UDK 616.34-006-08
Review article
Received: 20 March 2015
Accepted: 15. April 2015

CONTEMPORARY TREATMENT OF RECTAL CARCINOMA

Hrvoje Šobat, Meliha Solak Mekić

University Hospital Center Sestre milosrdnice, University Hospital for Tumors Zagreb, Croatia

Summary

In the last few decades we have witnessed a great advancement in the treatment of rectal carcinoma. This advancement has partly been enabled by the development of new surgical techniques, magnetic resonance imaging as an optimal diagnostic tool and of new histopathological techniques for resected specimen evaluation. Other important contributions include the development of sophisticated radiotherapy treatment techniques which, applied with new cytostatics and smart drugs, induce a better tumor response while reducing toxicity. Although each discipline has contributed to a better understanding of the disease, it is the multidisciplinary approach that has yielded success in treatment so far.

Keywords: neoadjuvant therapy; *short course* radiotherapy; *long course* radiotherapy; concomitant chemotherapy; pathologic complete response.

INTRODUCTION

Carcinoma of the rectum, together with colon cancer, is the third most common malignancy. It appears frequently and at the same rate in women and men - 9.4% of the newly detected patients and 7.9% of all causes of death from malignant disease.

In the last two decades we have witnessed great changes in the detection and treatment of rectal carcinoma. These changes have been mainly founded on improvements in the fields of preoperative classification of the disease, surgical techniques, histopathological evaluation of the resected specimen and application of multidisciplinary procedures with the aim of ensuring a better long-term outcome for patients. A crucially important concept is the "mesorectal excision" based on a precise dissection of the anatomical plane surrounding the mesorectal adipose tissue. Numerous studies, including randomized controlled trials, clearly show the

importance of the total mesorectal excision as a surgical technique which has led to a statistically significant decrease in local recurrence rates in tertiary referral hospitals. Surgery has been so far the most important therapeutic procedure in the treatment of rectal cancer, although multidisciplinary and individualized approaches have been gaining more significance recently. Magnetic resonance imaging (MRI) has become the primary diagnostic tool for preoperative evaluation of patients due to its ability to precisely display the mesorectal fascia. Establishing of a tumor infiltration has been suggested as a mandatory stage in the radiological processing of every patient. The development of radiological classification of rectal carcinoma is closely connected with changes in the histopathological evaluation techniques for measuring the microscopic distance of the tumor from the circumferential resection margin (CRM) of the resected specimen. CRM represents the distance from the edge of the soft tissue preparation/soft tissue margin to the deepest penetration of the tumor. After the operation, the description of the CRM margin presents an essential component of the pathological finding. This procedure provides surgeons with the choice of the optimal surgical plane. Low-lying tumors pose a major challenge for successful treatment. The restricted space between the bony structures of the pelvis reduces the possibility of radical surgical removal, resulting in a high risk of local recurrence [1]. Most cases of recurrence (85%) appear within the first three years after the end of the treatment [2].

THE ROLE OF RADIOTHERAPY IN THE RECTAL CANCER TREATMENT

Research on modalities and timing of chemoradiotherapy application departs from the science-based facts about better local control and prolonged survival in patients with T3-4 N+ tumors treated with adjuvant chemoradiotherapy (NSABP R – 01 [3] and NSABP R – 02 [4].

Multiple European phase III randomized studies have assessed the role of radiotherapy and chemotherapy in the neoadjuvant treatment of rectal cancer. Based on the results of these studies, neoadjuvant radiotherapy was accepted by ESTRO in 2007 as a standard approach in the treatment of patients with locally advanced disease (T3-4 N+). Preoperative treatment benefits range from the reduction of the tumor, to pathologic complete regression/pathologic complete response (pCR) in 10-25% of patients. Radical local resection is facilitated and the likelihood of a margin-free tumor resection is increased.

Short course preoperative radiotherapy (SCPRT) has proved superior in decreasing local recurrence in operable tumors compared to adjuvant radiotherapy (5% vs. 11%) [5]. Studies comparing *long* and *short course preoperative radiotherapy* have shown no

difference in the local recurrence rate, total survival rate, dissemination risk and late toxicity between these two groups [6]. Less side effects and fewer treatment fractions make SCPRT cheaper and more accessible than the adjuvant chemoradiotherapy. The SCPRT is optimal in the treatment of T3 tumors located in the middle third of the rectum with a negative CRM. In "potentially" operable, CRM positive or low-lying tumors concomitant preoperative chemoradiotherapy based on *long course schedule* (LC) is the preferred choice.

Following the first application of *short course preoperative* radiotherapy in England, two major studies have confirmed its significance in the treatment of rectal cancer. Between 1980 and 1993, more than 2,000 patients were included in the Swedish Rectal Cancer trials, of which the most important one is the Swedish Rectal Trial 1 conducted between 1987 and 1990 [7].

The Swedish study showed a statistically significant decreased local recurrence rate in *short course* radiotherapy followed by surgery compared to surgery alone. The local recurrence rate decreased from 27% to 11% ($p<0.001$), 5-year survival rate increased from 48% with surgery alone to 58% with SCRT followed by surgery ($p = 0.004$). A recent report confirmed that the benefits shown were sustained after a 13-year follow-up. The applied radiation benefit (a reduced local recurrence rate) was briefly called into question after published results of only 8.2% local recurrence in patients treated with the total mesorectal excision technique (TME) only. A crucial question which arose in that period was whether a *short course* radiotherapy only compensated the poor radiotherapy technique. For that reason further studies were conducted to examine the role of *short course* radiotherapy combined with total mesorectal excision.

The study from the Dutch Colorectal Cancer Group randomized patients into a group subjected to preoperative pelvic irradiation at a dose of 5x5 Gy and a control group operated without any irradiation. It was shown that the local recurrence rate after 5 years could be further reduced to 2.4 % even after TME ($p = 0.001$) [8]. Unlike the Swedish study, the Dutch study did not show any improvement in the total survival rate by adding radiotherapy to the treatment.

The study from the Medical Research Council CR07 compared the application of SCRT and surgery to initial surgery and postoperative chemoradiotherapy, the latter being limited to patients with the tumor found on the circumferential resection margin. The percentage of local recurrence was reduced by almost half – from 11% using TME only to 5% by adding SCRT before TME. In this study, pathologists assessed the plane obtained in the resected specimen (mesorectal, intramesorectal and muscularis propria). A larger percent of local recurrence was found in the muscularis propria plane, while a decrease in local recurrence was observed in all

three planes when SCPRT was applied [5]. Later studies have confirmed the success of preoperative radiotherapy in reducing local recurrence, even in cases with the optimized surgical technique.

LITERATURE EVIDENCE SUPPORTING APPLICATION OF *LONG COURSE* PREOPERATIVE RADIOCHEMOTHERAPY

This approach was initially developed as a postoperative adjuvant therapy and introduced in Northern American official guidelines since 1990 when adjuvant postoperative chemotherapy and concomitant chemoradiotherapy with 5-FU were recommended for all patients with T_{3-4} or node-positive rectal cancer.

In Europe, two phase III randomized studies were conducted between 1993 and 2003, comparing long course preoperative radiotherapy (45 Gy in 25 fractions) to concurrent 5-FU/LV with the same radiotherapy protocol. The studies mentioned were FFCD 9203 and EORTC 22921 [9,10]. Both have shown that the addition of concurrent 5-FU/LV causes an acceptable increase of acute toxicity and leads to the pathologic down-staging of the disease. Furthermore, both studies have displayed a decrease in local recurrence rate from 15% to 8-10%, with no difference in the disease free or overall survival.

A third study was conducted by GRCSG (German Rectal Cancer Study Group). According to the treatment results in 823 patients with T_{3-4} or N+ rectal cancer 5-year survival was 76% and 74% in the groups treated before or after the operation. Local recurrence was 6% in the group with neoadjuvant radiochemotherapy and 13% in the control group with adjuvant radiochemotherapy (p=0.006). Significantly fewer side effects grade 3 and 4 were in neoadjuvant group – 27% than in the adjuvant group – 40% (p=0.001) [11]. Later published results of the same group (GRCSG) after a 11-year follow-up kept the level of statistical significance in terms of local recurrence, with no impact on the length of survival [12].

These results have led to significant changes, the consequence of which is a shift in treatment from postoperative to preoperative chemoradiotherapy. This treatment strategy has been further supported by the results of the NSABP R-03 study.

In that trial, a similar comparison of pre- and postoperative radiotherapy has been carried out which enrolled 267 patients [13]. After a median follow-up of 8.4 years, a significantly better 5-year disease free survival (DFS) in neoadjuvantly treated patients was observed – 64.7 % versus 53.4% (p=0.011). There was no difference in overall survival (OS) of 74.5% vs. 65.6% (p=0.065).

This treatment is widely applied today. Concurrent chemotherapy can be based on the combination of 5-FU/LV or on oral fluoropyrimidines, such as capecitabine.

DIRECT COMPARISION OF *SHORT COURSE* VS. *LONG COURSE* RADIOTHERAPY

Two studies have compared *short course* preoperative radiotherapy with *long course* preoperative chemoradiotherapy. Bujko et al. have compared the outcomes of a short-course (5x5 Gy) and long-course (28x1,8 Gy) neoadjuvant chemoradiotherapy. The 5-year local recurrence rates were 9% and 14% (p = 0.17) for SCPRT and CRT, respectively. The rate of late complications did not differ significantly – 10% (*short-course*) vs. 7 % (*long-course*) [14]. The Trans Tasman Group (TROG) trial also randomized 326 patients with resectable rectal cancer to receive either SCPRT or preoperative CRT to compare the local recurrence rates [6]. Between these two groups no differences were noted in the occurrence of local recurrence, overall survival rate, dissemination and late toxicity.

The radiation technique necessary to reduce the early and late side effects risk has recently not significantly changed. It assumes radiation simulation with the patient in prone position placed on the table with a hole for the abdomen. The small gut should be shown by applying the contrast media and modern tools for radiation planning should be used (3-D).

OXALIPLATIN, IRINOTECAN AND BIOLOGICAL AGENTS IN PREOPERATIVE CHEMORADIOTHERAPY OF RECTAL CANCER

5-FU is fundamental in all chemoradiotherapy and adjuvant chemotherapy protocols used in the treatment of rectal cancer. It is believed that the effectiveness of these protocols can be improved by introducing new drugs successful in the treatment of colorectal cancer and that this can lead to a better control of distal metastases, as well as a higher survival rate. Oxaliplatin administered together with 5-FU and leucovorin has a significant effect in the treatment of metastatic colorectal cancer. This finding has caused an interest in its use as a part of a combined protocol for the treatment of locally advanced disease.

Aschele et al. have conducted a study on the synergistic effect of oxaliplatin (STAR-01) in 747 patients in Italy [15]. The pathological complete response rate was the same (16%) in two randomized groups, and the rate of grade 3 and 4 adverse reactions was 24% in the group with oxaliplatin and 8% in the control group (p=0.001).

In the ACCORD study, 598 patients with T_{3-4} N+ rectal cancer were randomized into groups of 45 Gy of radiation in 25 fractions with concomitant capecitabine or 50 Gy in 25 fractions with concomitant capecitabine and oxaliplatin. Complete pathological response was recorded in 19.2% of patients receiving oxaliplatin vs. 13.9% in the control group (p=0.09), while grade 3 or 4 toxicity was observed in 25% vs. 11%

in the control group (p=0.001). There was no difference in sphincter preservation during surgery (75% vs. 78%) [16]. Somewhat conflicting results were reported in a study performed by Rödel et al. CAO/ARO/AIO-04 where 1236 patients were randomized into groups of neoadjuvant radiotherapy with 5-FU or 5-FU with oxaliplatin [17]. A significantly higher complete pathological regression rate was recorded (17% vs. 13%) in the control group (p=0.038) with no significant difference in the incidence of grade 3 and 4 side effects.

Although the incidence of acute side effects was monitored in most studies, they cause only short-term discomfort and stop spontaneously or with symptomatic medication completely. Based on the results of these studies, the adding of oxaliplatin does not contribute to the reduction of the primary rectal tumor in neoadjuvant chemoradiotherapy, but increases the rate of acute side effects [15-17]. Currently, the application of oxaliplatin in the neoadjuvant treatment setting with radiation is not warranted outside of research protocols.Therefore is necessary to wait and observe the results from these studies, particularly in terms of disease free survival (DFS).

Irinotecan administered together with 5-FU and leucovorin has a significant effect in the treatment of metastatic colorectal cancer and it improves both progression-free and overall survival [18]. This finding, the same as in the use of oxalipatin, has resulted in an interest in developing its use as part of a combined protocol for the treatment of a locally advanced disease. Iles et al. have conducted a study on the synergistic effect of irinotecan and 5-flourouracil (NWCOG-1) on 31 patients with inoperable locally advanced rectal cancer [19]. Preoperative restaging with MRI showed a reduction in tumor stage in 79% of patients after the treatment, while 81% had clear circumferential resection margins. The regimen was well tolerated.

Gollins et al. have conducted a study on the synergistic effect of capecitabine and irinotecan (NWCOG-2) on 110 patients with MRI-defined locally advanced rectal cancer. The regimen appears more effective in down-staging by using a single-agent, fluoropyrimidine, than historical reports suggest. The pathologic complete response rate was 22% and the study showed a strong correlation between the efficacy of CRT down-staging as expressed by reduction of the histologic stage to ypCR or microfoci and superior overall survival [20]. Currently, the application of irinotecan in the neoadjuvant treatment setting with radiation is being further investigated.

The integration of EGFR and VEGF targeting therapies in preoperative chemoradiation protocols was based on vast theoretical knowledge, relatively good results of preclinical studies and significant effect in the treatment of metastatic colorectal cancer. Phase II studies showed no clear clinical benefit and detected a problem in the use of pCR as the final endpoint [21-23].

The rate of tumor complete response rate (pCR) was somewhat higher in bevacizumab containing protocols, but the incidence of general, bevacizumab-related adverse effects (hypertension, proteinuria, mucosal bleeding, arterial thrombosis) and postoperative complications (pelvic infection, delayed wound healing, anastomotic leak, fistulas) was relatively high in several trials [21-23]. A better understanding of the mechanisms responsible for the disappointing results is necessary before proceeding to phase III trials.

ASSESSMENT OF TREATMENT EFFECT

Nowadays there are great expectations on the treatment outcome forecast based on biological evidence of heterogeneity which determines the tumor (presence of EGFR expression, mutation status of BRAF, dMMR and KRAS).

Studying KRAS, BRAF and PI3KCA mutations in rectal cancer, Derbel et al. have failed to determine the predictors of the outcome of neoadjuvant treatment in a group of 98 patients [21]. They concluded that further research on a larger number of patients and greater statistical power was needed.

In the last decade, the search for biological markers that predict clinical outcomes has shifted toward the microenvironment in which the tumor grows. Gallon et al. have found that complete histologic regression occurred significantly more frequently in patients with a relative number of lymphocytes in the WBC >26% before treatment (p=0.023), absolute lymphocyte count >1,634 x109/L (p=0.004), hemoglobin levels >12.0 g/dL before treatment and clinical findings of N – stage disease (p=0.018) [22].

It is possible to find similar claims in the literature about the beneficial effects of high levels of circulating lymphocytes on the outcome of the treatment of colorectal cancer [25,23]. A biological marker cluster which correlates to clinical outcomes is still unknown.

A further question is if we can obtain an adequate characterization of tumor heterogeneity based on clinical observation. According to recently published pooled data of randomized trials for locally advanced rectal cancer, there are four groups of patients with different tumor heterogeneity (very good, good, bad, ugly) [24]. In clinical trials, all of them were included and there is no reliable endpoint that could be used to estimate a beneficial impact of treatment on the overall survival. With rectal cancer there are no reliable surrogate endpoints as with other cancers (for example: prostate specific antigen is a good surrogate endpoint for survival in prostate cancer). The fractions of ugly and bad tumors conceal the treatment benefits of the group of good and best, thus preventing us from tailoring therapy on individual ba-

sis. Due to this inability, many characteristics of colorectal cancer were investigated with the intention of discovering possible factors which could predict the outcome of neoadjuvant chemoradiotherapy: tumor volume, the level of carcinoembryonic antigen (CEA), tumor distance from the anal verge and the period of time between the completion of radiotherapy and the definitive surgery [25,26].

A complete pathological response is associated with a significantly longer survival, while the N+ lymph node finding after neoadjuvant treatment is an unfavorable prognostic indicator regardless of the extent of the primary tumor regression [27,28]. The meta-analysis done by Lee et al. has demonstrated that the partial regression of tumor is associated with a 50% improvement in the length of disease free survival (DFS) and should be considered a favorable prognostic factor [29].

PET/CT imaging and the accumulation of FDG in tumor tissue (SUV) could be a predictor of tumor regression with 81 % sensitivity and 100 % specificity, with a 90% of overall reliability, as demonstrated by Bampo et al. [30]. Early recording showed no significant regularity, but the results of the SUV later recording was different between patients with complete and incomplete regression at the level of p=0.006. The possibility of distinguishing complete from incomplete tumor regression before histological examination after 6 weeks of radiotherapy (ie. before surgery) could lead to a less radical operation (the gospel only crop scar on the intestine and establish continuity) or even to a wait-and-see attitude and omitted surgery. The PET/CT with biological predictors could help in screening patients and determining the optimal timing for accessing surgery or even cancel the previously planned surgery [31].

While it is scientifically proven that complete regression after neoadjuvant treatment significantly prolongs the length of the disease free survival, the prognostic value of partial regression is less reliable. Several authors propose their own ways of scoring, eg. "tumor regression grade" (TRG) or "rectal cancer regression grade" (RCRG) in order to facilitate the further research of this issue. These schemes, if proven their reliability in the future, may become more important than the current TNM system introduced before the invention of neoadjuvant treatment approach. By then, the classification of tumor characteristics according to the TNM system should mark the way data are collected (eg, the suffix "c" – clinically, "mr" – by NMR, "p" – histologically, "ct" by CT scan). It can somewhat reliably predict the course of illness in patients with complete tumor regression or those with no response to neoadjuvant treatment.

We aim to achieve individual treatment by using the primary and surrogate endpoints based on the data obtained from clinical characteristics of patients and tumor heterogeneity.

Statistical prediction models have found multivariate correlations between the patient and the tumor characteristics with the outcome. One of the best and simplest methods with possible wide application is the interpretation of the prediction model with the help of a nomogram or calculator. It is a visual and numerical representation of mathematical relations between individual variables important for predicting patients' outcomes. The first step in compiling nomograms/calculators is gathering epidemiological data from large registries of outcomes of malignancies.

Bowles et al. have developed a mathematical model of interactive likelihood of 5- and 10-year survival by using the data on age, sex, race, tumor differentiation and the type of surgery [32]. Covariances were preoperative or postoperative radiotherapy, patients without treatment or stage IV disease. They have created the online calculator that can be used with reference to page www.mdanderson.org/rectalcalculator. Assessment results are valuable, but only orienteering aid in predicting the course of disease and the planning of further treatment or intensity of monitoring.

The possible subject of further research will be the prognostic significance of pelvic lymph node status after partial tumor regression, which will probably help us to further stratify the same group of patients and contribute to a better understanding of the disease.

DO ALL THE PATIENTS NEED SURGICAL PROCEDURE AFTER NEOADJUVANT THERAPY?

The optimal time for surgery after completion of a neoadjuvant radiotherapy is difficult to be unambiguously determined. On the basis of published results, there are indications that an interval longer than the generally accepted (6 weeks) could lead to higher rates of complete regression and operations with sphincter preservation. Arguments for the expectative attitude could result from the research that has already begun. In the group of 70 patients with low rectal tumors located stage $T_{2-4}N_{0-2}M_{0,}$ Habr-Gama et al. have applied 54 Gy of radiation plus chemotherapy 5-FU/LV for 6 cycles every 21 days [33]. Complete clinical remission has been observed in 68 % of patients. Local recurrence occurred in this group to 17% in the first year, 10% after the second year, and 57 % is healthy after 5 years of follow-up. A total of 50 % of the patients was never operated. In these stages of the disease and the specific position of the tumor it is a significant contribution to the quality of life. Careful follow-up enabled a timely "salvage" operation in case of need.

An interesting Rapido study has just started in which two groups were randomized: a control group with conventional neoadjuvant therapy (50 Gy with capecitabine) and an experimental group where the introductory 5x5 Gy of radiation were

followed by six cycles of chemotherapy with capecitabine and oxaliplatin. Upon completion of the neoadjuvant treatment, all patients will be operated according to the principle of TME. The studied outcome will be not only the rate of local recurrence, but especially the impact on overall survival without signs of disease [34].

In a certain way, the above mentioned studies attempt to detect and separate the group of patients who have tumors with favorable clinical and pathological characteristics, and those who have already in the epidemiological studies been classified into the group of patients with very good and good tumors, as well as ensure them a more conservative treatment approach.

RESULTS OF NEOADJUVANT TREATMENT IN UNIVERSITY HOSPITAL FOR TUMORS IN ZAGREB, CROATIA

Between January 2011 and December 2014 at the University Hospital for Tumors, we have treated 78 patients with $T_{2\text{-}4}N_{+}$ rectal tumors by using two preoperative treatment approaches. We have used *short course* (SCRT) radiotherapy and *long course* chemoradiotherapy (LCCRT) protocols. Clinical and pathological characteristics of all of the patients were defined: gender, age, T and N stages of the disease, and tumor position (distance measured from the anal verge – "low" (0-5 cm), "medium" (5-10 cm) and "high" 10-15 cm)). Mesorectal fascia infiltration was assessed with the use of magnetic resonance imaging (MRI). Fifteen patients have received a total dose of 25 Gy in 5 fractions (*short course*). In accordance with current guidelines, the total treatment duration, including surgical procedure, was 10 days. The remaining 63 patients have received a total dose of 45-50.4 Gy in 25-28 fractions with concomitant chemotherapy based on fluoropyrimidines. The patients underwent an operation in 6 to 8 weeks after the combined treatment was completed. We have performed postoperative analyses of the type of surgical procedure, the degree of histological response according to the Ryan classification (degrees of regression – 0, 1, 2, 3) and the application of postoperative systemic treatment.

Concomitant chemoradiotherapy induced a complete response in 14.3% patients and a partial response in 52.4% patients. In the group of patients treated with *short course* protocol, there was only one patient with a partial response, and none with a complete response. In the group of patients treated with a *long course* chemoradiotherapy, a statistically significant difference was noted in the T and N stages of the disease and in the circumferential resection margin infiltration.

These results are a consequence of treating a larger percent of patients in advanced stages of the disease with concomitant chemoradiotherapy. Out of 25 patients with "low" tumors (< 5cm), a local recurrence occurred in one patient treated

with SC and in one patient treated with long course chemoradiotherapy. Among the patients treated with SCRT, one patient developed local recurrence after 15 months of follow-up, while in the LCCRT group six patients developed local recurrence after a median follow-up of 14.7 months (range 3–26 months). No statistically significant difference in the cumulative incidence of local recurrence (HR = 2.2 CI= 0,3581-10,273, p=0.4469) was noted when comparing patients treated with SCRT to those treated with LCCRT. There was no statistically significant correlation between positive lymph nodes and distal metastases, although a positive trend was noted. Anal sphincter preservation amounted to 73.3% in the group treated with SCRT, as compared to 31.7% in the group treated with LCCRT.

So, a longer patient follow-up, an individualized approach and gathering experience will enable further improvements in the treatment of these patients.

CONCLUSION

Despite the fact that previous studies have answered some very important questions, the problem of taking care of patients belonging to neither group remains. Consequently, two consensus documents (EURECCA and ESMO) have been produced, with guidelines on different strategies for staging and treatment with the aim of helping clinicians in their everyday work [35,36].

References

[1] Arredondo J, Baixauli J, Beorlegui C, Arbea L, Rodríguez J, Sola JJ, et al. Prognosis factors for recurrence in patients with locally advanced rectal cancer preoperatively treated with chemoradiotherapy and adjuvant chemotherapy. Dis Colon Rectum. 2013;56(4):416-21. doi: 10.1097/DCR.0b013e318274d9c6.

[2] Chauvenet M, Lepage C, Jooste V, Cottet V, Faivre J, Bouvier AM. Prevalence of patients with colorectal cancer requiring follow-up or active treatment. Eur J Cancer. 2009;45(8):1460-5. doi:10.1016/j.ejca.2009.01.012.

[3] Fisher B, Wolmark N, Rockette H, Redmond C, Deutsch M, Wickerham DL, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. J Natl Cancer Inst.1988;80(1):21-9.

[4] Wolmark N, Wieand HS, Hyams DM, Colangelo L, Dimitrov NV, Romond EH, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst. 2000;92(5):388-96.

[5] Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a mul-

ticentre, randomised trial. Lancet. 2009;373(9666):811-20. doi: 10.1016/S0140-6736(09)60484-0.

[6] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol. 2012;30(31):3827-33. doi: 10.1200/JCO.2012.42.9597.

[7] Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med. 1997;336(14):980-7.

[8] Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al; Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345(9):638-46.

[9] 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(28):4620-5.

[10] Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355(11):1114-23.

[11] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al; German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731-40.

[12] Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926-33. doi: 10.1200/JCO.2011.40.1836.

[13] Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27(31):5124-30. doi: 10.1200/JCO.2009.22.0467.

[14] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006 Oct;93(10):1215-23.

[15] Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol. 2011;29(20):2773-80. doi: 10.1200/JCO.2010.34.4911.

[16] Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol. 2010;28(10):1638-44. doi: 10.1200/JCO.2009.25.8376.

[17] Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T,et al; German Rectal Cancer Study Group. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol. 2012;13(7):679-87. doi: 10.1016/S1470-2045(12)70187-0. Epub

[18] Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Engl J Med. 2000;343(13):905-14.

[19] Iles S, Gollins S, Susnerwala S, Haylock B, Myint S, Biswas A, et al. Irinotecan+5-fluorouracil with concomitant pre-operative radiotherapy in locally advanced non-resectable rectal cancer: a phase I/II study. Br J Cancer. 2008;98(7):1210-6. doi: 10.1038/sj.bjc.6604292.

[20] Gollins S, Sun Myint A, Haylock B, Wise M, Saunders M, Neupane R, et al. Preoperative chemoradiotherapy using concurrent capecitabine and irinotecan in magnetic resonance imaging-defined locally advanced rectal cancer: impact on long-term clinical outcomes. J Clin Oncol. 2011;29(8):1042-9. doi: 10.1200/JCO.2010.29.7697.

[21] Derbel O, Wang Q, Desseigne F, Rivoire M, Meeus P, Peyrat P, et al. Impact of KRAS, BRAF and PI3KCA mutations in rectal carcinomas treated with neoadjuvant radiochemotherapy and surgery. BMC Cancer. 2013;13:200. doi: 10.1186/1471-2407-13-200.

[22] Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. 2006;313(5795):1960-4.

[23] Morris M, Platell C, Iacopetta B. Tumor-infiltrating lymphocytes and perforation in colon cancer predict positive response to 5-fluorouracil chemotherapy. Clin Cancer Res. 2008;14(5):1413-7. doi: 10.1158/1078-0432.CCR-07-1994.

[24] Valentini V, van Stiphout RG, Lammering G, Gambacorta MA, Barba MC, Bebenek M, et al. Selection of appropriate end-points (pCR vs 2yDFS) for tailoring treatments with prediction models in locally advanced rectal cancer. Radiother Oncol. 2015 Feb 21. pii: S0167-8140(15)00074-2. doi: 10.1016/j.radonc.2015.02.001.

[25] Das P, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, Wolff RA,et al. Predictors of tumor response and downstaging in patients who receive preoperative chemoradiation for rectal cancer. Cancer. 2007;109(9):1750-5.

[26] 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(4):582-9. doi: 10.1097/SLA.0b013e3181b91e63. PubMed PMID: 19710605.

[27] Yeo SG, Kim DY, Kim TH, Chang HJ, Oh JH, Park W, et al. Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). Ann Surg. 2010;252(6):998-1004. doi: 10.1097/SLA.0b013e3181f3f1b1.

[28] Kaminsky-Forrett MC, Conroy T, Luporsi E, Peiffert D, Lapeyre M, Boissel P, et al. Prognostic implications of downstaging following preoperative radiation therapy for operable T3-T4 rectal cancer. Int J Radiat Oncol Biol Phys. 1998;42(5):935-41.

[29] Lee YC, Hsieh CC, Chuang JP. Prognostic significance of partial tumor regression after preoperative chemoradiotherapy for rectal cancer: a meta-analysis. Dis Colon Rectum. 2013;56(9):1093-101. doi: 10.1097/DCR.0b013e318298e36b.

[30] Bampo C, Alessi A, Fantini S, Bertarelli G, de Braud F, Bombardieri E, et al. Is the standardized uptake value of FDG-PET/CT predictive of pathological complete response in locally advanced rectal cancer treated with capecitabine-based neoadjuvant chemoradiation? Oncology. 2013;84(4):191-9. doi: 10.1159/000345601.

[31] Foster JD, Jones EL, Falk S, Cooper EJ, Francis NK. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. Dis Colon Rectum. 2013;56(7):921-30. doi: 10.1097/DCR.0b013e31828aedcb. Review. PubMed PMID: 23739201.

[32] Bowles TL, Hu CY, You NY, Skibber JM, Rodriguez-Bigas MA, Chang GJ. An individualized conditional survival calculator for patients with rectal cancer. Dis Colon Rectum. 2013;56(5):551-9. doi: 10.1097/DCR.0b013e31827bd287.

[33] Habr-Gama A, Sabbaga J, Gama-Rodrigues J, São Julião GP, Proscurshim I, Bailão Aguilar P, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56(10):1109-17. doi: 10.1097/DCR.0b013e3182a25c4e

[34] Nilsson PJ, van Etten B, Hospers GA, Påhlman L, van de Velde CJ, Beets-Tan RG, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer-the RAPIDO trial. BMC Cancer. 2013;13:279. doi: 10.1186/1471-2407-13-279.

[35] van de Velde CJ, Boelens PG, Borras JM, Coebergh JW, Cervantes A, Blomqvist L,et al. EURECCA colorectal: multidisciplinary management: European consensus conference colon and rectum. Eur J Cancer. 2014;50(1):1.e1-1.e34. doi: 10.1016/j.ejca.2013.06.048.

[36] Glimelius B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi81-8. doi: 10.1093/annonc/mdt240.

Sažetak

Suvremeno liječenje karcinoma rektuma

Posljednjih desetljeća svjedoci smo velikog napretka u liječenju karcinoma rektuma. Razvoj novih kirurških tehnika, magnetske rezonance kao optimalnog dijagnostičkog alata i novih histopatoloških tehnika evaluacije reseciranog uzorka omogućili su dio ovih promjena. Ostatak je posljedica razvoja sofisticiranih radioterapijskih tehnika koje u kombinaciji s novim citostaticima i pametnim lijekovima postižu bolji odgovor tumora na primijenjeno liječenje uz smanjenje toksičnosti. Iako je svaka disciplina doprinijela boljem razumijevanju bolesti, tek je multidisciplinarni pristup omogućio sadašnju razinu uspjeha liječenja.

Ključne riječi: neoadjuvantna terapija; kratki radioterapijski protokol; dugi radioterapijski protokol; konkomitatna kemoterapija; patološki kompletni odgovor.

Corresponding author:
Hrvoje Šobat
E-mail: hrvoje.sobat@gmail.com