THERAPY

Combination therapy of colorectal carcinoma

Vokurka J, Spurny V, Kabela M

*1st Department of Surgery, Medical Faculty, Masarykiensis University, St. Anna Medical University Hospital, Brno, Czech Republic.*vokurka@med.muni.cz

Abstract

The aim of the study was to optimise the present therapy for colorectal carcinoma according to the standard therapeutic protocol.

At the Ist Department of Surgery of the LF MU St. Anna Hospital in Brno and at the Department of Radiation Oncology of the same hospital, 262 patients with colorectal carcinoma were treated in period 2000–2002. Neoadjuvant radiotherapy concomitant with chemotherapy was applied for 5–6 weeks. After this procedure, a 5–6-week break, the restaging and the surgical intervention have followed. A radical surgical operation was carried out in 74.1 % cases. The survival of stage IV patients was worse compared to other stages, and the presence of organ metastases markedly impaired the prognosis. We have shown in our study, that radical surgery is still the best therapeutic method for colorectal tumors. Within the surgical technique, the use of a harmonic scalpel has proved beneficial, as it enables a bloodless operative field while ensuring the necessary radicality and preserving the nerve plexuses.

Neoadjuvant chemo-radiotherapy is considered a method of choice in rectal tumors surgery; it shows better results than radiotherapy only. Its inclusion into standard protocols has been still hindered by the lacking evidence of effectiveness at the II or I level. The possibility of administering oral fluoropyrimidines makes these studies even more attractive *(Fig. 6, Ref. 30)*.

Key words: colorectal carcinoma, surgery, radiotherapy, chemotherapy.

The Czech Republic ranks the first worldwide regarding the incidence of colorectal carcinoma. In spite of the fact that the therapy of colorectal carcinoma has considerably changed in the last decade, about 36 people/100,000 inhabitants die per year, which accounts for approximately 15 % of all deaths of tumor etiology. The base for the treatment of colorectal carcinoma is new surgical methods and improved effectiveness of combined non-surgical preoperative and postoperative treatment methods (2, 4). Their mutual optimisation reduces the risk of local relapses, enables sphincter-preserving operations and in palliative interventions improves the patients' quality of live.

Material and methods

The group of 262 patients was treated at the 1st Department of Surgery of LF MU St. Anna Hospital and at the Department of Radiation Oncology of the same hospital in the period from 1.1.2000 to 31.12.2002. Records on patients' hospitalisation were used for the evaluation of the clinical course. In addition, data from the National Oncological Register were evaluated as an anonymous table.

The following data were recorded: demography (sex, age), tumor incidence in direct relatives, incidence of metachronous and synchronous affection in personal history, subjective and objective troubles, spectrum of examinations leading to diagnosis, tumor staging and grading, incidence and localisation of metastases, type of operation, postoperative therapy and the length of survival.

Males comprise 66 % of total 262 patients. The mean age of all patients was 65.6 ± 12.5 years with the median 67 years, range 24–93 years. Ethylism was not recorded. In the group, there were only 36 smokers (13.7 %). Tumor disease in family history was recorded in 17 % of patients but only 1.5 % reported a colorectal carcinoma.

1st Department of Surgery, Medical Faculty, Masarykiensis University, St. Anna Medical University Hospital, Brno, and Department of Clinical and Radiation Oncology, St. Anna Medical University Hospital, Brno, Czech Republic

Address for correspondence: J. Vokurka, MD, PhD, 1st Dept of Surgery St. Anna FN in Brno, Pekarska 53, CZ-65691 Brno, Czech Republic Phone: +420.5.43182360, Fax: +420.5.43182373

The clinical stage of malignant tumors was established on the basis of the TNM classification in accordance with UICC 1997.

The surgical interventions were divided into three groups: radical, palliative and probatory. We considered radical all resections of the colon with the complete removal of the tumor and adjoining lymphnodes. As a rule, we have performed total mesorectal excisions with preservation of pelvic autonomous nerves in radical interventions as recommended by other authors (5, 12, 13, 15, 17, 19). In this study, we do not deal with the importance of per-operative identification and evaluation of the sentinel node biopsy in colorectal carcinoma (26, 27).

All interventions without radical removal of the tumor or metastases (14) were considered palliative. In an inoperable situation, only explorative laparotomy was performed.

The preoperative radiotherapy with conventional fractionation with concomitantly administered chemotherapy is the standard therapy of locoregionally advanced (T3, T4, N+) and primarily inoperable tumors of rectum and recto-sigmoideum at a large number of medical establishments (16, 18). Our patients were irradiated with a linear accelerator and concomitantly chemotherapy was administered to them, i.e. 5fluorouracil/leucovorin. After 5–6 weeks, the restaging (TRUS, ultrasound of the liver, X-ray of the lung) and the operation followed. The pre-operative radiochemotherapy was well tolerated, its sided-effects were of only a short duration and manageable with symptomatic therapy.

All patients had a CT scan in order to plan the treatment. Using the CT data set, the rectum, lymph nodes, and other critical structures were identified.

Prone patients were treated with a 15-MV linear accelerator. The radiotherapy was applyied using a three-field technique consisting of a PA and two lateral fields. The patients received 45 Gy in 25 fractions with 1.8 Gy using a large pelvic field including the gross tumor volume and regional lymph nodes. The boost field size was decreased to exclude the small bowel from the field with additional 5.4 Gy in three 1.8 Gy fractions.

The Kaplan-Meier method was used for the statistical evaluation of the survival.

Results

Tumors in separate parts of the colon were localised as following:
- coecum and ascending colon: 15 %
- hepatic flexure: 5 %
- transverse colon: 1.9 %
- splenic flexure: 7.8 %
- descending colon: 6.4 %
- sigmoid and rectum: 63.9 %

Synchronous incidence of colorectal carcinoma was recorded in 1.5 % of all cases, metachronous incidence in 3.7 % of patients. Previous polypectomy was reported in 6.7 %. Not a single case of familial polyposis was recorded in our group of patients.

The symptoms of the disease are shown in Figure 1.

In addition to routine internal and laboratory tests, the spectrum of preoperative examinations included also colonoscopy
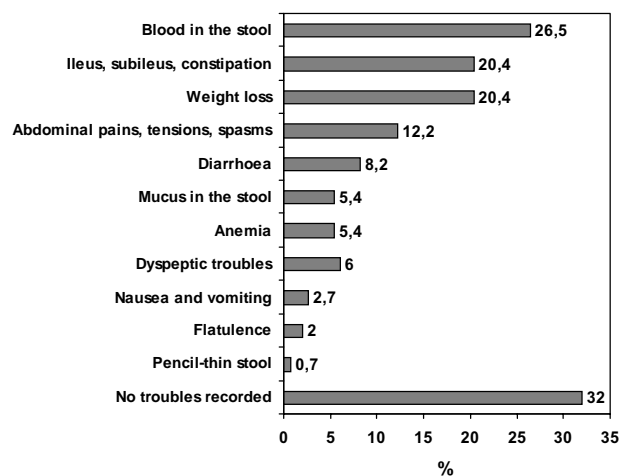

Fig. 1. Symptoms of the disease.

(in 72.9 % patients), rectoscopy (65.7 %), TRUS (22.2 %), CT (28.6 %) and NMR (2.1 %). X-ray examinations of the colon were performed in 7.4 % of the patients.

Malignant adenocarcinoma was diagnosed in 91.1 % of all patients. Regarding other types of malignancies, only one case of carcinoid in colon ascendens was recorded.

Stage I of the disease comprised 6.8 % of the patients, stage II 36.7 %, stage III 24.5 % and stage IV 22.5 %. Benign neoplasms were present in 8.2 %. The stage could not be determined in 1.4 % of the patients.

G1 was established in 11.1 %, G2 in 41.5 % and G3 in 5.9 % of patients. The grading could not be retrieved in the rest of the patients.

Operation due to tumor recurrence was recorded in 5.2 % of all patients.

Cumulative survival ratio is shown in Figure 2. Survival with respect to the stage of disease is shown in Figure 3; survival with respect to age is shown in Figure 4; survival with respect to the type of operation is shown in Figure 5. Cumulative survival with respect to the histological type of malignant disease is shown in Figure 6.

A radical operation was performed in 74.1 % of all patients, palliative surgery in 25.2 %. Inoperable cases were recorded in 0.7 % of all patients. Miles' operation was performed in 20.74 %, operation according to Dixon in 6.7 %, resection according to Hartmann in 3 %, and low-low anastomoses in 2,2 % of all operations.

The incidence of tumor metastases was evaluated in 27 patients: in 74 % of all cases were the metastases localised in the liver. Metastases in the peritoneum were found in 14.8 %, and metastases in the omentum, mesenterium or lung were present in 3.7 %, equally for each localisation.

Discussion

The incidence of colorectal carcinoma was higher in males than in females, ratio 2:1.
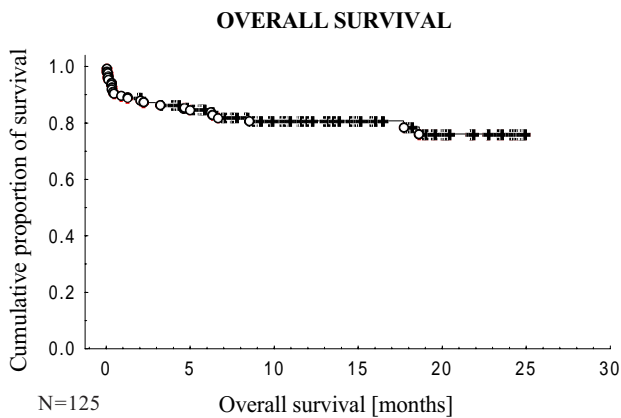
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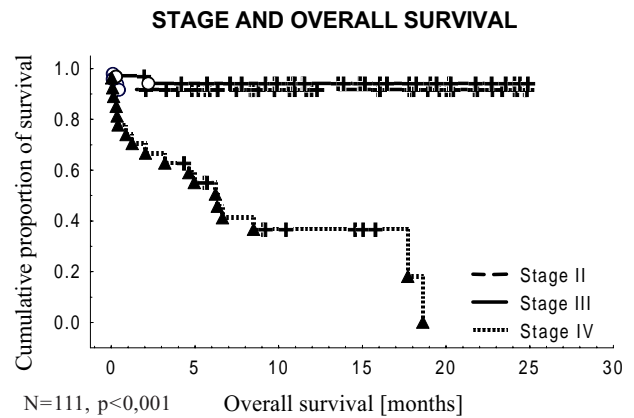

Fig. 2. Overall survival.

STAGE AND OVERALL SURVIVAL

Fig. 3. Survival with respect to the stage of disease.

AGE AND OVERALL SURVIVAL
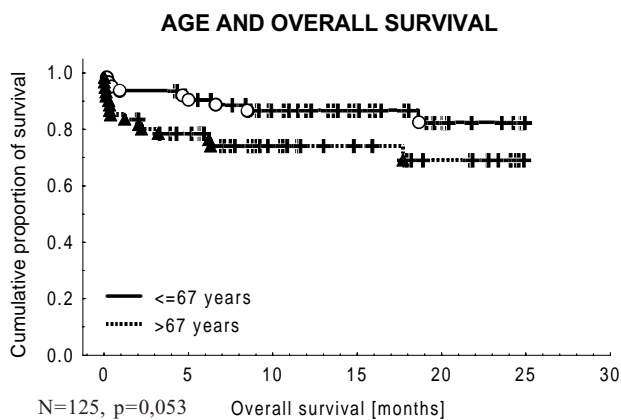

Fig. 4. Survival with respect to age.

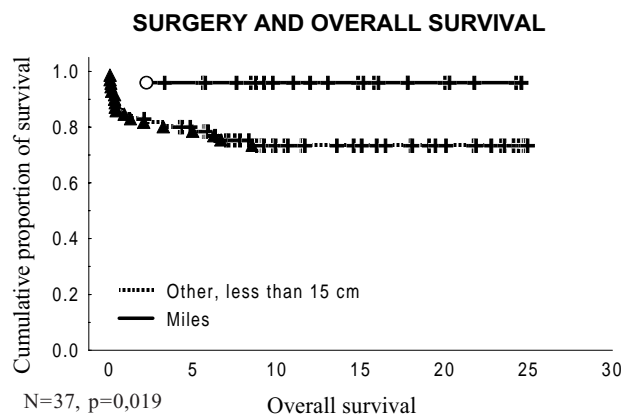**SURGERY AND OVERALL SURVIVAL**

Fig. 5. Survival with respect to the type of operation.
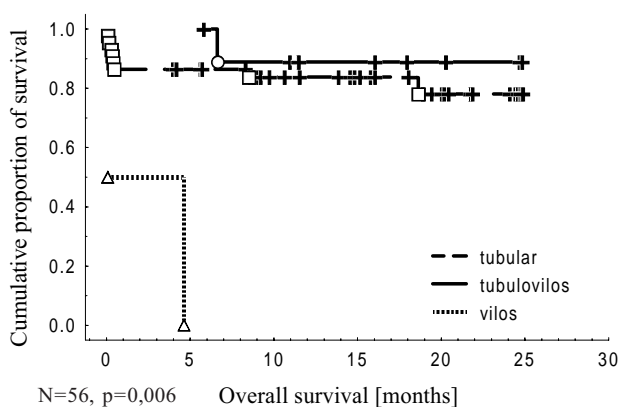

Fig. 6. Cumulative survival with respect to the histological type.

The most frequent symptom was blood in the stool. Surprisingly, this symptom was recorded only in less than half of all patients. The oftenly mentioned mucus in the stool was established in only six patients. A frequent complication was the stenosis of digestive tract of various degrees. Subileous to ileous condition was the first serious symptom in less than a fifth of all patients. This suggests a long, clinically silent, phase of the disease. Including rectoscopy, all patients were examined with an endoscopic method. A very important method is a transrectal ultrasound in case of low-positioned tumors. It provides valuable information about the tumor invasion and its relations to surrounding structures (8, 21, 22). However, the TRUS method was only being introduced into practice in our patients. Therefore, the number of patients examined is relatively low. At present, we perform the TRUS examinations in all patients with low-positioned tumors.

The use of harmonic scalpel proved useful in operation. The ultracision instrument blade vibrates longitudinally at 55 kilohertz. It ensures a bloodless operative field with the option of careful capillary hemorrhage staunching. A good view of the operative field is, in our opinion, the base of a faultless operation with preservation of nerve plexuses while enabling a desirable radicality of the intervention (6, 29).

The patients' survival undoubtedly depends on the stage of the disease and on the histological classification of the tumor. The worst prognoses were recorded in stage IV patients, low grading and villous-type tumors. Figure 3 shows a small difference between the survival of stage II and III patients in contrast to the difference between stage III and IV. This fact can be explained by the unfavorable effect of the metastatic process in patients in the latter stage (20, 21, 24). We have compared the survival of patients with the Miles operation with other types of interventions for tumors localised within 15 cm from the anocutean line. The longer survival of patients after the Miles operation can be explained by its radicality.

We have used radiotherapy in rectal cancers both before and after the operation. The preoperative radiotherapy, depending on the extent of the disease process, can be classified as short-term and long-term radiotherapy (1, 25, 28, 30).

We use a short-term radiotherapy in extensive T3–T4 tumors not affecting the regional lymphnodes. The total dose 25 Gy is divided into 10 fractions applied within 5 days. Then the patient is operated on within one week.

We use a long-term radiation therapy in extensive locally advanced tumors with metastatic regional lymphnodes. In such cases, we apply 50 Gy in 1.8 Gy fractions within 6 weeks. In these patients, radiotherapy is completed by chemotherapy, 5-fluorouracil, and is applied continuously (for 6 hours though a portable dosing device) in a dose of 1000 mg in 5 days, in the 1st, 4th and the 7th week of the radiation therapy. After 3–4 weeks, after the end of the radiation therapy, the effect is evaluated and the patient is a subject to a surgical intervention.

A randomised study has shown that concomitant chemotherapy produces better results.

The planned target volume (PTV) includes the tumor and also perirectal, obturator, presacral internal and common iliac lymphnodes and, if necessary, also the anal region and external iliac lymphnodes.

Currently, the most used preoperative method is a combination of radiotherapy, i.e. 45–50.5 Gy of pelvic irradiation at 1.8 Gy per fraction with simultaneous administration of 5-fluorouracil, either as a bolus in combination with leucovorin or as continuous infusion (21). It has not been proven that either regimen is better than the other; most authors prefer the administration in form of an infusion (7).

Regarding the combination therapy, most attention has been paid to oral fluoropyrimidines, i.e. UFT and capecitabine. The administration of 5-FU in continuous infusion is costly, inconvenient for the patient, requires a central venous catheter, a pump, and is associated with possible complications such as thrombosis, infection or bleeding up to 40 % cases. The oral administration of fluoropyrimidines is safe and associated with only few side effects.

UFT is an oral combination of uracil and tegafur. Tegafur is metabolised to 5-FU after the intestinal absorption, uracil inhibits the catabolism of 5-FU through competitive inhibition of uracil-dehydrogenase, which remains active for a long time and simulates continuous administration of 5-FU (10).

Capecitabine (XELODA®) is an oral fluoropyrimidine carbamate: it is sequentially activated to 5-FU, which is preferentially released in the tumor tissue thus minimising the system side effects. Capecitabine simulates continuous administration of 5-FU; another advantage is its pronounced radiosensitisation effect. The effective dose of capecitabine amounts to 825 mg/m^2 administered 2 times a day during radiotherapy (total dose of 45 Gy, daily dose of 1.8 Gy) (8).

Other preparations used in combination with radiotherapy are following: Tomudex, CPT 11, oxaliplatin and eniluracil.

After neoadjuvant chemo-radiotherapy, the pCR frequency has been reported as 14–61 % in recent papers. A downgrading of the clinical stage of the disease has been proven in high percentage (68–83 %) (7).

Neoadjuvant chemoradiotherapy is considered a method of choice in rectal tumors; it shows better results than radiotherapy alone. Its inclusion into the standard protocols has been prevented by the lacking evidence of effectiveness at the II or I level. The possibility of administering oral forms of fluoropyrimidine makes these studies even more attractive.

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