

RADIATION THERAPY AS A METHOD IN THE COMBINED TREATMENT OF RECTAL CANCER

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Abstract. *This article provides information on radiation therapy as a method of complex treatment of rectal cancer.*

Key words: *Radiation therapy, colorectal cancer, chemoradiotherapy, mesorectumectomy.*

ЛУЧЕВАЯ ТЕРАПИЯ КАК МЕТОД КОМБИНИРОВАННОГО ЛЕЧЕНИЯ РАКА ПРЯМОЙ КИШКИ.

Аннотация. *В статье представлена информация о лучевой терапии как методе комплексного лечения рака прямой кишки.*

Ключевые слова: *Лучевая терапия, колоректальный рак, химиолучевая терапия, мезоректумэктомия.*

Introduction:

Currently, there is a high prevalence of colorectal cancer (RCC), which is reflected in its leading position in terms of incidence rates in economically developed countries, including Russia [1,2,3]. According to statistics, cancer ranks third among the causes of death from malignant tumors among men and fourth among women in Russia [4,5]. In 2017, 29,918 new cases of the disease were recorded, leading to the death of 16,360 patients [6,7].

Depending on the stage of the disease, treatment of patients with resectable cancer can be surgical only or combined with other antitumor methods (combination treatment). The most common of the latter are preoperative radiation therapy (RT): large-fraction RT ROD 5 Gy to SOD 25 Gy, small-fraction RT ROD 2 Gy up to SOD 46-50 Gy) and chemotherapy (systemic, intrapelvic). And also, various combinations of these methods - chemoradiotherapy (CRT) [2, 6, 8, 10, 12].

Analysis of the results of both surgical and combined treatment of patients with RCC shows that its failures are mainly due to local relapses and distant metastases of the tumor.

The development of relapses is associated primarily with the dissemination of tumor complexes through the blood and lymphatic vessels, and less often with implantation. The occurrence of relapses is also facilitated by the depth of tumor invasion into surrounding tissues >5 mm, the distance from the tumor to its own fascia <1 mm [6, 8, 10, 13,14].

Progress in the surgical treatment of patients with rectal cancer is due not only to the technology of total mesorectumectomy (TME) for rectal resection [12,15]. Unfortunately, adherence to the principles of TME does not always provide the desired result, and the frequency of local relapses depends, among other things, on its quality: with good quality - 9%, with satisfactory - up to 12%, with poor quality - up to 19% [3, 13, 14].

Purpose of the study: to evaluate the immediate and long-term results of combined treatment of patients with resectable rectal cancer at stages IIA -b - IIIA -b, carried out using preliminary endovascular chemoembolization of cancer, and compare these results with the effectiveness of various methods of preliminary radiation therapy.

Materials and methods: The study was carried out at the Department of Oncology of Samarkand State Medical University on the basis of the Samarkand branch of the Russian Scientific and Practical Medical Center and R. The work is based on an analysis of the results of treatment of 160 patients with resectable stage IIA -B and IIIA -B cancer from 2021 to 2024.

The staging of the disease was carried out according to the International TNM system (version 8, 2017), where IIA (T3N0M0), IIB (T4aN0M0), IIIA (T1-2N1M0 / H[^]MO), IIIB (T3-4BN1M0 / T2-3N2aM0).

Depending on the nature of treatment (surgical / combined options), patients were divided into 4 groups (n=160).

The study group (IG) included 40 patients (prospectively) who underwent combined treatment: neoadjuvant chemoembolization of rectal arteries (CE RA) + radical surgery (R0, 72 hours after the endovascular procedure) for the period from 2011 to 2017.

In order to compare the results obtained in the IG, we formed 3 clinical comparison groups (GCS 1, 2 and 3) - retrospectively by sampling medical histories from the archives of the Russian Railways Medicine Clinical Hospital, Krasnoyarsk for the period from 2003 to 2010:

1. GCS 1 (n=40) - surgical treatment (R0);
2. GCS 2 (n=40) - combination treatment: neoadjuvant large-fraction radiation therapy (5 x 5 Gy up to a total focal dose of 25 Gy (CRT SOD 25 Gy) + radical surgery (R0, 24-48 hours after the end of radiation therapy);
3. GCS 3 (n=40) - combination treatment: neoadjuvant endovascular radio modification metronidazole (ERM MZ) + high-dose radiation therapy with a single focal dose of 13 Gy (VLT ROD 13 Gy) + radical surgery (R0, 20-24 hours after the end of radiation therapy).

The criteria for inclusion in the groups were:

- the presence of resectable rectal cancer (STAGES IIA -B and IIIA -B) with tumor localization in the upper/middle/lower ampulla;
- the general condition of the patient on the ECOG scale is from 0 to 2 points.
- age up to 70 years;
- absence of previous chemotherapy, immunotherapy, radiation or hormonal therapy.

Exclusion criteria were:

- presence of distant metastases;
- Preoperative radiotherapy technique
- All patients in the main group received intensive preoperative irradiation with a total dose of 25 Gy. Irradiation was carried out from Monday to Friday at a daily dose of 5 Gy. In order to reduce the likelihood of acute radiation reactions, the daily dose was given in two fractions of 2.5 Gy twice a day with a break of 4-6 hours between fractions. Irradiation was carried out using a linear accelerator " Philips SL 75" or " Philips SL 20" - in 45 (75.0%) patients and a gamma therapeutic installation "ROKUS-M" - in 15 (25.0%) patients.

Discussion:

- Preventing the development of local relapses of rectal cancer is an urgent problem in modern oncology. Developing deep in the pelvis, they cause compression of nerve structures and organs, causing great suffering to patients. And it is on the prevention of relapses, and not on their treatment, that the main efforts of specialists involved in the treatment of this complex group of patients should be focused.

- The relapse rate for rectal cancer clearly depends on the stage of the disease: for stage I it is 7-10%; at stage II - 17-20%; at stage III 25-30% [127, 253]. Other clinical and morphological factors also play a role in the development of relapses, but the depth of tumor invasion and the condition of regional lymph nodes and the low degree of tumor differentiation are of decisive importance.

- Over the past 20 years, tremendous changes have occurred in the surgical treatment of rectal cancer. The principle of “case” in the removal of the rectum became generally accepted after the discovery of data on the fascial spaces of the pelvis. Total mesorectumectomy has become the gold standard for rectal cancer surgery in many countries. Thanks to the development of staplers and surgical instruments, it has become possible to perform sphincter-preserving operations in 70-80% of patients.

- Using surgical treatment alone, some surgeons have been able to reduce the local recurrence rate to 3-10%, which in itself is an excellent result [6,7]. However, neither knowledge of the anatomy and physiology of the tumor, nor brilliant surgical technique are able to completely prevent the development of relapses in patients in the so-called risk group - stages P-III of rectal cancer. This is especially true for patients with multiple metastases to regional lymph nodes, the relapse rate of which is 30%, and the 5- year survival rate does not exceed 40% [16]. In such patients, it is simply necessary to use additional treatment methods, primarily adjuvant radiation therapy.

- Therefore, many authors associate ways to improve treatment outcomes for patients with stage P-III rectal cancer with the development of combined treatment methods. The purpose of preoperative irradiation is to reduce the biological potential of tumor cells and thereby increase the ablasticity of the surgical procedure, as well as to affect subclinical metastases. Despite the almost half-century history of preoperative irradiation for rectal cancer and the positive results of combined treatment obtained by many authors, the effectiveness of this method for various categories of patients remains largely unclear.

A comparative analysis of patients by gender and age in the comparison groups (Table 1) did not reveal statistically significant differences ($p>0.05$).

Study results:

Thus, among 40 patients in the surgical treatment group (GCS 1), there were 62.5% women and 37.5% men aged 40 to 70 years. The number of women in this group was 1.7 times higher than the number of men, and the average age of the patients was 54 ± 4.4 years.

Accordingly, of the 40 patients in GCS 2 who underwent combined treatment with preoperative CRT SOD 25 Gy - 60.0% were women and 40.0% were men, their ratio was 1.5:1, average age - 56 ± 3.5 of the year.

Almost similar indicators were registered in GCS 3, where combined treatment included preoperative endovascular radio modification metronidazole and VLT ROD 13 Gy. There were 1.7 times more women than men. Average age - 55±4.2 years.

Table 1 - Distribution of patients by gender and age (n = 160)

Comparison groups _	GKS 1 HL n=40 (1)		GKS 2 KLT SOD 25 Gy n=40 (2)		GKS 3 VLT ROD 13 Gy with ERM MZ program n=40 (3)		ISIS HE RA n=40 (4)	
	n	%	n	%	n	%	n	%
Gender of patients								
Men	15	37.5	16	40.0	15	37.5	17	42.5
Women	25	62.5	24	60.0	25	62.5	23	57.5
Age of patients								
40 - 49 years old	8	20.0	10	25.0	9	22.5	elev	27.5
50 - 59 years	eleve	27.5	12	30.0	13	32.5	12	30.0
60 - 69 years old	19	47.5	17	42.5	18	45.0	16	40.0
70 years old	2	5.0	1	2.5	-	-	1	2.5
Credibility	p 1, 2, 3, 4 > 0.05							

Among 40 patients in the study group (IG) who underwent combined treatment using the endovascular RACHEL procedure, 57.5% were women and 42.5% were men, their ratio was 1.4:1, the average age was 54±3.9 years.

The most numerous contingent in all groups were patients aged 50-69 years: in the study group - 70.0%, in clinical comparison groups (1, 2 and 3), respectively - 75.0%, 72.5% and 77.5%.

The distribution of patients included in the study according to the criteria of the International TNM System (version 8, 2017) is presented in Table 2.

The pT1 criterion corresponded to the spread of the tumor in the mucosal and submucosal layers of the intestinal wall. The number of patients meeting this criterion was identified in only 2 cases (1 patient each in GCS 1 and IG).

1. Intensive preoperative radiotherapy at a dose of 25 Gy (equivalent to 40 Gy with traditional fractionation) despite an increase in the number of general to 35% (grades 1-2 - 31.7%; grade 3 - 3.3%) and local to 13.3% (1-2 degrees - 10%; 3 degrees - 3.3%) of radiation reactions, was realized in all patients, in no case did it become a reason to transfer the operation abroad at an optimal time for it, and did not increase the number of postoperative complications.

2. Radiation therapy changed the proliferative activity of tumor cells, significantly reducing the level of proliferation proteins (PCNA before treatment 59.2±2.2, after treatment 29.6±2.1, p=0.0003; cyclin A before treatment 23.7±2.0, after treatment 18.9±1.5, p=0.03).

The pT2 criterion in the comparison groups (tumor invasion into the native muscle layer) was recorded somewhat more often - in 23/160 (14.4%) cases.

Table 2 - Distribution of patients according to TNM criteria (n = 160)

Comparison groups _	GKS 1 HL n=40 (1)		GKS 2 KLT SOD 25 Gy n=40 (2)		GKS 3 VLT ROD 13 Gy with ERM MZ program n=40 (3)		ISIS HE RA n=40 (4)	
	n	%	n	%	n	%	n	%
pT criterion								
T 1	1	2.5	-	-	-	-	1	2.5
T 2	6	15.0	6	15.0	5	12.5	6	15.0
T 3	28	70.0	thirty	75.0	29	72.5	28	70.0
T 4a	5	12.5	4	10.0	6	15.0	5	12.5
pN criterion								
N 0	13	32.5	eleve	27.5	12	30.0	13	32.5
N 1	21	52.5	22	55.0	22	55.0	23	57.5
N 2	6	15.0	7	17.5	6	15.0	4	10.0
pM criterion								
M0	40	100.0	40	100.0	40	100.0	40	100.0
Credibility	p 1, 2, 3, 4 > 0.05							

Tumor invasion meeting the pT3 criterion was observed in the largest number of patients (2/3 cases). In clinical comparison groups (1, 2 and 3), respectively - 70.0%, 75.0% and 72.5%. In the study group this figure was 70.0%. The depth of the lesion, determined by the pT3 parameters, was set in cases where the tumor grew through all layers of the PC wall in the middle or lower ampullar region with spread to the adjacent perirectal tissues (T3a < 1 mm / T3b - 1-5 mm / T3c - 5-15 mm / T3d > 15 mm). For tumors of the superior ampullary part of the PC (covered by peritoneum), pT3 characterized the spread of the tumor to the subserous layer (without invasion of the serous membrane).

IIA -B rectal cancer was diagnosed in 49/160 (30.6%) patients included in the study (Table 3). In the clinical comparison groups (1, 2 and 3), respectively - in 32.5%, 27.5% and 30.0% of patients, in the study group - in 32.5% (p>0.05).

Conclusions:

Intensive preoperative radiotherapy at a dose of 25 Gy (equivalent to 40 Gy with traditional fractionation) despite an increase in the number of general to 35% (grades 1-2 - 31.7%; grade 3 - 3.3%) and local to 13.3% (1-2 degrees - 10%; 3 degrees - 3.3%) of radiation reactions, was realized in all patients, in no case did it become a reason to transfer the operation abroad at an optimal time

for it, and did not increase the number of postoperative complications. Radiation therapy changed the proliferative activity of tumor cells, significantly reducing the level of proliferation proteins (PCNA before treatment 59.2 ± 2.2 , after treatment 29.6 ± 2.1 , $p=0.0003$; cyclin A before treatment 23.7 ± 2.0 , after treatment 18.9 ± 1.5 , $p=0.03$).

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