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THE IMPORTANCE OF MULTIDISCIPLINARY APPROACH IN THE TREATMENT OF RECTAL CANCER

Zrinka Rendić-Miočević[1], Antonio Juretić[2], Lidija Beketić-Orešković[3]

[1] University Hospital for Tumors, Clinical Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia;
[2] University of Zagreb School of Medicine, Department of Clinical Oncology, and University Hospital Center Zagreb, Oncology Clinic, Zagreb, Croatia;
[3] University of Zagreb School of Medicine, Department of Clinical Oncology, and University Hospital for Tumors, Clinical Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia

Summary

Colorectal cancer is the 3rd most common malignant disease worldwide and it represents the major public health issue. Nowadays, multidisciplinary approach is common in diagnostics and treatment of all malignant diseases, rectal cancer is an example for importance of various medical disciplines collaboration in achieving optimal treatment outcome. This paper is a short overview of most important clinical trials which defined optimal therapeutical approach to the patients with locally advanced rectal cancer. Actual guidelines and recommendations for treatment of patients with stage II or III rectal cancer include preoperative radiotherapy (RT) with or without concurrent chemotherapy, and radical surgical resection (with mandatory total mesorectal excision-TME). Such multidisciplinary approach to the therapy of these patients significantly reduced rates of local recurrence, and increased likelihood of pathologic complete response and sphincter-preserving surgery, with low rates of acute treatment toxicity. In order to further improve treatment outcomes, there are ongoing studies which investigate novel systemic drugs (immunotherapy-antibody-drug conjugates) as well as modern radiotherapy techniques (IMRT- intensity modulated RT, IGRT- image guided RT, VMAT- volumetric modulated arch RT) in patients with rectal cancer .

Keywords: rectal cancer; preoperative (neoadjuvant) chemoradiotherapy; total mesorectal excision; multidisciplinary treatment.

Colorectal cancer is the third most commonly diagnosed cancer in males and the second in females, with 1.4 million new cases and 690.000 deaths estimated to have occurred in 2012 worldwide [1]. Rates are substantially higher in males than in females. Nowadays, it is generally considered that significant percentage of rectal cancer is connected to lifestyle risk factors, such as obesity (especially abdominal), increased consumption of red and processed meat, physical inactivity, smoking and heavy alcohol use, and only about 10% is caused by inherited genetic syndromes (FAP, HNPCC, Turcots syndrome, Peutz-Jeghers syndrome). Some calculations predict that 2.4 million cases of colorectal cancer will be diagnosed annually worldwide by 2035. More than 95% of colorectal cancers are adenocarcinomas originating from epithelial cells of the colorectal mucosa, other rare versions are adenosquamous carcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, medullary, neuroendocrine and undifferentiated carcinoma [2]. The proportion of rectal cancer among cancers of the large intestine (colorectum) varies from 27% to 58%, depending on the cancer registry and classification of recto-sygmoid tumors.

Rectal cancer is a typical example for importance of multidisciplinary approach in the treatment of malignant disease. Disciplines involved in the care for rectal cancer patients (from diagnosis and treatment to posttreatment rehabilitation) include: radiology, pathology, molecular biology, abdominal surgery, anesthesiology, medical oncology, radiation oncology and rehabilitational medicine. This text focuses on multidisciplinarity in the treatment of rectal cancer patients.

From the beginnings of rectal cancer treatment, it was evident that surgery alone is not sufficient treatment, since there was high proportion of patients with local or distant failure after tumor resection (with exception of patients with early, stage I tumors). Adjuvant radiotherapy with or without chemotherapy has been widely used for decades in order to improve outcomes in patients with rectal cancer. For locally advanced disease, postoperative chemoradiotherapy significantly improves both local control and overall survival as compared with surgery alone or surgery plus irradiation [3]. This information prompted a National Institutes of Health (NIH) consensus conference, convened in 1990, to recommend postoperative adjuvant chemoradiotherapy as standard treatment for patients with rectal cancer classified as stage II (i.e., a tumor penetrating the rectal wall, without regional lymph-node involvement) or stage III (i.e., any tumor with regional lymph-node involvement) [4].

In the last two decades numerous multidisciplinary clinical trials that addressed effects of preoperative (neoadjuvant) or postoperative (adjuvant) radiotherapy with or without chemotherapy for patients with rectal cancer have been conducted. Advantages of preoperative irradiation (as opposed to postoperative RT) are related to both tumor response and normal tissue preservation. First, reduction of tumor

volume prior to surgery may facilitate complete resection and increase the likelihood of sphincter-sparing procedure. Also, irradiation of intact tissue (surgery-naive ie. better oxygenated) may result in increased sensitivity to RT. With preoperative radiotherapy, radiation-induced injury to small bowel trapped in the pelvis by postoperative adhesions, can be avoided. Preoperative RT targets tissues and structures that will be resected afterwards, which increases the likelihood of performing an anastomosis with healthy colon. Before the decision of neoadjuvant treatment, staging with pelvic magnetic resonance imaging (MRI) is obligatory. One potential disadvantage of using neoadjuvant approach is the possibility of over-treating early stage (stage I) rectal tumors which, based on definitive patohistological finding, don't require adjuvant therapy.

There are currently two main approaches of preoperative pelvic radiotherapy for resectable rectal cancer: short-course irradiation and long-course chemoradiotherapy. Although the radiation techniques and target volumes are similar, the fractionation and timing of surgery differ. In general, short-course radiation delivers 25 Gy (5 Gy/fraction in 5 fractions) of radiation followed by surgery 1 week later. Long-course chemoradiotherapy delivers 50.4 Gy (1.8 Gy/fraction in 28 fractions) of radiation concurrently with chemotherapy (usually fluoropyrimidines or its derivatives) followed by surgery 4 to 8 weeks later. These competing approaches evolved in parallel; short-course radiation developed in northern Europe and Scandinavia and long-course chemoradiotherapy (CRT) in the United States and selected European countries.

Two landmark trials support the use of short-course preoperative radiation. In 1997. Swedish Rectal Cancer Trial group published results of multicentric clinical trial investigating effects of preoperative neoadjuvant radiotherapy on local control and overall survival in rectal cancer patients [5]. 1168 patients were randomized into two arms: radiotherapy arm, where patients were preoperatively treated with short-course radiotherapy (25 Gy in 5 fractions; surgery was performed within one week after completion of RT) and control arm where patients received only surgical treatment (anterior or abdominoperineal resection). The irradiation did not increase postoperative mortality. After five years of follow-up, the rate of local recurrence was 11% in the group that received radiotherapy before surgery and 27% in the group treated with surgery alone ($P<0.001$). This difference was present in all subgroups of patients defined according to Dukes' classification. The overall five-year survival rate was 58% in the radiotherapy-plus-surgery group and 48% in the surgery-alone group ($P=0.004$). The cancer-specific survival rates at nine years among patients treated with curative resection were 74% and 65%, respectively ($P=0.002$). The Swedish Rectal Cancer Trial was one of the first clinical trials that showed clear benefit of

preoperative radiotherapy not only in terms of local recurrence rate reduction but in terms of improved survival as well. This was the only randomized trial which has revealed a significant advantage in survival.

The results prompted Dutch group of authors to conduct the CKVO 95-04 trial [6] which used the same design but mandated surgeons to use of total mesorectal excision (TME): 1861 patients with resectable rectal cancer and without evidence of metastatic disease were randomly assigned (ratio 1:1) to TME preceded by short-course (25 Gy in 5 fractions) pelvic irradiation or TME alone. 10-year cumulative incidence of local relapse was 5% in the RT+TME group and 11% in the TME-alone group (p<0·0001). The effect of radiotherapy became stronger as the distance from the anal verge increased, but only in patients with a positive circumferential resection margin. Overall survival did not differ between the two arms. For patients with TNM stage III cancer with a negative circumferential resection margin, 10-year survival was 50% in the RT+TME arm versus 40% in the TME-alone group (p=0·032). Both the initial and long-term reports revealed a significant improvement in local control with preoperative radiation, although no difference in overall survival was observed.

The German Rectal Cancer trial [7] long term follow up results, reported in 2012. compared preoperative and postoperative CRT. In this trial, 799 eligible patients with stage II/III rectal cancer were randomised to preoperative CRT (50,4 Gy in 28 fractions + FU 1000 mg/m2 during the first and fifth weeks of radiotherapy), TME surgery, and adjuvant FU chemotherapy, or the same schedule of CRT used postoperatively (postoperative arm received an additional boost dose of 5,4 Gy on the tumor bed). 10-year overall survival was 59.6% in the preoperative arm and 59.9% in the postoperative arm (P = 0.85). The 10-year incidence of local relapse was 7.1% and 10.1% in the pre- and postoperative arms, respectively (P = 0.048). No significant differences were detected for 10-year cumulative incidence of distant metastases (29.8% and 29.6%; P =0 .9) and disease-free survival. Preoperative approach was superior in terms of treatment compliance, toxicity, tumor downstaging, sphincter preservation and 5-year local control. This trial changed the standard of care for patients with cT3-4 and/or N+ disease to preoperative longcourse chemoradiotherapy in Germany, most parts of Europe, and the USA.

There is still an ongoing controversy about optimal preoperative approach. The first randomized trial comparing short-course RT vs. Long- course CRT in patients with resectable cT3-4 rectal cancer was published by Bujko et al. [8]. The aim of the study was to compare overall survival, local control and late toxicity in 312 patients randomized in two treatment groups: short-course RT group (25 Gy in 5 fractions; surgery within 7 days) or long-course CRT group (50.4 Gy in 28 fractions of 1.8 Gy, bolus 5-FU/LV; surgery 4-6 weeks later). Acute toxicity was higher in the CRT group

(18.2% vs. 3.2%; P < 0.001). Although the long-course chemoradiotherapy arm had lower incidence of positive radial margins (4% *vs.* 13%; *P* = .017), there were no significant differences in crude local recurrence rates (9% vs. 14%; P = 0.170) or 4-year survival (66.2% vs. 67.2%; P = 0.960). Severe late toxicity was 10.1% vs. 7.1% (P = 0.360), respectively.

TROG 01-04 [9] is a multicenter randomized trial in which 326 patients with cT3Nx adenocarcinoma located in the lower 2/3 of the rectum were randomly assigned to short-course(SC) RT versus long-course (LR) CRT. Patients in both arms received 6 months of postoperative adjuvant chemotherapy. Rates of local recurrence after 3-year follow-up were 7.5% for SC vs. 4.4% for LC (P=0.24); 5-year distant recurrence rates were 27% for SC vs. 30% for LC (P=0.92). Overall survival rates at 5 years were 74% for SC vs. 70% for LC (P=0.62).Late toxicity rates were not substantially different (SC 5.8% vs. LC 8.2%; P=0.53). A subset analysis of the 79 patients with distal tumors revealed a cumulative incidence of local recurrence of 12.5% in SC arm vs. 0% in LC arm. Although LC chemoradiotherapy arm had a 3% lower local recurrence rate at 3 years and a 2% lower local recurrence rate at 5 years, neither were statistically significant. Authors conclude that the results of local recurrence rates have either no clinically important difference or speak in favor of LC chemoradiation. Also, LC could be more effective in reducing local recurrence rates for distal tumors.

Surgery of rectal cancer also experienced important improvements in the last two decades. TME (total mesorectal excision) is a surgical technique which was introduced into surgical practice and became widely used in rectal cancer surgery during 1990's. A significant length of the bowel around the tumor is removed, together with the belonging lymphatic drainage. The term *total mesorectal excision* strictly applies when performing a low anterior resection for tumors of the middle and the lower rectum, wherein it is essential to remove the rectum along with the mesorectum up to the level of the levator muscles. The principles of TME are also applied during an abdominoperineal excision of the rectum and for tumors of the upper rectum, although these are considered distinct from standard TME. In an abdominoperineal excision of the rectum where the tumor exists below the level of the levators, the lateral margins of the tumor are inferior to the mesorectum and the benefits of total mesorectal excision do not apply. Anterior resections involving the upper rectum may be completed with mobilization of the rectum to beyond 5 cm of the lower margin of the tumor, and which is often above the level of the levator and is sometimes referred to as *partial mesorectal excision*. TME results in a lower recurrence rate than traditional approaches and a lower rate of permanent colostomy. Postoperative recuperation is somewhat increased over competing methods. When practiced with diligent attention to anatomy there is no evidence of increased risk

of urinary incontinence or sexual dysfunction [10]. TME is now considered the gold standard for tumors of the middle and the lower rectum.

Chemotherapy used to treat rectal cancer can be categorized into one of two large groups: chemotherapy that is part of pre- or postoperative treatment (usually applied concommitantly or sequentially with pelvic irradiation) and chemotherapy for metastatic colorectal cancer. This text will be focused on chemotherapy in neoadjuvant and adjuvant setting in combination with radiotherapy.

A number of randomized clinical trials have evaluated and confirmed the effectiveness of adding chemotherapy to radiation in preoperative setting after clinical/radiological staging, as well as in postoperative adjuvant treatment, following pathological staging in patients with locally advanced rectal cancer. Benefits of addition of chemotherapy concurrent with pelvic irradiation include: local senzitization of tumor tissue (and normal tissue as well, but to a lesser extent), systemic control of the disease by eradicating possible micrometastases, increased likelihood of pathologic complete response and sphincter preservation. Drugs applied concurrently with radiotherapy are primarily radiosensitizing agents, with main intent to make irradiated (tumor) tissue more responsive to radiation-induced cell injury and/or death. 5-fluorouracil (5-FU), given either as an iv. infusion or orally (as prodrug capecitabine, that is enzymatically converted to (5-FU) in the body), appears to have the most favorable balance of efficacy and tolerability at the present time, so it is routinely used in concommitant chemoradiotherapy for rectal cancer. Oral administration without need for central IV access makes capecitabine an attractive and increasingly used option. Oxaliplatin and irinotecan have also been evaluated in neoadjuvant setting, but both demonstrated increased toxicity without substantial associated improvement in outcomes. There is currently a great need for finding new radiosensitizing agents and predictive biomarkers to help optimize the use of existing therapeutics.

A group of French authors published results of a clinical trial (FFCD 9203) which compared preoperative radiotherapy with and without concurrent chemotherapy [11]. 733 patients with T3-4NxM0 rectal adenocarcinoma were randomized into: RT group (preoperative radiotherapy with 45 Gy in 25 fractions; surgery planned 3-10 weeks after RT completion) and CRT group (same treatment protocol with addition of 5-FU 350 mg/m^2 + leucovorin (LV) 20 mg/m^2 during weeks 1 and 5 of RT). All patients received adjuvant chemotherapy with the same 5-FU/LV regimen. Although patients in the CRT group had significantly higher rates of pathologic complete response (11.4% vs 3.6%; $P < 0.05$) and less local recurrences (8.1% vs. 16.5%; $P<0.05$) there was no benefit of adding chemotherapy to preoperative RT in terms of 5-year overall survival (67.9% vs. 67.4%; P=0.684). Also, patients in CRT group had higher frequency of grade 3 and 4 acute toxicity (14.6% vs 2.7%;P <0 .05). Preoperative con-

current chemoradiotherapy despite a moderate increase in acute toxicity and no impact on overall survival significantly improves local control and is recommended for T3-4, N0-2, M0 adenocarcinoma of the middle and distal rectum.

EORTC 22921 phase III trial [12,13] evaluated effects of adding chemotherapy to preoperative pelvic irradiation and the value of postoperative chemotherapy on survival improvement in patients with T3-4 resectable rectal cancer. Preoperative trial design was similar to French study, except patients were also randomized into two groups depending on whether they received postoperative chemotherapy or not. Patients (n=1011) were allocated to the following four arms: arm 1, preoperative RT 45 Gy in 25 fractions; arm 2, preoperative CRT (addition of 5-FU 350 mg/m^2 + LV 20 mg/m^2 during weeks 1 and 5 of RT); arm 3, preoperative RT + 4 courses of postoperative chemotherapy; and arm 4, preoperative CRT + 4 courses of postoperative chemotherapy. Addition of chemotherapy to preoperative irradiation resulted in enhanced tumoricidal effect of radiotherapy: significant reductions in tumor size, pTN stage and lymphatic, vascular and perineural invasion were observed in preoperative CRT group compared to preoperative RT only. There was no significant difference in overall survival between the groups that received chemotherapy preoperatively (P=0.84) and those that received it postoperatively (P=0.12). The combined 5-year overall survival rate for all four groups was 65.2%. The 5-year cumulative incidence rates for local recurrences were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy (P=0.002). Finally authors conclude that chemotherapy, regardless of whether it is administered before or after surgery, confers a significant benefit with respect to local control. Although chemotherapy had no significant effect on overall survival between the arms, its use in combination with preoperative RT is highly encouraged since it induces downsizing, downstaging, and significant changes in histologic tumor characteristics.

In 2012. Bonnetain et al. published results of pooled analysis of EORTC 22921 and FFCD 9203 trials [14]. Using meta-analysis methodology, this trial established that addition of 5FU-based chemotherapy to preoperative radiotherapy improves pathological complete response (pCR) and local control (LC) rates. Compared to only preoperative RT, CRT did not prolong overall survival (OS) or progression-free survival (PFS). This trial also evaluated strength of certain pathological and clinical parameters as potential surrogates for OS (identifying surrogate end points for long-term clinical outcomes such as OS would allow clinicians to reduce trial duration as well as assess their patients' prognosis during or shortly after the treatment). The authors stated that pathologic complete response pCR) and local control (LC) cannot qualify as reliable surrogates for PFS or OS.

In the ACCORD-12 trial [15,16] two neoadjuvant chemoradiotherapy protocols are compared in terms of outcome parameters as well as toxicity. A total of 598 patients with T3-4N+ resectable rectal cancer were randomly assigned to preoperative concurrent chemoradiotherapy with CAP45 (45 Gy in 25 fractions with concurrent capecitabine) or CAPOX50 (50 Gy in 25 fractions with concurrent capecitabine + oxaliplatin). Surgery was performed 6 weeks after CRT completion. Pathologic complete response (sterilization of the operative specimen) was achieved in 13.9% vs.19.2% of patients, respectively (P=0 .09). After 3-year follow-up, there was no significant difference between local recurrence rates (6.1% vs. 4.4%), overall survival (87.6% vs. 88.3%) or disease-free survival (67.9% vs. 72.7%). More preoperative grade 3 to 4 toxicity occurred in the CAPOX50 group (25 v 1%; P < .001). In conclusion authors suggest that the benefit of oxaliplatin was not demonstrated and its use with concurrent irradiation is not recommended.

Interestingly designed RAPIDO trial [17] is a two-arm prospective randomized multicentric trial comparing conventional preoperative long-course concurrent chemoradiotherapy (45-50 Gy in 25 fractions with capecitabine) with introductory short-course radiotherapy (25 Gy in 5 fractions) followed by 6 cycles of chemotherapy (capecitabine and oxaliplatin) before surgery. The hypothesis is that short-course radiotherapy with neo-adjuvant chemotherapy increases disease-free and overall survival without compromising local control. The trial is still ongoing and oncologists worldwide are impatiently waiting for publication of the results.

There are still large variations between European countries in strategies of cancer care and subsequently, in cancer outcome. EURECCA (European Registration of cancer care) is a population-based colorectal cancer registry, but also involves multidisciplinary panel of experts, founded by leading professionals in all fields of medicine involved in cancer care. It's primary objective is to reduce treatment variances between countries or even within the same country and improve colorectal cancer care in Europe through registry, feedback and definition of core strategies in diagnostics, staging and treatment of colorectal cancer patients [18]. The panel formed a number of expert consensuses (with large to minimal equivocality); consensus is achieved for every step in diagnostic and treatment process of colorectal cancer patients, but panel strongly supports multidisciplinary team discussions in decision making for each patient. Also, diagnostic and treatment algorithms were developed and published by the panel, in order to provide up-to-date support to multidisciplinary teams involved in care for colorectal patients [18].

In conclusion, decision for the treatment of rectal cancer must mandatory be multidisciplinary. Surgical resection remains the therapeutic cornerstone, but the addition of neoadjuvant radiotherapy and chemotherapy is showing substantial be-

nefits. It is therefore necessary to subject all rectal cancer patients to multidisciplinary facility, where patients can be treated according to all actual recommendations and by that they receive best possible care and chance to fight the disease. Naturally, for every individual rectal cancer patient, individualized treatment plans based on a well-defined protocols should be designed.

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Sažetak

Važnost multidisciplinarnog pristupa u liječenju karcinoma rektuma

Kolorektalni karcinom je treća maligna bolest po učestalosti u svijetu, te predstavlja značajan javnozdravstveni problem. Multidisciplinarni pristup danas je uobičajen kod dijagnostike i liječenja onkoloških bolesti, a karcinom rektuma tipičan je primjer za važnost suradnje različitih medicinskih disciplina u postizanju optimalnog terapijskog učinka. U ovom preglednom radu prikazan je kratak presjek najvažnijih studija koje su definirale optimalni pristup liječenju bolesnika sa lokalno uznapredovalim karcinomom rektuma. Današnje smjernice i preporuke za liječenje karcinoma rektuma stadija II i III uključuju preoperativnu radioterapiju sa ili bez konkomitantne kemoterapije, te radikalan kirurški zahvat (uz obaveznu totalnu mezorektalnu eksciziju-TME). Takvim se multidisciplinarnim pristupom kod tih bolesnika značajno reducirala stopa lokalnih recidiva, te povećala stopa patoloških kompletnih odgovora i zahvata sa očuvanjem analnog sfinktera, uz nisku stopu terapijske toksičnosti. Daljnje studije koje ispituju nove sistemske terapije (imunoterapija-konjugati antitijela i lijekova), kao i modernije radioterapijske tehnike (IMRT, IGRT, VMAT) kod bolesnika sa karcinomom rektuma, a kojima bi se dodatno unaprijedili terapijski ishodi, su u tijeku.

***Ključne riječi*:** karcinom rektuma; preoperativna (neoadjuvantna) kemoradioterapija; kompletna mezorektalna ekscizija; multidisciplinarno liječenje.

Corresponding author:
Lidija Beketić Orešković
E-mail: lidijabeketicoreskovic@gmail.com