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TREATMENT OF RECTAL CARCINOMA

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Summary

Carcinoma of the rectum represents a major public health issue, affects many patients and causes controversies about the optimal treatment modalities and their timing. Based on the results of numerous studies neoadjuvant chemoradiotherapy is newly often favorised in all localized tumors, except the earliest ones. With this multimodal approach a significant tumor regression with acceptable side-effects can be achieved and later surgical procedures alleviated or even omitted in highly selected cases.

In this review paper the latest data on rectal cancer treatment and expected future research ideas are explained and discussed in detail.

KEY WORDS: *rectal cancer, radiotherapy, chemotherapy, multimodal treatment*

LIJEČENJE KARCINOMA REKTUMA

Sažetak

Rak rektum predstavlja značajan javnozdravstveni problem, zbog brojnosti pacijenata i nedoumica oko optimalnog slijeda raznih vidova liječenja. Na temelju rezultata brojnih studija neoadjuvantna kemoradioterapija se u zadnje vrijeme pretpostavlja u liječenju lokaliziranih tumora, izuzev najranijih stadija. Takvim multimodalnim pristu pommože se postići značajna regresija tumora uz prihvatljive popratne pojave, čime su kasniji kirurški postupci olakšani ili ih se čak može izbjeći u izabranih pacijenata.

U ovom preglednom članku se podrobno iznose i raspravljaju najnovijipodaci o liječenju raka rektuma i ideje o očekivanim budućim istraživanjima.

KLJUČNE RIJEČI: *rak rektuma, radioterapija, kemoterapija, multimodalno liječenjenje*

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 newly detected patients and 7.9% of all causes of death from malignant disease.

The tumor bed is best defined by the distance from the ano-cutaneous border. Low positioned tumors pose a major challenge for successful treatment. The cramped conditions between the bony structures of the pelvis reduce the likelihood of radical surgical removal, resulting in a high risk of local recurrence[1]. Most of recurrences (85%) appear in first three years after the treatment[2]. A multidisciplinary approach is required and recommended because of increased risk of local recurrence and the treatment consequences which impair the quality of life (digestion, urination, sexual life).

Research on the modalities and timing of radiotherapy application departs from science-based

facts about better local control and prolonged survival in patients with T_{3-4} N+ tumors treated with adjuvant radiotherapy (NSABP R – 01[3] and NSABP R – 02[4]).

Based on the results of numerous studies, preoperative chemoradiotherapy was accepted by ESTRO in 2007 as a standard approach in the treatment of patients with locally advanced disease (T_{3-4} N+). Preoperative treatment advantage is the reduction of the tumor up to the pathological complete regression (in 10-25 % of patients). Radical local resection is facilitated and the likelihood of margin-free resection of tumor is increased. Postoperative radiation is indicated in underestimated disease, should the pathologist findings show a stage higher than expected on the basis of imaging methods before surgery.

The essential component of the pathologist findings after the operation is the description of the circumferential edge (CRM margin). It represents the distance from the edge of the soft tissue preparation to the deepest penetration of tumor. Applied radiation benefit (reduced local recurrence rate) was briefly questioned by published results of only 8.2% local recurrence in patients treated with total mesorectal excision technique (TME). In another study from the Dutch Colorectal Cancer Group, patients were randomized to preoperative pelvic irradiation at a dose of 5x5 Gy, or to the control group which was operated without prior irradiation. It was shown that the rate of local recurrence after 5 years can be further reduced to 2.4 % even after TME ($p = 0.001$)[5].

According to the treatment results of GRCSG (German Rectal Cancer Study Group) 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 neoadjuvantradiochemotherapy, and 13% in the control group with adjuvant radiochemotherapy (p=0.006). Significantly less grade 3 and 4 side effects were found in the neoadjuvant group - 27% than in the adjuvant group - 40% (p=0.001)[6]. The later published results of the same group (GRCSG) after a 11-year follow-up remained statistically significant in terms of local recurrence, with no impact on the survival length[7].

A similar comparison of pre- and postoperative radiotherapy was carried out in a R-03 NSABP study[8] (National Surgical Adjuvant Breast and Bowel Project) which enrolled 267 patients. A significantly better 5-year disease free survival (DFS) in preoperatively treated patients - 64.7 % versus 53.4% (p=0.011) was observed after a median follow-up of 8.4 years. There was no difference in overall survival (OS) of 74.5% vs. 65.6% (p=0.065).

Oxaliplatin administered together with 5-FU and leucovorin has significant activity in the treatment of metastatic colorectal cancer. In primary rectal tumor treatment, adding of oxaliplatin does not contribute to its reduction in preoperative chemoradiotherapy, but increases the rate of acute side effects[9]. In the ACCORD study, 598 patients with T_{3-4} N+ rectal cancer were randomized into groups of 45 Gy radiation delivered in 25 fractions with concomitant capecitabine or 50 Gy in 25 fractions with concomitant capecitabine and oxaliplatin. After six weeks of chemoradiotherapy, TME was performed in 98% of patients in both groups. Complete pathological response was recorded in 19.2% of patients having received 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 anal sphincter preservation during surgery (75% vs. 78%).

Aschele et al. have conducted another similarly designed study on the synergistic effect of oxaliplatin (STAR-01) in 747 patients in Italy[10]. The pathological complete response rate in two randomized groups was the same (16%), 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). Although the incidence of acute side effects has been monitored in most studies, they cause only short-term discomfort and resolve spontaneously or with symptomatic medication completely. Late side effects are more important (especially after radical surgery such as TME) because they impair the quality of life (anal sphincter incontinence, sexual dysfunction).

Somewhat conflicting results were reported from a study performed by Rodel et al. CAO/ARO/AIO-04[11] where 1236 patients were randomized into groups of preoperative radiotherapy with 5-FU or 5-FU with oxaliplatin. 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.

By now, the application of oxaliplatin in the preoperative treatment setting with radiation is

not recommended outside of research protocols. It is necessary to wait and observe the results from these studies, particularly in terms of disease free survival (DFS).

Youn et al.[12] investigated the possible synergistic effects of sorafenib administration together with radiation in the treatment of rectal cancer. They have treated three colorectal cancer cell lines and observed that most of the tumor cells stopped in the G2-M phase. The repair of DNA damage caused by radiation was delayed, while the rate of apoptosis in intestine glandular crypts in both groups was equally frequent.

Bujko et al.[13] compared the outcomes after a "short -course" (5 x 5 Gy) and "long -course" (28 x 1,8 Gy) preoperative radiotherapy. The late complications rate did not differ significantly, respectively 10% ("short -course") vs. 7 % ("long -course").

Many colorectal cancer characteristics were investigated with the intention to discover the possible factors which could predict regression and prognosis after preoperative radiotherapy: tumor volume, the serum level of carcinoembryonic antigen (CEA), tumor distance from the anal verge[13], the time elapsed between the completion of radiotherapy and the definitive surgery[14].

Gallon et al.[15] have studied 51 patients after preoperative chemoradiotherapy. The tumor burden decreased in 54.9% and the complete histologic regression was documented in 11.9%. The probability of tumor reduction was significantly associated with hemoglobin levels before treatment > 12.0 g/dl (p=0.044) and relative lymphocytes number in the WBC before treatment >26% (p=0.022). Complete histologic regression was significantly more frequently observed in patients with relative number of lymphocytes in the WBC >26% before treatment (p=0.023), absolute lymphocyte count > 1,634 x10^9/L (p=0.004), with clinical findings of N- stage disease (p=0.018) and those with the hemoglobin level >12.0 g/dL before treatment. The authors conclude that the outcome of preoperative treatment depends not only on the biological characteristics of the tumor, but also on the "micro-environment" in which the tumor grows. In the literature, it is possible to find similar claims about the high level of circulating lymphocytes beneficial effect on the outcome of colorectal cancer treatment [15,16].

Derbel et al. failed to determine the outcome predictors after preoperative treatment by studying KRAS, BRAF and PI3KCA mutations in rectal cancer. The observed variables in the group of 98 patients were local recurrence and distant metastases rate[17]. They have concluded that further research with a larger number of patients and greater statistical power is needed.

Complete histologic regression after preoperative treatment is associated with a significantly longer survival (KROG-09-01)[18], while the N+ lymph node finding after preoperative treatment is an unfavorable prognostic indicator regardless of the extent of the primary tumor regression[19]. Meta-analysis of Lee et al.[20] clearly demonstrated that the partial regression of tumors is associated with a 50% improvement in the length of disease free survival (DFS) and should be considered as a favorable prognostic factor.

PET/CT imaging and the accumulation of FDG in the tumor tissue (SUV) could be a valuable predictor of tumor regression with 81% sensitivity, 100% specificity and 90% of overall reliability, as demonstrated by Bampo et al.[21]. PET/CT has been performed twice: two and six weeks after standard preoperative radiotherapy in 31 patients. The complete histologic remission was accomplished in 30%. Early recordings showed no significant regularity, but the results of the SUV recorded later were different between patients with complete and incomplete regression at the significant level of p=0.006. Final decision on the role of PET/CT in determining the need of treatment continuation will be possible after future research with more patients. A reliable early assessment of insufficient tumor response would be valuable because of the possible intensification of radiotherapy in these patients. Distinguishing complete from incomplete tumor regression after 6 weeks of radiotherapy and before operation could lead to less radical or even avoided surgery (wait-and-see attitude). PET/CT could assist in screening patients and even determining of the optimal timing for accessing operation[22].

The optimal time for surgery after completion of preoperative radiotherapy is difficult to be determined unambiguously. 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 more anal sphincter saving operations.

The argument for a "watch and wait" attitude could result from the research that has al-

ready begun. In the group of 70 patients with low rectal tumors staged $T_{2-4}N_{0-2}M_0$Habr-Gama et al.[23] applied 54 Gy of radiation plus 6 cycles of 5-FU/LV chemotherapy, administered every 3 weeks. Complete clinical remission was observed in 68% of patients. Local recurrence occurred in this group in 17% during the first year, 10% in the second year, and 57% remained healthy after 5 years of follow-up. A significant contribution to the quality of life in these disease stages was the fact that 50% of the patients have never been operated. In the case of need timely "salvage" operation is always possible in carefully monitored patients.

An interesting Rapido study has just started with two randomized groups of patients: a control group with conventional preoperative therapy (50 Gy with capecitabine) and an experimental group where after the introductory 5 x 5 Gy radiation follow six cycles of chemotherapy with capecitabine and oxaliplatin. Upon the completion of preoperative treatment, all the patients will be operated according to the principle of TME. The monitored outcome will not only be the rate of local recurrence but especially the impact on overall disease-free survival[24].

While it is scientifically proven that complete regression after preoperative treatment significantly prolongs 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 further research. These schemes, if proven their reliability, in the future may become more important than the current TNM system (introduced before the preoperative treatment approach was invented). Until 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 is reliably to predict the course of illness in patients with complete tumor regression or those with no response to preoperative treatment.

The first step in using the epidemiological data from large disease outcome registries was made by Bowles et al.[25]. They have developed an interactive mathematical model of 5- and 10-year survival likelihood by using data on age, sex, race, tumor differentiation and the type of surgery performed. Covariates were preoperative or postoperative radiotherapy, patients without treatment or stage IV disease. An online calculator was created that can be found on www.mdanderson.org/rectalcalculator. Assessment results are valuable, but orientation aid in predicting the course of disease and in the planning of further treatment or monitoring.

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

Zhan et al.[26] were interested in the treatment outcome of shortened preoperative radiotherapy. Preoperative treatment lasting for 5-6 weeks in China is not the golden standard because of the radical surgery tradition and patients preference for being less absent far from home for treatment. After 30 Gy of applied radiotherapy in 10 fractions surgery followed within 14 days. The rate of complete histologic regression in 101 patients was only 5%, with 50% partial regressions. After five years 5% of local recurrence was observed in the preoperative radiotherapy group and 18% in the control group (p=0.02). There was no significant perioperative complications increase.

The technique of radiation has recently not changed significantly. Radiation simulation assumes prone positioning of the patient on the table top with a hole ("belly-board") with a contrast view of the small intestine and the use of modern radiation planning tools such as 3-D and IMRT.

All the abovementioned findings were collected and published after the debate in two new recommendations for the treatment of colorectal cancer, the European registry for the treatment of cancer (EURECCA)[26] and the American Society for colorectal surgery[27].

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