Exp Oncol 2022
44, 3, 178–185

REWIEWS

Experimental ONCOLOGY

OVERVIEW OF DISCUSSIONS AND DECISION-MAKING ON TOTAL NEOADJUVANT THERAPY OF DISTAL RECTAL CANCER

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Advances implemented in the complex treatment of distal rectal cancer led to a decrease in the number of loco-regional recurrences to 5–10%, but high rates of distant metastases remain at up to 30%. They lead to disappointing long-term oncological results, which requires the search for improvement of each of the stages of complex treatment. As a consequence of the questionable effectiveness of adjuvant polychemotherapy for distal rectal cancer, the question of the possibility of transferring drug treatment from an adjuvant to a neoadjuvant regimen is reasonably raised. The presented options for full neoadjuvant therapy have been developed and tested in leading oncology centers and are based on National Comprehensive Cancer Network Version 1.2022 recommendations. It is premature to make categorical conclusions regarding the recommendation of one or another variant of their implementation. Our preliminary clinical results confirmed the need for an additional stage of restaging in the second option, after 16 weeks of polychemotherapy before chemoradiation, in order to exclude the generalization of the disease. Therefore, there is a need for a prospective, controlled intercentre study to answer some unresolved questions.

Key Words: **distal rectal cancer, total neoadjuvant therapy, complex treatment, stages of treatment, drug treatment, radiation therapy.**

DOI: 10.32471/exp-oncology.2312-8852.vol-44-no-3.18497

According to the results of the International Agency for Research on Cancer, in 2018 there were 18.1 million new cases of cancer and 9.6 million cancer-related deaths, excluding non-melanoma skin cancer. Colorectal cancer is the most common malignant disease among men and the second most common one among women. In Ukraine, rectal cancer accounts for almost a half of colon cancer cases [1]. Despite the achievements in the treatment of patients with cancer of the middle and lower ampullary localization of the rectum, there remains a significant rate of local recurrences (5–15%) and a high rate of distant metastases (within 30%), which is the main reason for disappointing treatment outcomes [2, 3]. Currently, research into the neoadjuvant component of complex treatment of distal rectal cancer is particularly relevant, as evidenced by the encouraging results of using "total neoadjuvant therapy" (TNT), with a combination of chemoradiotherapy (CRT) protocols [4, 5].

A sufficiently long period of decision-making was observed, which is based on a significant number of multicentre clinical studies, which led to the formation of strategic directions of the TNT filling algorithm, or, as it can be found in the specialized literature, complete neoadjuvant therapy. Let us try to present some studies that formed the basis of this concept.

Two paradigms were formed depending on the sequence of the TNT components: the first one was CRT followed by neoadjuvant chemotherapy and the second one was neoadjuvant chemotherapy followed by CRT. Each of these approaches focused on the adherence to the treatment protocol followed by an assessment of disease-related outcomes.

The first TNT strategy was presented by a prospective multicentre Phase II study conducted by Garcia-Aguilar *et al.* [6]. Patients were prescribed CRT (with simultaneous administration of 5-FU), then neoadjuvant chemotherapy followed by surgery. The study included four treatment groups that differed in the number of cycles of neoadjuvant chemotherapy after CRT before surgery; these groups of patients were assigned to 0, 2, 4, or 6 cycles of chemotherapy according to the FOLFOX6 scheme (5-FU/leucovorin/oxaliplatin). The rate of completion of planned treatment ranged from 77% to > 90%. The authors presented a tumor regression rate of 38% with six cycles of mFOLFOX6 after CRT compared with 18% in patients treated with CRT alone. These results became basic in the justification of this strategy.

The strategy was confirmed by the results of the Polish II, phase 3 study [7]. Based on extensive practical experience, randomized results are presented in T3/T4 patients who received a short course of radiation therapy (RT) (25 Gy in 5 fractions) followed by 3 cycles of FOLFOX6, as well as a group of patients using a classical course of CRT (50.4 Gy for 5 weeks) with subsequent FOLFOX6. Despite chemotherapy courses after CRT before surgery, the frequency of postoperative complications did not differ among the treatment groups [7–9].

An important confirmation of this strategy was also the prospective randomized study RAPIDO, in which patients in the control group received standard treatment (neoadjuvant CRT followed by surgery and adjuvant chemotherapy), and in the research group — RT 25 Gy in 5 days followed by neoadjuvant chemotherapy and later surgical treatment. The results showed 95% completion of therapy with all pa-

Submitted: August 16, 2022.

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Abbreviations used: CAPOX – capecitabine/oxaliplatin; CRT – chemoradiotherapy; FOLFOX – 5-FU/leucovorin/oxaliplatin; RT – radiotherapy; TNT – total neoadjuvant therapy.

tients undergoing R0 surgery. Long-term oncological outcomes were also determined, the first endpoint of which was 3-year recurrence-free survival [10]. The obtained results were continued in the CREATE study, phase 3, which had clearly defined parameters of the study with an attempt to evaluate the results of treatment in patients who received complex treatment and considering adjuvant chemotherapy [11].

A study conducted by the Angelita and Joaquim Gama Institute (Faculty of Medicine, University of São Paulo) [12] obtained promising clinical results of complete tumor regression after CRT. Subsequently, the researchers tried to increase it by adding chemotherapy after CRT for an 8- to 10-week interval, followed by an evaluation of the response to treatment, which significantly improved the results. The authors, based on the obtained results, first developed a strategy of organ preservation, also known in the scientific literature as the "watch and wait" approach with the mandatory stay of patients under a strict observation regime.

Habr-Gama *et al.* [13] after CRT additionally included the third cycle of 5-FU/leucovorin chemotherapy, instead of two with a radiation dose (54 Gy). Optimistic results of complete tumor regression up to 57% were obtained. Using molecular imaging with radiolabeled glucose and positron emission tomography, the researchers demonstrated that the addition of chemotherapy during the "waiting period" after CRT markedly reduced the likelihood of tumor metabolic recovery. The obtained result confirms that the additional chemotherapy in the preoperative period leads to a significant increase in the proportion of patients to whom sphincter-preserving surgery is indicated [13, 14].

Therefore, based on modern achievements, the first strategy of TNT has the following execution algorithm for patients with distal rectal cancer, which we present in Fig. 1.

The second TNT strategy is based on the Spanish study Grupo Cancer de Recto 3 (GCR-3) [15]. It was a two-group II phase. Patients with T3/T4 rectal cancer were randomized to receive 4 cycles of capecitabine/oxaliplatin (CAPOX) before neoadjuvant CRT followed by surgery. Significantly more patients completed per-protocol neoadjuvant chemotherapy (91 *vs* 54% in the adjuvant chemotherapy group; $p < 0.001$). Protocol compliance rate (94 *vs* 57%, respectively; $p = 0.001$), toxicity profile (19 *vs* 54% grade ¾ toxicity; $p = 0.004$). These results were much better than those published previously.

Similar results were previously presented in the EXPERT and EXPERT-C phase 2 studies [16, 17]. High adherence and tolerability rates of 89% and EXPERT-C > 90% were demonstrated, regardless of whether cetuximab was included in the chemotherapy regimen. Thus, studies have shown high adherence rates when using this treatment algorithm.

The analysis of the treatment results presented by the group of Zaborowski *et al.* [5] is important

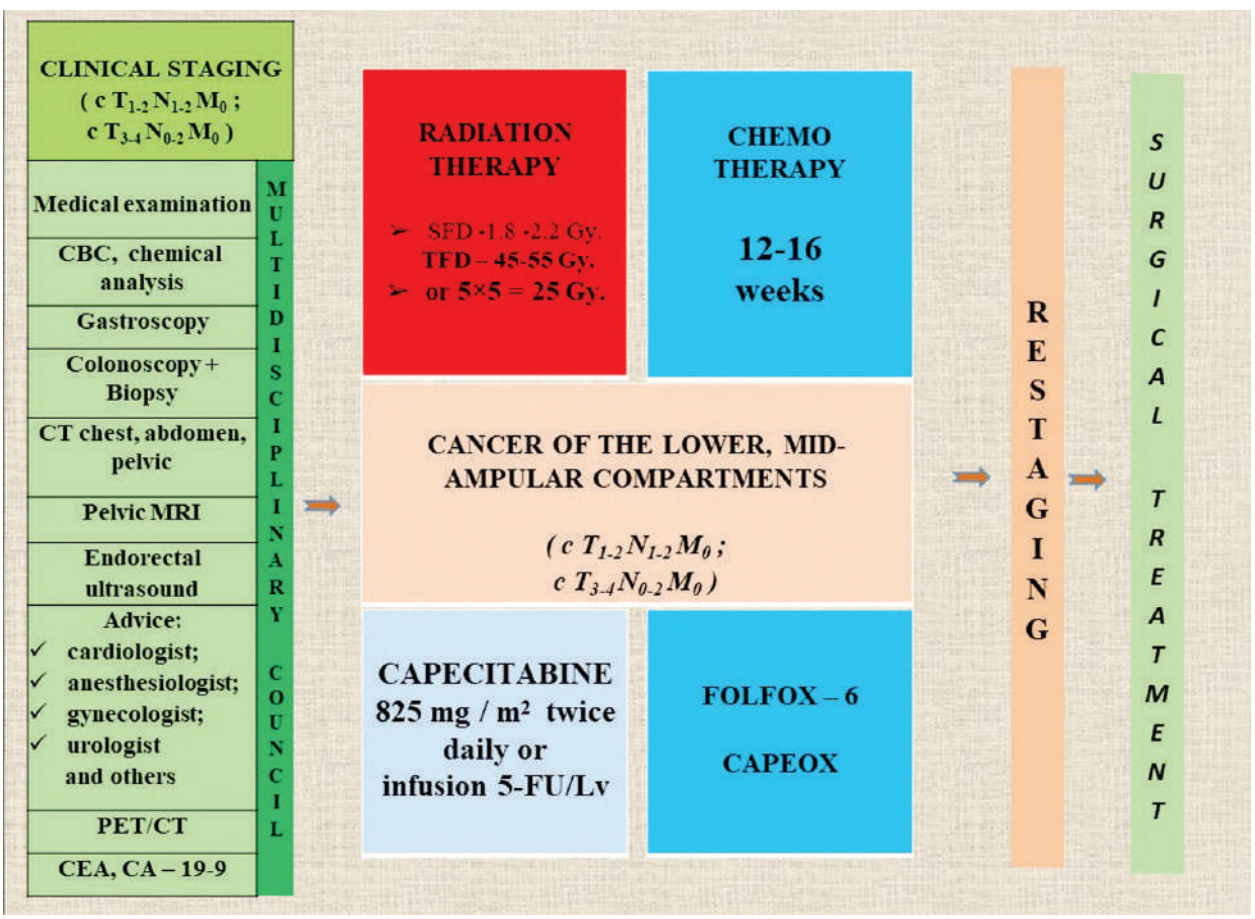

Fig. 1. Phased implementation of complex measures according to the first strategy of total neoadjuvant therapy in the treatment of distal rectal cancer

in justifying this strategy at the request of the PRISMA group. The analysis included 612 patients with cancer of the middle and lower ampullary regions of the rectum who received preoperative chemotherapy before CRT followed by rectal resection. The median follow-up was 53.7 (range 26–80) months. Among the ten included studies, seven reported 5-year survival data. Oncological results are summarized: weighted average 5-year overall and recurrence-free survival was 74.4% and 65.4%, respectively; local and distant recurrence rates among all included studies were 3.5 (range 0–7) and 20.6 (5–31)%, respectively. Local recurrence was defined as disease recurrence within the pelvis. Disease outside the pelvis was considered a distant recurrence. The diagnosis of disease recurrence was based on a combination of cytological, histopathological, biochemical, and radiological data.

According to the presented recommendations and based on our own previous clinical experience in the treatment of 24 patients with distal rectal cancer who underwent 16 weeks of polychemotherapy according to the FOLFOX or CAPOX scheme followed by CRT (long course of RT + capecitabine), two patients were suspected of appearance of metastases in the liver, which required an additional restaging stage. That is why we consider it expedient to implement this option in the sequence shown in Fig. 2.

Justification of cycle number, schemes, and doses of medication treatment for TNT; value of the time interval before the operation. One of the sides of this debate is the CONTRE study of Brown University [18], which prospectively presented the indicators obtained in a group of patients with 8 cycles of mFOLFOX6 before CRT, with its completion in 92% of cases. The authors reported that all patients underwent R0 resection between 6 and 10 weeks after completion of CRT, and in 33% of cases complete tumor regression was confirmed. The obtained results are similar to the results of the study presented above by Garcia-Aguilar *et al*. [6] for the group with 6 cycles of neoadjuvant FOLFOX therapy (R0 resection rate — 100% with complete tumor regression (PCR) rate — 38%). The above is a reason to consider options for neoadjuvant chemotherapy using 6–8 cycles of FOLFOX to evaluate the effectiveness of TNT.

A comparison of the results when using both strategies is presented in a study at the Memorial Sloan-Kettering Cancer Center [19]. In a retrospective cohort analysis, 811 patients were randomized to receive 8 cycles of FOLFOX [or equivalent CAPOX] followed by CRT, or CRT followed by 8 cycles of FOLFOX. In both groups, in patients with complete tumor regression, a wait-and-see approach was adopted, while in patients without regression, surgery was performed. The study demonstrated a higher rate of sustained complete clinical response at 1 year with TNT compared with standard neoadjuvant CRT and adjuvant chemotherapy (22 *vs* 6%).

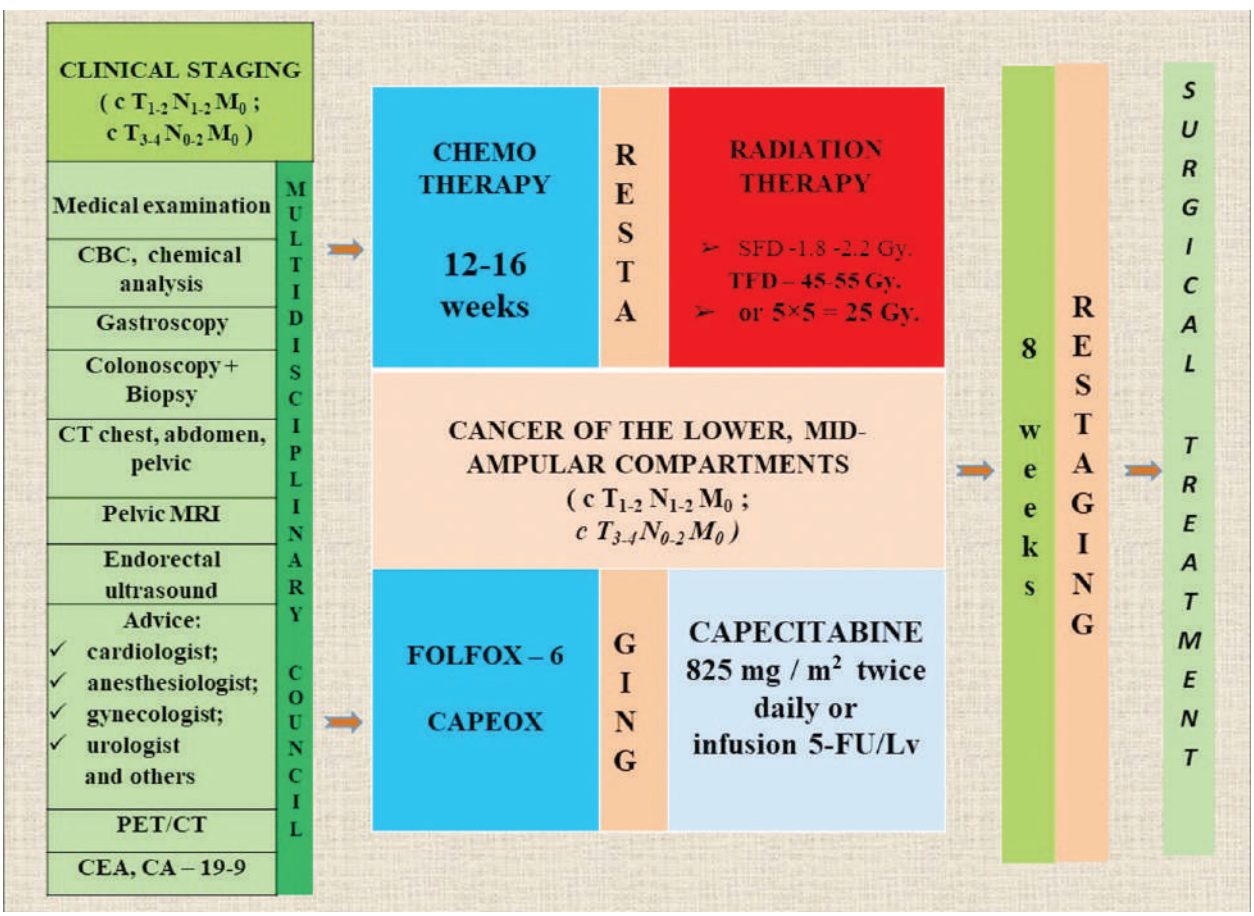

Fig. 2. Phased implementation of complex measures according to the second strategy of total neoadjuvant therapy in the treatment of distal rectal cancer

This problem is currently very relevant because it raises the question of the possibility of conservative treatment of the patients. A large multicenter randomized phase II study is currently underway [20]. Patients are randomized to receive FOLFOX before (induction) or after (consolidation) standard CRT. Patients with a complete clinical response with restaging confirmed on repeat magnetic resonance imaging and endoscopic examination will be treated conservatively, while patients with an incomplete response will be treated surgically. The primary important outcome is 3-year recurrence-free survival.

The experience gained suggests that the primary tumor is more sensitive to neoadjuvant therapy according to the FOLFOX scheme. Brown University's CONTRE (comprehensive neoadjuvant treatment of rectal cancer) trial [21] reported a tumor regression rate of 33% after eight cycles of mFOLFOX6 before CRT, with a tolerance rate of 92%.

Golo *et al.* [22] conducted one cycle of preoperative chemotherapy before CRT and two cycles after it, with tolerance rates of 86 and 94%, respectively.

Now, the introduction of high doses of systemic chemotherapy aimed at destroying subclinical micro metastases and, thus, reducing distant metastases, is promising in carrying out systemic chemotherapy. Optimizing systemic therapy will increase disease regression and increase pathological response rates. Tumor regression will lead to improved recurrence-free survival, which is a favorable prognostic indicator [23].

In 2020, a systematic review and meta-analysis were conducted by Kasi *et al.* [24], which included a study in which 2416 patients were considered. Based on the results of the study, it was concluded that TNT is a promising treatment strategy, it increases the chances of achieving complete tumor regression, as well as the chances of surgery with preservation of the sphincter and lowers the chances of applying an ileostomy. However, none of these results were statistically significant. Preoperative CRT is effective primarily for local disease control, but not as effective for preventing distant metastases, which has a key impact on overall and recurrence-free survival, requiring further evaluation by prospective randomized trials.

The role of neoadjuvant CRT regimes as a component of TNT. The use of optimal doses and timing of chemotherapy in combination with standard RT before surgery is a concept that can not only affect subclinical micro-metastases but also overcome the resistance often observed in adjuvant therapy. Current cancer protocol guidelines (National Comprehensive Cancer Network, European Society of Medical Oncology) state that the standard treatment for locally advanced rectal cancer is short or long-term preoperative radiation therapy with neoadjuvant chemotherapy, subsequent surgery, and adjuvant chemotherapy. Ambiguous recommendations for the appointment of RT regimen have caused discussions in the choice of one or another regimen among radiation oncologists in Europe and North America. Radiation oncologists in Western Europe are more inclined to use a short course of preoperative RT instead of long-term CRT, while specialists in North America and Eastern Europe prefer classical fractionation CRT. Therefore, we will consider the results of studies that analyzed the advantages and disadvantages of RT modes as part of neoadjuvant therapy.

In a randomized trial, Ngan *et al.* [25] compared the obtained oncological results after the use of short and long courses of neoadjuvant radiation therapy for rectal cancer. The results were obtained in 326 patients, out of which 163 patients received a short course of RT and 163 the long one. The follow-up time was 5.9 years (the range from 3.0 to 7.8 years). The three-year cumulative morbidity rate when using a short course was 7.5%, and when using a long course, it accounted for 4.4% (the difference of 3.1%; 95% confidence interval from — 2.1 to 8.3; $p = 0.24$). The authors found no significant difference in the frequency of distant metastases, overall and recurrence-free survival, or late toxicity in the studied groups.

A controlled study by Latkauskas *et al.* [26], determined the rate of improvement in the stage of rectal cancer after a short or long course of RT with surgery 6 weeks after completion of preoperative treatment in 83 randomized patients with stage II and III disease. The results of the study are as follows: the frequency of performed R0 resections was 91.3% in the CRT group and 86.5% in the group with a short course of RT ($p = 0.734$); accordingly, the frequency of sphincter preservation was 69.6 *vs* 70.3% ($p = 0.342$), and the frequency of postoperative complications was 26.1 *vs* 40.5% ($p = 0.221$). Pathological reduction of the stage (stage 0 and I) was observed in 18 (39.1%) patients after a long course of CRT and in 8 (21.6%) patients with a short course of RT ($p = 0.07$), respectively, tumor reduction — 2.5 cm *vs* 3.3 cm ($p = 0.04$).

In the previously mentioned Stockholm III study [27], the influence of extending the period from irradiation to surgery on treatment results was found. Patients who received a short course of radiation but had an interval of 4–8 weeks, instead of 1, between radiation therapy and surgery had a better rate of complete tumor regression, which was 12.0% compared with the previous 1.7%. This was confirmed by the conclusion from the meta-analysis of Petrelli *et al.* [28], which testified that the extension of the waiting period after neoadjuvant RT is an important factor influencing the oncological treatment results.

In these discussions, the results of the III phase randomized study by Bujko *et al.* are of great importance [7]. They were obtained from 515 patients with cT3/T4 rectal cancer with a median follow-up of 35 months. Group A consisted of 261 patients with a short course of 5 × 5 Gy followed by 3 cycles of FOLFOX4 and group B with a long course of CRT. Both groups had a 12-week interval between preoperative therapy and surgery. Acute toxicity of preoperative treatment was lower in group A than in group B ($p = 0.006$); any toxicity was 75 *vs* 83%,

grade III–IV 23 *vs* 21%, and toxic deaths 1 *vs* 3%, respectively. The R0 resection rate and complete pathologic response rate in groups A and B were, respectively, 77 *vs* 71% ($p = 0.07$) and 16 *vs* 12% ($p = 0.17$). Although the differences in local efficacy were not observed, the longer overall survival was in favor of 5 × 5 Gy schedule with 3 cycles of chemotherapy.

Humayun *et al.* [29] analyzed the treatment results in 108 patients with locally advanced rectal cancer depending on the prescription of the RT regimen. The patients were divided into two groups: group A received a short course of RT (25 Gy in 5 fractions) followed by a 2-month course of FOLFOX4 chemotherapy, while group B received a classic (long) RT course (45–50 Gy in 25–30 fractions) with 5-FU infusion. Response to treatment was assessed 11–12 weeks after its initiation using RECIST criteria, toxicity — according to CTCAE V 4.0, and pathological response, according to histological samples. There was no statistically significant difference between the studied indicators (frequency of objective response, disease progression, complete tumor regression) between the two groups.

A meta-analysis was conducted by Zhao *et al.* [30] to compare the pros and cons of short-term and long-term regimens of neoadjuvant CRT for stage II and III rectal adenocarcinoma demonstrated the same effectiveness and safety of a short or long RT course as part of neoadjuvant regimens. The authors point to the prospect of using methods of intensity modulated radiation therapy, volume modulated arc therapy, or stereotaxic radiation therapy to reduce the late toxicity of a short RT course associated with a high dose of fraction. The presented publications testify that TNT can be more successful than neoadjuvant CRT followed by adjuvant chemotherapy.

Considering the published results of the comparison of RT regimens in complex neoadjuvant treatment of rectal cancer, which did not provide a statistically significant difference between them, Cohen *et al.* [31] analyzed the cost-effectiveness of a short course of RT compared with a classic long course of RT in the treatment of stage III rectal cancer in the United States. This is the first model for assessing economic effectiveness when comparing intensive and classic regimens of RT based on oncological outcomes and costs. The authors concluded that an intensive course of RT is likely to be more cost-effective, and future studies should focus on providing reliable estimates of cost-utility and health status for these patients.

Despite the prospects of TNT, there are still practically justified recommendations for the use of CRT for cancer of the distal parts of the rectum, as shown in Fig. 3.

Discussions and controversies regarding the implementation of TNT. The existing theoretical shortcomings associated with the strategy of TNT, in particular the delay of radical surgery and the negative impact on work capacity, are argued. The administration of a full dose of systemic therapy can significantly affect the patient's suitability for surgery, potentially leading to an increase in the interval to surgery and progression of the disease in the postoperative period [2]. In addition, delaying surgery may lead to local disease progression, leading to more technically difficult dissection, increased intraoperative complications, and decreased overall survival, as radical sphincter-sparing surgery remains an integral component of the rectal cancer treatment paradigm.

The questions are being debated: whether radiation treatment is necessary — perhaps only chemotherapy treatment will be sufficient. These questions should be answered by the PROSPECT phase 2/3 study, which will be based on two randomized groups of patients with T3/T4 rectal tumor spread. Patients in the standard group received neoadjuvant CRT followed by surgery and adjuvant therapy (FOLFOX), and patients in the research group received 6 cycles of neoadjuvant chemotherapy (FOLFOX). When receiving a response to treatment in this group of patients, surgical treatment followed by adjuvant chemotherapy was performed, and patients who did not receive a positive response were prescribed neoadjuvant CRT followed by surgery. The goal of the study is to determine overall and recurrence-free survival [32].

A similar phase 2 BACCHUS study is being conducted by Glynne-Jones *et al.* [33] aiming to abandon radiation therapy before surgical treatment if a positive result is obtained for neoadjuvant chemotherapy according to the FOLFOX scheme.

NCCN recommendations version 1.2022. These discussions formed the basis of the NCCN Version 1.2022 [34] rectal cancer treatment recommendations. According to the recommendations, at the diagnosis of T_3, N_{any}, with clean margins of circumferential resection (CRM–), or T_{1-2}, N_{1-2}, it is recommended to treat in two directions: I — complete neoadjuvant therapy, which is preferred, and II — neoadjuvant therapy. Complete neoadjuvant therapy can be carried out in three options: the first is FOLFOX or CAPOX (12–16 weeks), after which CRT is performed (long course of RT + capecitabine or 5-FU infusion); with the second one, they change the sequence of neoadjuvant therapy, first CRT (long course of RT + capecitabine or 5-FU infusion) then FOLFOX or CAPOX (12–16 weeks); the third option is the same as the second, only CRT is replaced by a short RT course (5 × 5 = 25 Gy.). After 8 weeks, restaging follows since the best tumor response occurs during this period. After receiving the results, if contraindications are felt, the operation is performed with the further observation of the patient. The direction of neoadjuvant therapy is recommended to be implemented as follows: by carrying out CRT (a long course of RT + capecitabine or infusion of 5-FU) or a short course of RT. Re-staging for 8 weeks, if there are no contraindications, surgery is performed followed by adjuvant therapy (FOLFOX or CAPOX (12–16 weeks)).

At the diagnosis of T_3, N_{any}, with involvement or questionable CRM; T_4, N_{any} or locally unresectable,

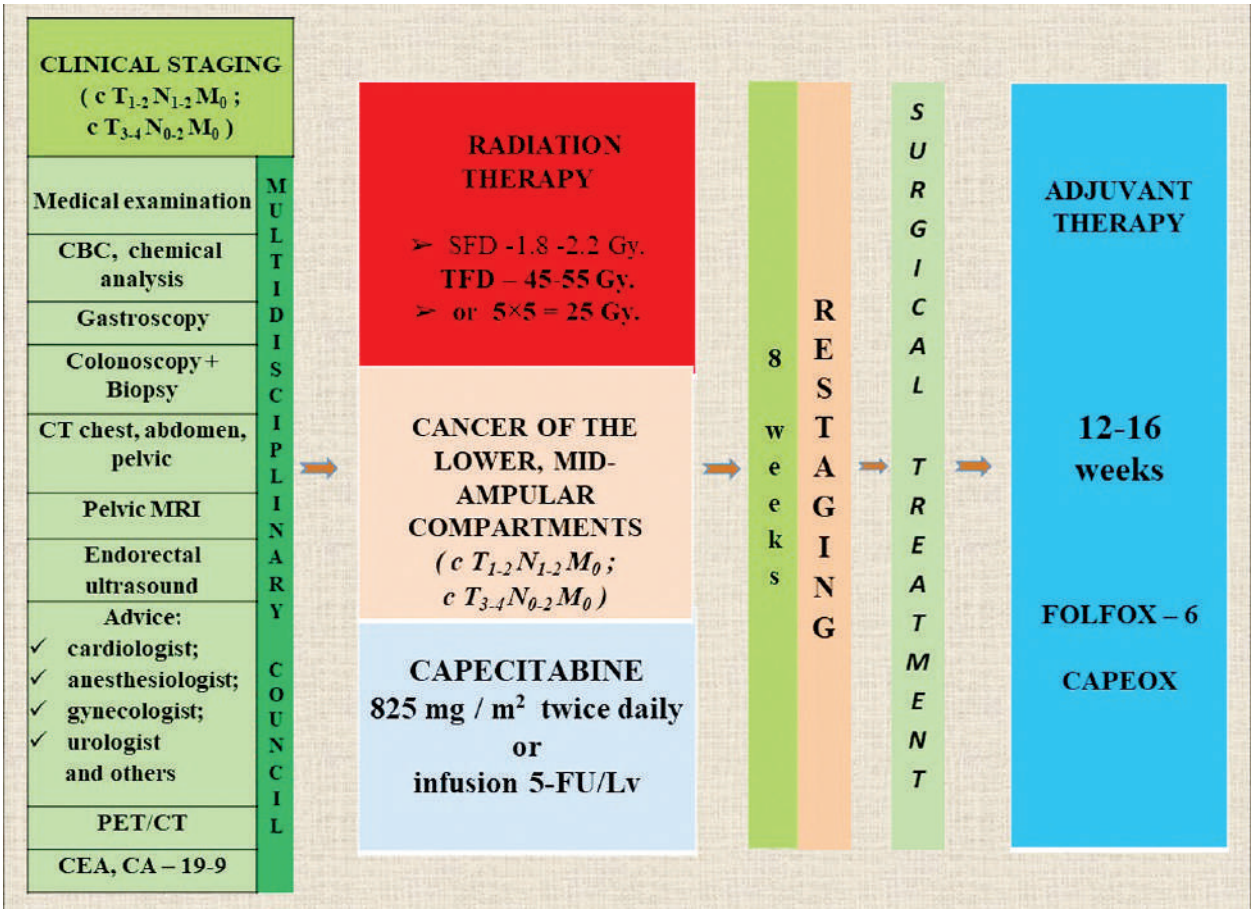

Fig. 3. Phased implementation of complex measures in the application of chemoradiation therapy in the treatment of distal rectal cancer

according to NCCN recommendations, treatment is carried out according to one of the options, exclusively in the direction of full neoadjuvant therapy, which is presented above. When diagnosing T_4, N+, the FOLFIRINOX regimen can be considered among the proposed chemotherapy regimens.

To sum up, the presented options for full neoadjuvant therapy have been developed and tested in leading oncology centers based on NCCN Version 1.2022 recommendations. However, it is premature to draw categorical conclusions regarding the recommendation of one or another variant of therapy, since they are only at the stage of wide implementation. However, our own previously obtained clinical experience indicates the need for an additional stage of restaging in the second option, after 16 weeks of polychemotherapy before CRT in order to exclude the generalization of the disease. The analysis of the term of full neoadjuvant therapy before surgical treatment, which is ⩾ 6 months on average, leads to the finding of stress disorders in patients, which necessitates their constant psychological and medical support. The occurrence of distress was explained by the combined effect of two factors: the delay in surgical removal of the tumor and the fear of generalization of the process in its presence. Therefore, there is a need for a prospective, controlled intercentre study, which will make it possible to answer the following questions: 1) which variant of neoadjuvant treatment is better to use; 2) what should be the psychological support of the patient; 3) how the frequency of performing R0 resection will change; 4) will the severity of the postoperative period change and will there be an increase in immediate and remote complications caused by multiorgan disorders as a result of total therapy; 5) what structural and functional changes in organs and systems will occur as a result of the therapy; 6) what oncological results will be obtained; 7) what is the economic feasibility of full neoadjuvant therapy, etc.

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ОГЛЯД ДИСКУСІЙ ТА ПРИЙНЯТТЯ РІШЕНЬ ЩОДО ТОТАЛЬНОЇ НЕОАД'ЮВАНТНОЇ ТЕРАПІЇ ПРИ ДИСТАЛЬНОМУ РАКУ ПРЯМОЇ КИШКИ

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Досягнення в комплексному лікуванні пацієнтів з дистальним раком прямої кишки призвели до зменшення кількості локо-регіонарних рецидивів до 5–10%, але зберігаються високі показники віддалених метастазів — до 30%. Саме вони призводять до невтішних віддалених онкологічних результатів, що вимагає пошуку покращення кожного з етапів комплексного лікування. У зв'язку із сумнівною ефективністю ад'ювантної поліхіміотерапії при дистальному раку прямої кишки обґрунтовано постає питання про можливість переведення медикаментозного лікування з ад'ювантної на неоад'ювантну схему. Представлені варіанти повної неоад'ювантної терапії були розроблені та протестовані в провідних онкологічних центрах і базуються на рекомендаціях Національної загальної онкологічної мережі (National Comprehensive Cancer Network — NCCN), версія 1.2022. Категоричні висновки щодо рекомендації того чи іншого варіанту його реалізації робити передчасно, оскільки вони лише на стадії широкого впровадження. Наші попередні клінічні результати підтвердили необхідність додаткового етапу рестадіювання у другому варіанті після 16 тиж поліхіміотерапії перед хіміопроменевою терапією, щоб виключити генералізацію захворювання. Тому існує потреба у проспективному контрольованому міжцентровому дослідженні, щоб відповісти на такі питання: 1) який варіант неоад'ювантного лікування краще застосувати; 2) який вид психологічної підтримки пацієнта слід обрати; 3) як зміниться частота виконання резекції R0 та спектр ускладнень; 4) які онкологічні результати буде отримано; 5) чи є економічно доцільною повна неоад'ювантна терапія тощо.

Ключові слова: дистальний рак прямої кишки, тотальна неоад'ювантна терапія, комплексне лікування, етапи лікування, медикаментозне лікування, променева терапія.