

**ORGAN-PRESERVING OPERATIONS IN THE COMPLEX TREATMENT OF
COLORECTAL CANCER: LITERATURE REVIEW****Dr. Uktam M. Kurbankulov^{1*} and Abrorbek A. Yusupbekov²**¹Researcher and MD at the Department of Oncology, Tashkent Medical HD Ademy.²Doctor of Medical Sciences, Deputy Director at the Republican Cancer Research Center, Tashkent, Uzbekistan.***Corresponding Author: Dr. Uktam M. Kurbankulov**

Researcher and MD at the Department of Oncology, Tashkent Medical HD Ademy.

Article Received on 20/08/2018

Article Revised on 09/09/2018

Article Accepted on 30/09/2018

ABSTRACT

By this review article authors aimed to evaluate information content, sensitivity, specificity of modern medical technologies (intraoperative ultrasound, transrectal ultrasound, Doppler, intraoperative cystoscopy, CT) in the diagnosis of locally advanced colorectal cancer. Based on the analysis and processing of immediate and long-term results of the combined and complex treatment methods, an integrated approach is developed in the treatment of patients with colorectal cancer, including new combinations of methods and schemes for specific therapy T₃-N₀M₀. Adequate clinical material can prove the feasibility of using organ-sparing surgical treatment methods for locally advanced forms of colorectal cancer. According to the results of the study, an algorithm is developed for the surgical, combined and integrated methods of treatment of colorectal cancer.

KEYWORDS: Colorectal cancer, sphincter-preserving operations, cancer recurrence, abdomino-perineal extirpation.

INTRODUCTION

In recent decades, an increase in the incidence of colorectal cancer (CRC) has been observed in many countries around the world. The annual occurrence of 50 new cases of colorectal cancer per 100,000 population determines the 5% population risk of developing the disease over a lifetime (Garin A.M., 1998; Davidov M.I., Axel E.M., 2002; Bertario L., 1999). The fact that there are more than 70 deaths per 100 newly diagnosed patients with CRC; within a year, about 40% patients will die after diagnosing in that year. This circumstance is because during the initial treatment of patients to the doctor, neglected forms of CRC (stage III-IV) are diagnosed in 62.4% of patients. In 25-30% of patients at the time of the operation, distant metastases are detected (Berdov BA, Nevolskikh AA, 1999; Demin DI and others, 2001; Oleinik VV, 2007; Labianca R. et al., 1997; Hobday TJ, Erlichman C., 2001; Minsky BD, 2001).

In this regard, increasing the effectiveness of the treatment of CRC today remains an urgent problem of modern oncology. In recent years, there has been a tendency to expand the indications for organ-preserving operations in the CRC. Many authors note that even with a pronounced spread of the cancer process, distant metastases may be absent, and it is possible to perform extended surgical interventions (Davidov, M.I. and others, 2006; Zouchenko, A.P. et al., 2006). At the same time, it is necessary to form clear criteria for their

fulfillment on the basis of a comparative analysis of long-term results of treatment, the frequency of locoregional relapses; the introduction of combined and integrated treatment programs that increase the ablaticity of surgical interventions (Knysh, VI, et al., 2001; Grigoriev, EG, and others, 2004; Zhinov, AV, Gorodnov, SV, 2006; Henne- Bruns D., Lotnert M., 2000).

Of course, the expansion of indications with organ-preserving operations should go hand in hand with working out clear criteria for their implementation based on a comparative analysis of long-term treatment results, mastering and implementing stitching devices, substantiating indications for using combined and complex treatment programs that increase the ablaticity of surgical interventions.

Diagnosis of early CRC remains unsatisfactory - a large number of patients (more than 25%) with initial treatment diagnose stage III-IV of the development of the tumor process (Simonov N.N., 2006; Navruzov S.N., 2003; Prorokov V.V., 2004; Villar A., 2004; Stearns W.N., 2004)., Which necessitates an improvement in the quality of diagnostics, the further scientific development of criteria allowing to form high-risk groups and the subsequent development of treatment tactics for patients. Despite the characteristic clinic, the improvement of diagnostics, about 1/3 of patients with CRC seek medical

help, already having a long-gone tumor process. According to many authors, 70-80% of patients with CRC come to clinics with stage III-IV disease. Among the reasons for the late diagnosis of CRC, the absence of a mandatory standard examination scheme for a patient suspected of having the disease, incomplete use of previously developed diagnostic methods, limited use of new examination methods (Fedorov V.D. et al., 1994; Vorobyev G.I. and et al., 2003; Engstrom P.F., 2000).

The main and most effective method of treatment of CRC is a surgical method with respect for the principles of oncological radicalism. However, the use of only a surgical method for the treatment of CRC demonstrates low efficacy - for 20-25 years, stably low 5-year survival rates after radical operations - 46-62%, which is an average of 52%. A number of authors relate the main causes of failures in the surgical treatment method to the occurrence of relapses and distant metastases that occur at various times after surgery. Approximately 68% of patients died due to cancer recurrence after surgery, and the incidence of loco regional metastases ranges from 20-40% (Prorokov VV, Zalit N.Y., 2002; Berdov B.A., Nevol A.A., 2002; Adamm R., 2004). These failures determine the feasibility of finding ways to increase an acceptable and effective treatment method through the use of combined and complex methods of treatment of CRC.

Among the many factors that determine the nature and extent of surgical interventions, primarily organ preserving, the fundamental role belongs to the degree of local spread of the tumor process and the level of tumor localization in the rectum. When the CRC typical operations depending on the height of the primary tumor are: anterior resection, abdominal-anal resection of the rectum with the reduction of the sigmoid, obstructive resection (Hartman's operation) and abdominal-perineal extirpation of the rectum (Fedorov V.D. and others, 1994; Gorodnov S.V., Zhinov A.V., 2005; Gruenberg T., 2005).

Common forms of the CRC are often the main reason for the abandonment of active surgical tactics. Often, patients in this group perform symptomatic palliative operations, in which there are a large number of postoperative complications and high rates of postoperative mortality. At the same time, the quality of life of these patients deteriorates significantly, which is caused by the growing influence on their bodies of an unresolved primary tumor and the progression of metastatic growth. The average life expectancy of these patients does not exceed 3-7 months (Kulikov, E.P. and others, 2001; Barsukov, Y.A., and others, 2002; Vorobyev, G.I., and others, 2003; Engstrom PF, 2000).

The main argument of opponents of superradical interventions is the high technical complexity and invasiveness of the latter. However, many surgeons do not agree with this proposition, since the long-term

global practice of performing combined and expanded operations not only allows us to hope for good long-term results, but also opens up tremendous prospects for improving the quality of life of patients by performing single-step or delayed plastic surgeries (Khanevich M.D. et al., 2003; P.V. Sarkov et al., 2004).

The trend towards the implementation of savings interventions in the form of abdominal resection and abdominal-anal resection of the rectum, naturally, in the absence of contraindications of oncological nature, can be attributed to the modern direction in locally advanced CRC. Postoperative mortality in these interventions is not much higher than that in normal operations — for example, 30-40% of patients undergoing combined operations undergo a 5-year term. One of the important contraindications to the performance of combined operations is the presence of concomitant diseases that are not amenable to correction in the preoperative period, especially in elderly patients (Shaposhnikov V.I., 2000; Shulutko A.M. et al., 2000; Adam R. et al., 2001).

The evolution of views on oncological and functional feasibility of operations for cancer of the upper, middle, and in some cases and lower rectal sections of the rectum ousted abdomino-perineal extirpation from the status of the “gold standard”, giving way to sphincter-saving operations. Among them, the most progressive and high-tech interventions include: intersphincteric resection of the rectum with complete or partial removal of the internal sphincter, ultralow anterior resections, as well as “close shave” resection with a distal line of resection immediately after the level of the palpation-defined tumor edge (Fedorov V. D., et al., 1994; Bondar, GV, et al., 2002; Odaruk, T.S., et al., 2005).

Given these factors, the entire spectrum of surgical interventions in the rectum can be divided into two categories - with and without preservation of the sphincter apparatus of the organ. Moreover, in recent years, a tendency to an increase in the number of organ-preserving operations has been clearly observed throughout large cancer clinics throughout the country. A similar pattern is noted in the RCRC after named N.N. Blokhina, where in recent years the percentage of sphincter-preserving operations has increased to 70.1% (Grigoriev, EG and others, 2004; Zhinov, AV, Gorodnov, SV, 2006; Henne-Bruns, D., Lotnert, M., 2000).

The last decades have been characterized by the search for optimal schemes for combined and complex treatment of CRC due to a combination of a surgical method with radiation or chemotherapy. Combined and complex therapy of the CRC is designed to improve the results of treatment of a severe category of patients with locally common process and the presence of metastases (Barsukov Y.A. and others, 2002; Bazin IS, 2006; Douillard J.Y. et al., 2000; Giantonio B., Catalano, P., 2005; Bosset JF et al., 2005). However, it should be

noted that at present there is no consensus on the feasibility of using complex treatment in the locally advanced process in the CRC, where the leading role is assigned to the surgical method of treatment.

At the same time, despite the conduct of chemoradiation therapy, the 3-year survival rates for locally advanced CRC do not exceed 13%, which indicates the absence of a trend towards improvement in these patients and indicates the need for further research in this direction (Barsukov Y.A., 2000; Knish V.I., 2001; Malakhov Y.P., 2004; Houdard C., 2004).

Recognition of the fact that, after a purely surgical treatment of stages II and III, the failure rate in the local tumor control is 15-50%, led to the use of additional (adjuvant) radiation therapy. Numerous prospective randomized studies conducted by multicenter cooperative groups have resulted in the practical use of combined adjuvant therapy, including radiation therapy and the use of 5-fluorouracil (Karyakin, O.B. and others, 1996; Knysh, V.I., and others, 2001; Navruzov S.N. et al., 2001; Sauer R. et al., 2004).

In modern clinical oncology, there is a constant search for the most effective methods of combining surgical intervention with various types of radiation therapy (preoperative, intra- or postoperative) (Dubois J., 2002; Adloff M., 2003).

Currently, one of the most promising options for combination therapy is the use of large-scale radiation therapy, the effectiveness of which has been proven by numerous clinical studies (Berdov BA, 1999; Barsukov Y.A., 1999; Kanaev S.V., 2003). Thus, there is a large number of opinions of various authors on the use of preoperative and postoperative radiation exposure in the CRC. To date, there are no clear indications on the timing, doses and methods of exposure to radiation therapy in this pathology, which indicates the need to find ways to improve and increase the effectiveness of this method of exposure. Most studies, according to literary data, show the effectiveness of preoperative radiation therapy in order to prevent local recurrences (Prorokov VV, 2001; Kanaev SV, 2002).

According to some researchers, preference should be given to conducting a short course of radiation therapy immediately before the operation, in a total dose of at least 20 Gy. Along with this, there are contradictory opinions of many authors that the problem of local relapses can be solved by improving surgical interventions and applying more aggressive surgical techniques (Chissov, V.I., 2003; Vashakmadze, SA, 2004).

Chemotherapy is another specific treatment used in the complex treatment of CRC. The impetus in the use of chemotherapy for the treatment of this category of patients was the creation of new drugs with antitumor activity, as well as the use of new regimens in the

treatment of CRC. A clinical study of these drugs has shown that their use as part of various regimens and combinations can increase the overall effectiveness of chemotherapy for patients with colorectal cancer and increase the life expectancy of this category of patients. Thus, the median survival of patients with metastatic cancer with purely symptomatic therapy was only 8 months, and with CT using 5-FU with leucovorin increased to 12 months, using modern CT with the inclusion of irinotecan and oxaliplatin in the regimens, it increased to 15 -17 months, and with the sequential use of combinations containing irinotecan or oxaliplatin, increased to 20 months (Perevodchikova N.I., 2004). It should also be noted about the different ways of CT - intraarterial, endolymphatic, intraportal.

Currently available research to improve early diagnosis, the use of various methods of combined and complex treatment and the introduction of preventive measures opens up real prospects for improving the long-term results of the treatment of CRC.

Thus, the existing trends to an increase in the incidence of CRC, high rates of postoperative mortality, the occurrence of frequent relapses and metastasis (20-25%), low rates of 5-year survival (50-58%), an unsatisfactory level of quality of life of patients, the difficulty of social and labor rehabilitation, indicate the relevance of the problem being studied, and indicates the need for research to optimize the combined and complex treatment methods for this category of flax.

REFERENCES

1. Martens MH, Maas M, Heijnen LA, Lambregts DM, Leijtens JW, Stassen LP, et al. Long-term outcome of an organ preservation program after neoadjuvant treatment for rectal cancer. *J Natl Cancer Inst*, 2016; 108.
2. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *New Engl J Med*, 2004; 351: 1731-40.
3. Aleksandrov V.B. Rectal cancer. –M.: Medicine, 2007.
4. Barsukov Y.A., Tkachev S.I., Bashev V.Kh. Pre- and postoperative radiation therapy in the combined treatment of colorectal cancer // *ROJ.*, 2006; 6: 13-16.
5. N. Protchenko. The limits of the spread of colorectal cancer // *Vopr. Oncol*, 2008; 4: 48-52.
6. Barsukov Y.A., Nikolaev A.V., Tamrarov R.I., Tkachev S.I. Comparative analysis of surgical and combined treatment of patients with operable rectal cancer (results of a randomized study) // *Practical Oncology*, 2008; 3(2): 35-37.
7. Navruzov S.N., Khakimov A.M., Mukhamedaminov Sh.K., Toshbekov B.U. et al., Combined Treatment of Colon Cancer, *Probl. oncol. Sat scientific st.* - Tashkent, 2001; 1: 263-268.

8. Prorokov V.V., Zalit N.Yu., Knysh V.I. Intensive preoperative hypoxradiotherapy in the combined treatment of patients with colon cancer // *Surgery*, 2003; 6: 38-42.
9. Bacon H.E. Present status of the quill through sphincter preserving procedure. *Cancer*, 2008; 128: 196-202.
10. Localio S., Eng K., Coppa G. Abdominosacral resection for midrectal cancer // *Ann. Surg.*, 2009; 198(3): 320-325.
11. Williams N.S. The rationale for preservation of the anal sphincter in patients with low rectal cancer // *Brit. J. Surg.*, 2009; 71(8): 575-580.
12. Mendenhall WM, Million RR, Pfaff WW. Patterns of recurrence in adenocarcinoma of the rectum and rectosigmoid treated with surgery alone: implications in treatment planning with adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys*, 1983; 9: 977-85.
13. Rödel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*, 2015; 16: 979-89.
14. Heald RJ. The 'Holy Plane' of rectal surgery. *J R Soc Med*, 1988; 81: 503-8.
15. Palmer G, Anderin C, Martling A, Holm T. Local control and survival after extralevator abdominoperineal excision for locally advanced or low rectal cancer. *Colorectal Dis.*, 2014; 16: 527-32.
16. Gérard JP, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol*, 2006; 24: 4620-5.
17. Coco C, Valentini V, Manno A, Rizzo G, Gambacorta MA, Mattana C, et al. Functional results after radiochemotherapy and total mesorectal excision for rectal cancer. *Int J Colorectal Dis.*, 2007; 22: 903-10.
18. Maas M, Beets-Tan RGH, Lambregts DMJ, Lammering G, Nelemans P.J., Engelen SME, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol*, 2011; 29: 4633-40.
19. Gao Y-H, Lin J-Z, An X, Luo J-L, Cai M-Y, Cai P-Q, et al. Neoadjuvant sandwich treatment with oxaliplatin and capecitabine administered prior to, concurrently with, and following radiation therapy in locally advanced rectal cancer: a prospective phase 2 trial. *Int J Radiat Oncol Biol Phys*, 2014; 90: 1153-60.
20. PROSPECT. PROSPECT: chemotherapy alone or chemotherapy plus radiation therapy in treating patients with locally advanced rectal cancer undergoing surgery (NCT01515787).
21. Kreis ME, Ruppert R, Ptok H, Strassburg J, Brosi P, Lewin A, et al. Use of preoperative magnetic resonance imaging to select patients with rectal cancer for neoadjuvant chemoradiation-interim analysis of the German OCUM Trial (NCT01325649). *J Gastrointest Surg*, 2016; 20: 25-32.
22. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro Jr U, Silva e Sousa Jr AH, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg*, 2004; 240: 711-7.
23. Habr-Gama A, Perez RO, Proscurshim I, Campos FG, Nadalin W, Kiss D, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg*, 2006; 10: 1319-28.
24. Appelt AL, Pløen J, Harling H, Jensen FS, Jensen LH, Jørgensen JCR, et al. Highdose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol*, 2015; 919-27.
25. Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol*, 2015; 16: 957-66.
26. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol*, 2015; 2045: 1-10.
27. Tulchinsky H, Shmueli E, Figer A, Klausner JM, Rabau M. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol*, 2008; 15: 2661-7.
28. Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg*, 2009; 250: 582-9.
29. Lefevre JH, Mineur L, Kotti S, Rullier E, Rouanet P, de Chaisemartin C, 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.
30. Sloothaak DAM, Geijsen DE, van Leersum NJ, Punt CJA, Buskens CJ, Bemelman WA, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg*, 2013; 100: 933-9.
31. Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: A meta-analysis of published studies. *Ann Surg*, 2016; 263: 458-64.

32. Evans J, Bhoday J, Sizer B, Tekkis P, Swift R, Perez R, et al. Results of a prospective randomised control 6 vs 12 trial: is greater tumour 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): 149.
33. Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean J-P, Partensky C, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol*, 1999; 17: 2396.