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NEOADJUVANT RADIOTHERAPY AND CHEMOTHERAPY IN LOCALY ADVANCED RECTAL CANCER: prospective, randomized phase III study, in colaboration with IAEA, ESTRO and UHC "Sestre milosrdnice"

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Summary

At the Department of Oncology and Nuclear Medicine UHC "Sestre milosrdnice" patients who had advanced rectal cancer were treated with preoperative radiotherapy and chemotherapy, in cooperation with the IAEA and ESTRO. Fifteen patients who met the criteria and signed informed consent were included. Patients were randomized into two groups: Group 1: standard group, neoadjuvant approach (chemotherapy 5-FU / leucovorin concomitantly with radiotherapy (45-50 Gy in 25 fractions); Group 2: short course group, chemotherapy 5-FU / leucovorin with radiotherapy (25 Gy in 5 fractions). The main objectives were to determine the rate of resectability after completion of neoadjuvant therapy and to determine the percentage of local control and overall survival.

***Keywords*:** neoadjuvant therapy; locally advanced rectal cancer.

INTRODUCTION

Rectal cancer is more frequent in developed than in developing countries. However, in the specific case of rectal cancer, the majority of patients present with advanced loco-regional disease, many of them are unresectable, many of borderline operability and are treated for palliation.

The past decade has witnessed a number of significant developments in the management of rectal cancer mainly from Western Europe and the USA. These

include the development of a surgical technique Total Mesorectal Excision (TME) which is now considered the "gold standard" for rectal surgery in many European countries. From the pathology viewpoint, the prognostic significance of obtaining negative circumferential resection margins (CRM) has been demonstrated. From the radiotherapy viewpoint a short fractionation schedule (25 Gy in 5 fractions over one week) has proven effective in improving local control and survival rates as a preoperative treatment.

The following text summarizes the state-of-art of the role of radiotherapy in rectal cancer resectable and un-resectable:

Management of cancer of the rectum has undergone a dramatic change in the past decade. Until recently surgery had remained the primary treatment modality, but in spite of "curative" resections, a significant proportion of patients develop local recurrence of disease (20% to 50%). Local tumour recurrence is highly correlated with both the depth of penetration of the tumour and the number of regional nodes involved by metastatic disease. Recent results of national cooperative group studies and several European randomized trials indicate that a multimodality treatment approach (surgery combined with radiotherapy/chemotherapy) results in a significantly better outcome than surgery alone.

NEOADJUVANT THERAPY

Considerable debate has evolved regarding the optimal approach to adjuvant therapy in rectal cancer. Although both pre- and postoperative adjuvant therapy can be effective, there has been a significant recent trend toward greater use of neoadjuvant treatment. Tumour down staging, improved resectability, and potential for expanded sphincter preservation options in the distal rectum also encourage the use of a neoadjuvant approach in the management of this disease. Historically several trials utilizing relatively moderate doses of preoperative radiation have been undertaken, with results consistently showing an improvement in local control but minimal or no improvement in overall survival [1-3]. Recent studies from Europe have demonstrated that appropriate neoadjuvant preoperative radiation results in improvement of both local control and survival, and these results have had a significant impact on the current management of this disease [4,5].

The Swedish rectal preoperative radiation trial included 1,168 patients from 1987 to 1990 with resectable, Dukes A–C rectal cancer [6]. Patients were randomized to 25 Gy in five fractions in 1 week followed by surgery 1 week later versus surgery alone. The surgery was rated as curative if margins were negative. With a median follow-up of 7 years there was a significant reduction in local control in all three Dukes

stages with preoperative radiation therapy as compared to surgery alone. The 5-year local recurrence with preoperative radiation treatment was 12% versus 27% for surgery alone. The local recurrence with preoperative radiation and curative surgery was 9% versus 23% with curative surgery alone. This study showed a 10% absolute overall survival advantage for preoperative radiation therapy of 58% versus 48% at 9 years ($p = 0.004$) and an advantage in cancer-specific survival among all patients of 74% in the preoperative arm versus 65% in the surgery only arm ($p = 0.002$).

One caveat of this study is that the surgery alone arm did not utilize TME, which may have resulted in an unacceptably high local failure rate of 27%. Late effects suggested more bowel movement frequency, incontinence, urgency, and soiling in the preoperative radiation treatment arm, although overall quality of life was rated good [7]. This trial set the standard of care in many European centres, but the dose of 5 Gy times five fractions may induce significant acute and late toxicity, and the short interval between radiation and surgery may not have allowed sufficient time for tumour regression (downstaging) for improved sphincter preservation. Justification for a longer interval after preoperative radiation treatment before surgery was given by a French trial, Lyon 90–01, which delivered 39 Gy in 3 Gy per fraction without any chemotherapy preoperatively [8]. Two hundred one patients were randomized after 6 to 8 weeks. The local control and overall survival after a median follow-up of 33 months were the same in both arms of the study. However, the pathological complete response was 7% versus 14% (p = NSS) and the pathological down staging was 10% versus 26% ($p = 0.007$) in favour of the longer interval before surgery.

The TME experience by Heald et al. [9] suggested that TME alone is sufficient for achieving low local recurrence rates. A Dutch (CKVO 95–04) multicenter, phase III study of 1,861 patients was undertaken to evaluate the role of short course preoperative radiation with TME. Patients were randomized to TME alone versus 25 Gy in five fractions followed by TME surgery [10]. No fixed tumours were included in the study, and half of the patients had T1 or T2 disease. The overall survival was the same in both arms of the study (82% at 2 years). However the local recurrence at 2 years was 8.2% in the TME-only arm as compared to 2.4% in the preoperative arm, highlighting the value of radiation treatment, even with TME. The sphincter preservation rate was the same in both arms, and there was no clear evidence of any downstaging effect. The perineal complication rate was slightly higher in the preoperative radiation arm of 26% versus 18% in the TME arm, while all other complications were equal. A more recent update indicates a higher incidence of sexual dysfunction and slower recovery of bowel function, more faecal incontinence, and generally poorer quality of life with short-course preoperative radiation.

Two meta-analyses of approximately 6,000 patients each were done to explore the benefit of preoperative radiation treatment. One analysis included 14 randomized controlled trials and reported that neoadjuvant radiation treatment was associated with significantly fewer local recurrences, improved specific survival, and an overall survival benefit [11]. The second meta-analysis, provided by the Colorectal Cancer Collaborative Group, also reported on 14 randomized controlled trials [12]. They noted a significant reduction in the risk of local recurrence and death from rectal cancer with preoperative radiotherapy.

NEOADJUVANT CHEMORADIOTHERAPY

The improvement in outcomes with combined chemoradiation and postoperative adjuvant therapy has led to similar recent approaches in the neoadjuvant therapy of this disease. In the United States this has become widely accepted, but in other parts of the world several groups have undertaken studies to examine the potential benefit from neoadjuvant chemoradiation as compared to radiation alone.

Preoperative radiation therapy was compared with combined preoperative chemotherapy and radiation therapy in a French study (Fédération Francophone de la Canérologie Digestive), FFCD 9203 [13]. Patients with resectable T3 and T4 tumours were randomized to 45 Gy of radiation alone versus radiation with concurrent bolus 5-FU (350 mg/m^2) plus leucovorin on days 1 to 5 during weeks 1 to 5. After surgery, four cycles of adjuvant chemotherapy were given. With a median follow-up of 69 months, there was an equivalent rate (51%) of sphincter-sparing surgery. Combined treatment led to improved pathological complete response rate of 11.4% versus 3.6% and an improved 5-year local failure rate of 8% versus 16.5%. There was, however, no difference in overall survival.

A similar study undertaken by the European Organization for Research and Treatment of Cancer (EORTC 22921) randomized patients to four arms, 45 Gy alone versus 45 Gy plus 5-FU leucovorin followed by surgery and patients further randomized to adjuvant therapy with 5-FU leucovorin [14]. Results of the study indicate similar results to the French study with increased downstaging (14% versus 5.3%; $p = 0.0001$) with no difference in five-year survival (56% versus 54%). However, local control was significantly improved with the addition of chemotherapy. This information suggests that while there is less recurrence, there is no conclusive evidence that combined treatment offers a survival benefit compared to radiation alone. There was, however, a higher incidence of acute toxicity associated with combined chemoradiation.

In contrast to these studies, institutional experience from the United States does suggest significantly higher downstaging with the use of preoperative chemother-

apy, and several institutional studies suggest an improvement in overall survival, and, therefore, notwithstanding the results from the randomized studies, most investigators currently utilize a combined modality approach to neoadjuvant therapy in this disease [15].

A study to determine whether a short course (5 Gy for five fractions) approach to neoadjuvant therapy is better than a protracted approach 50.4 Gy using 1.8 to 2 Gy fractions with concomitant bolus 5-FU and leucovorin given during weeks 1 and 5 was undertaken by the Polish rectal cancer group [16]. Although a higher pathologic complete-response rate was seen with chemoradiation (16% vs. 1%), fewer positive radial margins (4% vs. 13%), and considerably reduced size of the tumour by approximately 1.9 cm no difference in the rate of sphincter preservation, local control or survival was seen.

There is considerable difference in the way chemotherapy has been administered in many of the trials undertaken and those that are ongoing. 5-FU has been used concurrent with radiation because of its well-established potentiating effect with radiation. However, several studies have used bolus 5-FU, while others have used leucovorin-modulated 5-FU during the first and last week of radiation. The results of the Intergroup study demonstrating a superiority of low-dose continuous infusion of 5-FU has been extrapolated to the neoadjuvant setting and appears to be the preferred approach to treatment [17]. New drugs, including oxaliplatin, irinotecan, and oral fluoropyrimidines, have recently been shown to be effective in the treatment of metastatic colorectal cancer. These have now been incorporated into testing of new strategies with neoadjuvant therapy. Capecitabine is an oral fluoropyrimidine prodrug that is readily absorbed in the gastrointestinal tract and mimics the efficacy of continuous infusion 5-FU while avoiding the risk of side effects and complications due to a central line for CVI 5-FU [18]. Capecitabine requires the presence of thymidine phosphorylase (TP) for conversion to the active form of 5-FU within the cells. TP is present in higher concentration in tumour cells, particularly colorectal cancer than in normal tissues, and this potentially creates a therapeutic advantage for capecitabine as compared to intravenous 5-FU [18]. Studies of capecitabine in combination with radiation have shown similar response rates to 5FU, and, therefore, this drug appears promising for trials in the neoadjuvant therapy [19,20]. Capecitabine is generally given in two divided doses, 825 mg twice a day during the course of radiation treatment. Acute toxicity of diarrhea, stomatitis, nausea, and neutropenia are also somewhat less with capecitabine than with 5-FU/leucovorin, however, the incidence of hand/foot syndrome is higher with capecitabine [21].

Several newer options for neoadjuvant therapy include the addition of irinotecan or oxaliplatin to 5-FU and radiation [22-25]. Early data from phase 1 and 2

trials suggest that an oxaliplatin dose of 60 mg/m^2 can be combined safely with continuous infusion 5-FU and standard radiation approaches with acceptable grade 3 toxicity and promising rates of pathological downstaging and with CR rates of 20% to 30%. Toxicity of irinotecan with a dose of 50 mg/m^2 once a week with continuous infusion 5-FU and radiation in the combined modality approach is somewhat higher but appears to be tolerable and also has yielded high response rates with complete responses of 25% to 30% [26]. Ongoing phase III trials in the United States and Europe are evaluating capecitabine and oxaliplatin delivered neoadjuvantly with radiation therapy.

RTOG 00–12 is a randomized phase II study of neoadjuvant combined modality combined-modality radiation for distal rectal cancer. One-hundred and three patients with T3 or T4 distal rectal cancer (<9 cm from the dentate line) were randomized to continuous venous infusion 5-FU plus hyperfractionated radiation treatment of 55.2 to 60 Gy (1.2 Gy twice a day) versus continuous venous infusion 5-FU and irinotecan with conventional fractionation radiation of 50 to 54 Gy (1.8 Gy per fraction). The response rate between the two arms was similar with a pathological complete response rate of 28%, higher than in other studies [27].

Radiation dose is of critical importance in downstaging of cancer. The dose response of rectal cancer is steep in the dose range of 40 to 60 Gy. Several studies have shown the impact of radiation dose escalation on the rate of pathological complete response to neoadjuvant therapy [28,29]. In a review of patients at Princess Margaret Hospital who received 40 Gy, 46 Gy, or 50 Gy in 2 Gy/fraction with continuous infusion 5-FU, the pathological complete response was 18%, 23%, and 33% respectively for the three dose levels [30]. The two-year local relapse-free survival was 72%, 90%, 89% and disease-free survival 62%, 84%, and 78% for the 40 Gy, 46 Gy, and 50 Gy levels respectively [31]. The overall survival was 72%, 94%, and 92% respectively. Doses of 46 Gy or 50 Gy were more effective than 40 Gy, but there was no difference between 46 or 50 Gy. Similar results have been reported from other studies as well.

PREOPERATIVE VERSUS POSTOPERATIVE

Three phase III trials were conducted to compare preoperative versus postoperative chemoradiation treatment. The first trial was an RTOG 94-01/Intergroup 0417 trial that accrued 53 patients but closed early due to poor accrual. NSABP R-03 was scheduled to accrue 900 patients but also closed after accruing 267 patients [32]. Patients with operable adenocarcinoma of the rectum were randomized (and stratified based on age and sex) to surgery followed by one cycle of 5-FU/LV and then concurrent bolus (weeks 1 and 5) 5-FU/LV with radiation treatment versus 5-FU/LV for 1

cycle then concurrent chemoradiation treatment followed by surgery. All patients received adjuvant 5-FU and leucovorin for four cycles. The study was underpowered, but the 1-year results showed a 10% sphincter preservation advantage in the preoperative arm (44% vs. 34%) with slightly higher grade 4 and 5 toxicity (34% vs. 23%) and diarrhea (24% vs. 12%) in this arm as well. The clinical complete response rate was 23%, and the pathological complete response rate was 10%. The disease-free survival at 1 year was 83% preop versus 78% postop (p = NSs).

The definitive phase III study in favor of preoperative radiation therapy was the CAO/ARO/AIO-94 study performed by the German Rectal Cancer group [33]. Eight hundred twenty-three clinically staged T3 and T4 or node-positive rectal cancers were randomized to arm 1: Preoperative chemotherapy and radiation therapy followed by TME 6 weeks later, or arm 2: TME followed by postoperative chemotherapy and radiation therapy. The radiation therapy used was 50.4 Gy in 28 fractions with a 5.4 Gy as a small volume boost in the postoperative arm. The chemotherapy used was 5-FU given as 1 g/m^2 per day during the 1st and 5th weeks of radiotherapy as a 120-hour continuous infusion. Both arms received four additional cycles of 5-FU at 500 mg/m^2 per day for 5 days every 4 weeks. All surgeons were trained in the use of TME and were asked prior to treatment to evaluate the possibility of sphincter preservation. The 5-year results revealed a pelvic recurrence ratio of 6% versus 13% (p = 0.02) in favor of the preoperative arm. The distant recurrence rate was 36% versus 38% (p = NSS), disease-free survival was 68% versus 65% (p = NSS), and overall survival was 76% versus 74% (p = NSS) for preoperative radiation versus postoperative, respectively. There was significant tumour downstaging after preoperative combined modality treatment with an 8% pathological complete response rate. Nodal positivity was 25% in the preoperative versus 40% in the postoperative arm. The sphincter preservation rate in 188 patients with low-lying tumours (declared by the surgeon prior to randomization to require an APR) revealed that 39% versus 19% had a sphincter-preserving low anterior resection (p = 0.004) in the preoperative versus the postoperative arm. There were fewer acute (27% vs. 40%) and late toxicities (14% vs. 24%) in preoperative-treatment group. Thus, preoperative combined preoperative chemotherapy and radiation therapy resulted in significantly less local failures in the pelvis by half and also provided twice the sphincter preservation. Importantly, there was no difference in overall survival or disease-free survival between the two arms.

LOCALLY ADVANCED RECTAL CANCER

Clinical T4 tumours may not be resected completely due to tumour fixation. Preoperative radiation treatment is recommended to facilitate curative resections.

M.D. Anderson investigators demonstrated that preoperative chemotherapy and radiation therapy increased overall survival (80% vs. 60%), local control (95% vs. 66%), and the number of sphincter preserving procedures (35% vs. 7%) as compared to radiation alone [34]. Memorial Sloan-Kettering Cancer Center reported a gross total resection rate of 97%, pathological complete response rate of 25%, 4-year local control of 70%, and 4-year overall survival of 67% when giving preoperative chemotherapy of 5-FU and leucovorin with 50.4 Gy of radiation followed by surgery [35]. Preoperative radiation and chemotherapy resulted in improved resectability rates and possible improved local control and survival.

The IORT experience at MGH was reviewed by Nakfoor et al. [36]. Preoperative continuous infusion 5-FU plus 50.4 to 54 Gy of radiation was given followed by a 4- to 6-week break and surgery. No intraoperative radiation was given if metastases were present at surgical exploration, if there were adequate margins >1 cm, or if there was less than T4 disease. Ten to 12.5 Gy were given for complete resection, 12.5 to 15 Gy for microscopic residual, and 17.5 to 20 Gy for gross residual disease. The 5-year local control was 90%, 65%, 55%, and the disease specific survival at 5 years was 65%, 45%, and 15%, for these three dose levels, respectively. The 5-year actuarial risk of complications was 15%, however. The risk of peripheral neuropathy was 20% for doses >15 Gy. IORT improves local control, especially with a gross total resection, but not survival for locally advanced rectal cancer.

Radu et al. [37] treated 46 patients with unresectable rectal cancer with or without synchronous distant metatstasis using the 5 Gy x 5 fractionation and delayed surgery if possible. Radical surgery (R0-R1) was performed in 92% of the patients without distant metastasis and in 46% of patients with distant metastasis.

Hatfield et al. [38], treated 43 patients with unresectable rectal cancer with short course (5 x 5 Gy) preoperative radiotherapy with planned delayed surgery. 41 patients completed radiotherapy. 24/41 patients (61%) underwent surgery and 24 (58%) underwent a radical (R0-R1) surgical resection.

Engineer et al. [39] compared concurrent chemo-radiotherapy (Capecitabine) to radiotherapy alone in unresectable rectal cancers. 55% of the initially unresectable tumours were deemed resectable with chemoradiotherapy compared to 33% in the radiotherapy group. The addition of chemotherapy was definitely superior to dose-intensified radiotherapy alone.

Braendengen et al. [40] randomized patients wih unresectable or locally recurrent rectal cancer to receive 50 Gy with standart fractionation versus 50 Gy with chemotherapy (5-FU/LCV) preoperatively. Radical surgery could be performed in 72 vs. 83% (p=0.07), a pathological complete remission could be observed in 8 vs. 21%, the local control was 60 vs. 74% (p=0.04) and the disease-free survival was 50

vs. 65%. More grade 3-4 toxicity was seen in the chemoradiotherapy group but the treatment was generally well tolerated.

These last 4 studies in unresectable rectal cancer patients constitute the background for the specific IAEA research proposal:

Prospective randomized phase III clinical trial comparing a short fractionation schedule of 25 Gy in 5 fractions over one week, to 50 Gy in 25 fractions over 5 weeks combined with chemotherapy as pre-operative treatment for locally advanced, unresectable rectal cancer.

The main goal is to establish the resectability rate of two different fractionation schedules in the preoperative treatment of unresectable rectal cancer, and also to determine the local control rate and overall survival rate in resected patient with determination of early toxicity rate of two fractionation schedules and pre-operative mortality.

Expected research outcome was determination of the relative value of two fractionation regimens in terms of the resectability rate for unresectable or borderline resectable rectal cancer patients.

RESULTS FROM OUR CLINIC

Fifteen patients with rectal cancer who were presented at the Digestive cancers tumor board and intended for neoadjuvant treatment were included into the study. All patients signed a written informed consent to participate in the trial. Inclusion criteria were as follows: PHD confirmation of stage III or T3N0 stage II rectal cancer, performance status 0-2.

Patients were randomized into two treatment arms. They were treated with either standard neoadjuvant approach comprising of adjuvant chemotherapy with 5-FU / leucovorin and concurrent long-course radiotherapy (45-50 Gy in 25 fractions) – treatment arm 1; or adjuvant chemotherapy with 5-FU / leucovorin with short-course radiotherapy (25 Gy in 5x) – treatment arm 2. To assure the consistency of data and results, the study was triple-blinded.

Seven patient were randomized into the treatment arm 1, and 8 patients into treatment arm 2. Therapy was well tolerated in both treatment arms, and all patients completed the whole course of intended chemoradiotherapy. In the arm 1, there was 1 (14.3%) patient with stomatitis, and 1 (14.3%) with febrile neutropenia. In the arm 2, there were 2 patients (25%) with stomatitis, 2 (25%) with diarrhoea, 1 (12.5%) with fatigue, and 1 (12.5%) with nausea. Summarized occurrence of adverse effects in both treatment arms is shown in *Table 1.* Although all-grade incidence of adverse effects was higher in the treatment arm 2 (6 vs. 2 patients in arm 1), all of them were low-

grade (3 of both grade 1 and 2). In the treatment arm 1, only 2 patients developed side effects of treatment, however, both of these were grade 3. One patient in the arm 1 developed grade 3 stomatitis, and the other one grade 3 febrile neutropenia. Thus, it can be concluded that short course radiotherapy is linked with mildly increased risk of adverse effects that are low-grade, while higher grade toxicity is more common with the application of long course radiotherapy.

Table 1. Observed adverse effects in both treatment arms.

Adverse effect	G1 (Arm 1 / 2)	G2 (Arm 1 / 2)	G3 (Arm 1 / 2)	G4 (Arm 1 / 2)	All grade (Arm 1 / 2)
Stomatitis	0 / 1	0 / 1	1 / 0	0 / 0	1 / 2
Diarrhea	0 / 0	0 / 2	0 / 0	0 / 0	0 / 2
Fatigue	0 / 1	0 / 0	0 / 0	0 / 0	0 / 1
Nausea	0 / 1	0 / 0	0 / 0	0 / 0	0 / 1
Febrile neutropenia	0 / 0	0 / 0	1 / 0	0 / 0	1 / 0

Resectability rate was found to be excellent in both subgroups of patients (100%). One patient from both treatment arms were lost to follow-up after the completion of neoadjuvant therapy, and all other patients were successfully operated as planned. With a median follow-up of 12 months (range 5 – 38 months), 4 patients developed distant metastasis (both 2 in arm 1 and arm 2). All of these 4 patients developed liver metastasis, while 2 patients also developed metastasis in lungs (also 1 in both arm 1 and arm 2). Recurrent local disease was found in only one patient, the one randomized into arm 2 who also developed liver metastasis. In total, 5 patients had significant regression of the tumor after completion of neoadjuvant therapy, resulting in lower disease stage in comparison with pre-surgical staging. In 3 patients, post-surgical stage of the disease was found to be higher than pre-surgical. However, this could be explained by insufficiently accurate clinical staging prior to the initiation of neoadjuvant chemoradiotherapy. For other 5 patients, it was not possible to assess potential regression of the primary disease, and 2 patients were lost to follow-up. Out of 5 patients who had obvious regression of the primary tumor, 4 patients (80%) were randomized to treatment arm 2. Based on this data, it can be concluded that short course radiotherapy could potentially be even more effective in reducing tumor mass than long course treatment.

With a median follow-up of 12 months (range 5 – 38 months), 10 patients were alive, and 2 patients were lost to follow-up. OS was not reached for neither arm 1 nor arm 2. Taking into account all the data, it can be concluded that neoadjuvant che-

motherapy with short-course concurrent neoadjuvant radiotherapy is a reasonable approach in patients with stage III and T3N0 stage II rectal cancer. This approach approve the use of short course therapy as non-inferior to the long course. In our subgroup of patients, short course treatment had better toxicity profile than long course treatment, while there was no difference in efficacy.

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Sažetak

Neoadjuvantna radioterapija i kemoterapija u bolesnika s lokalno uznapredovalim rektalnim karcinomom: randomizirana studija faze III u suradnji KBC "Sestre milosrdnice" s IAEA-om i ESTRO-m

U Klinici za onkologiju i nuklearnu medicine KBC "Sestre milosrdnice" u suradnji sa IAEA i ESTRO-m proveli smo ispitivanje o primjeni preoperativne radioterapije i kemoterapije u bolesnika s uznapredovalim karcinomom rektuma. U ispitivanje smo uključili petnaest bolesnika koji su zadovoljili uključne kriterije i potpisali informirani pristanak. Bolesnici su randomizirani u dvije skupine: skupina 1: standardni neoadjuvantni pristup (kemoterapija 5-FU / leucovorin konkomitantno uz radioterapiju (45-50 Gy u 25 frakcija); skupina 2: kemoterapija 5-FU / leukovorin uz radioterapiju (25 Gy u 5x). Glavni cilj bio je utvrditi stopu resektabilnosti nakon provedene neoadjuvantne terapije te odrediti postotak lokalne kontrole i ukupnog preživljenja.

Ključne riječi: neoadjuvanta terapija; lokalno uznapredovali rektalni karcinom.

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