses of neoadjuvant chemotherapy using the XELOX regimen, patients with stage II and III rectal cancer received radiation therapy with capecitabine as a radiosensitizer, and then, after surgery, capecitabine was used for another 12 weeks in an adjuvant regimen [11]. Based on the study results, it was recommended to continue studying capecitabine. The role of adding irinotecan to the standard combination of 5-fluorouracil with leucovorin in adjuvant chemoradiotherapy of patients with stage II–III rectal cancer was assessed in a randomized phase III study [12]. Unfortunately, the use of irinotecan was accompanied by increased toxicity.

In June 2011, the ASCO congress discussed in detail the issues of further optimization of treatment of patients with rectal cancer. In a large randomized study NSABP R-04, the immediate efficacy of four different chemotherapy regimens, which were used concurrently with preoperative radiation therapy, was compared [16]. The study included 1608 patients with clinical stage II or III rectal cancer with the potential possibility of performing sphincter-preserving surgery, who underwent preoperative RT (45 Gy in 25 fractions over 5 weeks + boost 54-108 Gy fractionally over 3-6 days) and the following drug therapy:

- long-term infusion of 5FU (225 mg/m2 ^{5} days a week);
- long-term infusion of 5FU (225 mg/m2 ^{5} days a week) + oxaliplatin (50 mg/m2 $^{\text{once}}$ a week for 5 weeks);
- capecitabine (825 mg/m2 $^{\text{twice}}$ daily 5 days a week);
- capecitabine (825 mg/m2 $^{\text{twice}}$ daily for 5 days a week) + oxaliplatin (50 mg/m2 $^{\text{weekly}}$ for 5 weeks).

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 15 Issue 05, May 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

The objectives of the study were pathologically confirmed complete regression (pCR) rate, sphincter-preserving surgery, and downstaging based on surgical material (local control rate data expected in 2013)[16]. 5-FU versus capecitabine and oxaliplatin versus non-oxaliplatin groups were compared. It was shown that the efficacy of capecitabine was not lower (and even slightly higher) than 5-FU: the pCR rate was 22.2 and 18.8%, respectively ($p = 0.12$), sphincter-preserving operations were performed in 62.7 and 61.2% of patients ($p = 0.59$), the stage decreased in 23.0 and 20.7% of cases ($p = 0.62$) with comparable toxicity: grade 3/4 diarrhea was recorded in 10.8 and 11.2% of observations [16]. In contrast to capecitabine, the results of adding oxaliplatin were not as positive: the addition of the drug did not affect the immediate efficacy of treatment, but it did lead to a significant increase in the incidence of grade 3–4 diarrhea from 6.6 to 15.4% ($p < 0.0001$) [16]. Although only immediate results of the study have been reported so far, the authors conclude that capecitabine is at least as effective as 5-fluorouracil and may become a new standard for chemoradiation therapy for RCC. The inclusion of oxaliplatin based on the results of this program is not recommended [16]. Large randomized trials comparing capecitabine and 5-fluorouracil in perioperative chemoradiotherapy for rectal cancer have convincingly proven that the use of capecitabine is associated with improved clinical outcomes. The presented data were widely discussed at the 13th World Congress on Gastrointestinal Cancer, held in June 2020. Based on the discussion, it was concluded that capecitabine can effectively and safely replace 5-fluorouracil in chemoradiotherapy programs; the addition of oxaliplatin is currently not recommended. In general, neoadjuvant radiotherapy in combination with chemotherapy based on the use of capecitabine as a radiosensitizer, followed by surgery and adjuvant chemotherapy, can be called a new standard of treatment for locally advanced rectal cancer.

LITERATURE

1. Andre T., Boni C., Mounedji-Boudiaf [et al.] Oxaliplatin, fluorouracil and leucovorinas adjuvant treatment for colon cancer // N. Engl. J. Med. 2004. V. 350. P. 2343-2351.
2. Arnold D. & Schmoll H.-J. (Neo-) adjuvant treatment in colorectal cancer // Ann. Oncol. 2005. V. 15 (suppl. 2). P. 133-140.
3. Bosset JF, Magnin V., Maingon P. [et al.] Preoperative radiochemotherapy in rectal cancer: long-term results of a phase II trial // Int. J. Radiat . Oncol. Biol. Phys. 2000. No. 46 (2). P. 323-327.
4. Cassidy J., Twelves C., Nowacki M. [et al.] Improved safety of capecitabine versus bolus 5-fluorouracil/leucovorin adjuvant therapy for colon cancer (the X-ACT phase III study) // Gastrointestinal Cancer Symposium. 2004. abstr. 219.
5. Cervantes A., Chirivella I., Rodriguez-Braun E. [et al.] A multimodality approach to localized rectal cancer // Annals of oncology. 2006. V. 18 (suppl. 10). P 129-134.
6. Chouaib S. et al., 2012; Chen T. et al., 2009; Dayanc BE, et al., 2008. DOI: 10.1116/S1470-2045(17)30786-4.

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 15 Issue 05, May 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

7. Crane CH, Skibber JM, Birnbaum EH [et al.] The addition of continuous infusion of 5-FU to preoperative radiation therapy increases tumor response, leading to increased sphincter preservation in locally advanced rectal cancer // Int. J. Radiat. Oncol. Biol. Phys. 2003. No. 57 (1). P. 84-89.

8. De Gramont A., Boni C., Navarro M. [et al.] Oxaliplatin/5FU/LV in adjuvant colon cancer: Updated efficacy results on the MOSAIC trial, including survival, with a median follow-up of six years // ASCO. 2007. V. 25 (suppl. 18). abstr. 4007.

9. Erlandsson J., Holm T., Pettersson D. et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomized, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017;18(3):336–46. DOI: 10.1016/S1470-2045(17)30086-4.

10. Evans J., Bhoday J., Sizer B. et al. Results of a prospective randomized control 6 vs 12 trial: is greater tumor downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy. Ann Oncol 2016;27(Suppl 6):vi149 (abstr. 4520). DOI: 10.1093/annonc/mdw370.01.

11. Glynne-Jones R., Sebag-Montefiore D., Maugahn TS [et al.] A phase I dose escalation study of continuous oral capecitabine with oxaliplatin and pelvic radiation (XELOX-RT) in patients with locally advanced rectal cancer // Ann. Oncol. 2006. V. 17. P. 50-56.

12. Kalofonos HP, Pentheroudakis G., Rigatos S. [et al.] A randomized phase III trial of adjuvant radio-chemotherapy comparing irinotecan (CPT-11), 5FU and leucovorin to 5FU and leucovorin in patients with rectal cancer // Annals Oncol. 2006. V. 17. (suppl. 9): Ab. 3320 (P. 116).

13. Kim SW et al., 2018; Fradkin S.Z. et al., 1982; Janssen HL et al., 2005; Lee-Kong SA et al., 2012.

14. Lefevre JH, Mineur L, Kotti S et al. Effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). J Clin Oncol 2016;34(31):3773–80. DOI: 10.1200/JCO.2016.67.6049.

15. MA Skibber., Rich TA, Ajani JA [et al.] Preoperative infusional chemoradiation therapy for stage T3 rectal cancer // Int. J. Radiat. Oncol. Biol. Phys. 1995. No. 32 (4). P. 1025-1029.

16. MC Roh.. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04 // J. Clin. Oncol. 2011. V. 29. (I 18S, Part I). R. 221S (abstr. 3503).

17. MD Becker., Sauer R., Hohenberger W. [et al.] Preoperative chemo/radiotherapy as compared with post-operative chemo/radiotherapy for locally advanced rectal cancer. // N. Engl. J. Med. 2004. V. 351. P. 1731-1740.

18. MD Smalley SR, Benedetti JK, Williamson SK [et al.] Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in post-operative adjuvant rectal cancer: GI INT 0144 // J. Clin. Oncol. 2006. No. 24 (22). R. 3542-3547.

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205
Volume 15 Issue 05, May 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

19. ME Anscher Tyler SD, Chari RS [et al.] Preoperative radiation and chemotherapy in the treatment of adenocarcinoma of the rectum // Ann. Surg. 1995. No. 221 (6). P. 778-787.
20. Minsky BD, Grann SG, Cohen AM [et al.] Preliminary results of preoperative 5-fluorouracil, low-dose leucovorin, and concurrent radiation therapy for clinically resectable T3 rectal cancer // Dis. Colon. Rectum. 1997. No. 40 (5). P. 515-522.