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Evaluation of Adjuvant Chemotherapy in Patients with Colorectal Cancer in Primorsko-goranska and Istarska County – A Twenty Years Retrospective Study

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A B S T R A C T

Colorectal cancer is the second most common malignant disease in developed countries, with about one million new cases worldwide every year, accompanied with high mortality rate. We examined the survival rate and recurrence (occurrence of distant metastases and/or local recurrence) of patients with colorectal cancer in Primorsko-Goranska and Istarska County who received adjuvant chemotherapy, compared to those who did not in the period since 1980. until 1999. This study involves 483 patients with colorectal cancer stages II and III of Primorsko-Goranska and Istarska County, which were underwent curative resections of colorectal cancer at the Clinical Hospital Centre Rijeka, and then treated with chemotherapy (288) or without Chemotherapy (195). We analyzed the five year survival rate and the recurrence of malignant disease in the adjuvant treatment group in comparison with not treated group with chemotherapy, depending on the stage of disease, degree of histological differentiation, patient age and location of cancer (colon or rectum). After follow-up of 60 months died 44.79% (129/288) of patients who received chemotherapy and 53.33% (104/195) of patients who did not receive chemotherapy. The relative risk of death (from any cause) in chemotherapy-treated group versus the group without chemotherapy was 0.82 ($p<0.008$). Recurrence of malignant disease in the chemotherapy group was 38.54% (111/288), and in the group without chemotherapy was 46.15% (90/195). The relative risk of recurrence of malignant disease in the chemotherapy group versus the group without chemotherapy was 0.78 ($p<0.001$). There was no difference in treatment efficacy regard to the localization of the tumor, but there were differences in efficiency with respect to disease stage, grade and age. Chemotherapy with 5-fluorouracil and leukovorin ameliorate the survival and reduces recurrence and distant metastases in patients with colorectal cancer stages II and III.

***Key words**: adjuvant chemotherapy, colorectal cancer, five-year survival rate, Istarska County, Primorsko-Goranska County*

Introduction

Colorectal cancer (CRC) is the second most common malignant disease in developed countries, with 1 million new cases and 500,000 deaths worldwide every year[1]. A similar situation exists in Republic of Croatia, where in 2007 were a total of 2835 incident cases of colorectal cancer (1620 men and 1215 women)[2]. In Croatia it is among the three most common cancer sites (behind lung and breast cancers). In 2007 among males, CRC was the second most common cancer site by making 15% of all newly carcinoma with an incidence rate of 75.9, behind lung cancer and in women after breast cancer, represented 13% of cases of malignancy in women with an incidence rate of 52.8. The overall incidence was 63.9 new cases per 100 000 population[2]. In Istria County in 2007th were a total of 143 incident cases of CRC with an incidence of 69.3 while in Primorsko-Goranska County were 197, with an incidence of 64.4[2]. Radical surgical resection is the base of treatment of diseased colon cancer and the most effective in the early stages of the disease. Curative surgery depends on the localization of tumors and vascular anat-

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omy of the colon and mesentery. Larger lesions require removal of the affected part of the intestine with the mesentery and associated lymph nodes, along the resection border at least 5 cm away from the edge of the tumor[3]. The surgical treatment of advanced disease includes chemotherapy and radiotherapy, which can diminish the risk of recurrence, without which is the rate of return of malignant disease (recurrence) of 30–50%. Moreover, quality assurance/quality control (QA/QC) program is required for all radiotherapy equipment (linear accelerators, simulators, cobalt units, brachytherapy units) according to international recommendations[4].

The aim of this study was to examine the survival and recurrence (occurrence of distant metastases and/or regional recurrence) in patients with colorectal cancer of Primorsko-Goranska County and Istria County, who received adjuvant chemotherapy in comparison with patients with colorectal cancer who did not receive this chemotherapy in the period since 1980 until 1999.

Subjects and Methods

Retrospective analysis with examining the history of the disease, all radically operated patients with curative colorectal cancer is determined by date of birth, place of residence, the exact date of surgery, tumor localization, type the applicable operating procedure, type of applied adjuvant therapy, tumor histological categorization and classification of tumors according to TNM classification and occurrence of return of malignant disease (distant metastases and/or regional recurrence). In the retrospective period from January 1980 until December 1999. We analyzed 483 patients with colorectal cancer stages II and III of the Primorsko-Goranska and Istria County, who were treated at the Clinical Hospital Center Rijeka. Patients were divided into a group treated with chemotherapy (288) and the group without chemotherapy (195). Both groups were equating with regard to age, tumor stage and localization. Patients who were treated with chemotherapy and were given 5-fluorouracil and leucovorin in the six five-day cycles every four weeks at a dose of 370 mg/m^2 of 5-fluorouracil and leucovorin 20 mg/m^2 intravenously.

Statistical analysis

Statistical analysis was performed in the »SPSS 16.0 for Windows«, while the graphics were made used the Excel for Windows. For evaluation, qualitative data were presented as number of cases and percentages. To examine differences in survival with respect to independent variables (use of adjuvant therapy, tumor stage, tumor grade, tumor localization, age) applied the Chi-square test. P value was considered significant level at 0.05. For analysis of survival depending on the tested variables (stage, grade and tumor localization, age, applied for adjuvant therapy) was used type of analysis of survival known as the life table Kaplan-Meier.

Results

Patients were followed in a period of 60 months. The average age of patients at the time of surgery was 64.52 years (Figure 1). Males were 60.87% (294/483) and women 39.13% (189/483) (Table 1).

TABLE 1
DISTRIBUTION OF PATIENTS BY GENDER

Sex	Frequency	Percentage (%)	Cumulative percentage (%)
Men	294	60.9	60.9
Female	189	39.1	100.0
Total	483	100.0	

Colon cancer had a 54.04% (261/483) and the rectum cancer 45.96% (222/483) of patients (Figure 2).

Stage II disease had a 38.10% (184/483) and stage III 61.90% (299/483) of all patients. Adjuvant chemotherapy received 59.63% (288/483) of patients, and 40.37% (195/483) was not treated with adjuvant chemotherapy (Figure 3).

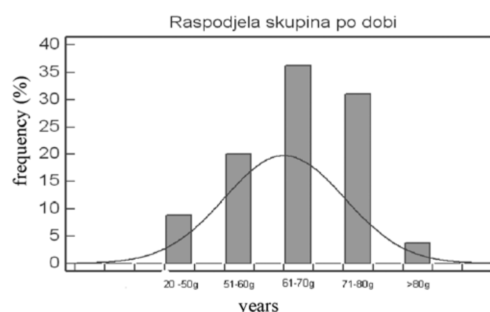

Fig. 1. Age distribution of the group with colorectal cancer.

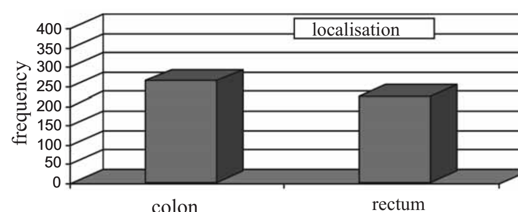

Fig. 2. Distribution of patients according to tumor localization.

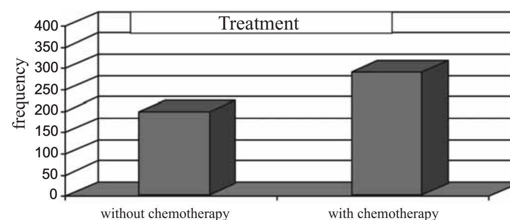

Fig. 3. Distribution of patients according to the received chemotherapy.

TABLE 2
SURVIVAL BY AGE GROUP

	Age groups (number, percentage and cumulative percentage)				
Survival	20–50 years	51–60 years	61–70 years	71–80 years	>80 years
0–2 years	8(18.6%;18.6%)	35(36.1%;36.1%)	67(38.3%;38.3%)	61(40.7%;40.7%)	9(50.0%; 50.0%)
2.1–5 years	6(14.0%;32.6%)	10(10.3%;46.4%)	16(9.1%;47.4%)	14(9.3%;50.0%)	7(38.9%; 88.9%)
5.1–8 years	13(30.2%;62.8%)	28(28.9%;75.3%)	49(28.0%;75.4%)	41(27.3%;77.3%)	2(11.1%;100.0%)
8.1–10 years	16(37.2%;100%)	24(24.7%;100%)	43(24.6%;100%)	34(22.7%;100%)	0(0.0%;100.0%)
Total	43 (100.0%)	97 (100.0%)	175 (100.0%)	150 (100.0%)	18 (100.0%)

In the examine group of 483 patients analyzed in the 5 year period died 48.24% (233/483). The five-year period died 35.33% (65/184) patients, stage II and 56.19% (168/ 299) of patients stage III (Table 2 and Figure 4).

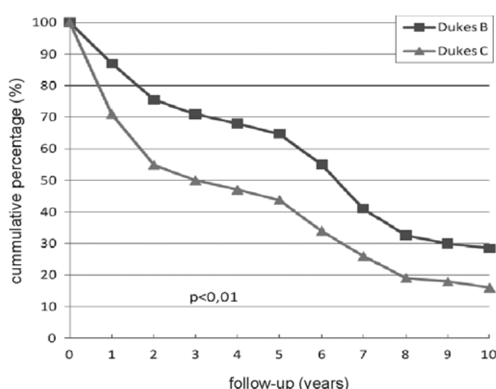

Fig. 4. Survival due to stage of disease at Dukes.

Return of malignant disease in a five-year period had a 41.61% (201/483) of patients, of which 21.73% (40/184) patients stage II and 53.85% (161/299) of patients with stage III disease. 24.29% (17/70) stage II patients without chemotherapy had a return of malignancy and 20.18% (114/23) patients with stage II chemotherapy. 58.40% (73/125) stage III patients without chemotherapy and 50.57% (88/174) of patients with stage III chemotherapy had a return of malignant disease. The five-year period died 53.33% (104/195) of patients without chemotherapy and 44.79% (129/288) of patients with chemotherapy (Table 3).

TABLE 3
THE APPLICATION OF CHEMOTHERAPY AND SURVIVAL

	Chemotherapy (number, percentage and cumulative percentage)	
Survival	Without chemotherapy	With chemotherapy
0–2 years	79 (40.5%; 40.5%)	101 (35.1%; 35.1%)
2.1–5 years	25 (12.8%; 53.3%)	28 (9.7%; 44.8%)
5.1–8 years	51 (26.1%; 79.4%)	82 (28.5%; 73.3%)
8.1–10 years	40 (20.6%; 100.0%)	77 (26.7%; 100.0%)
Total	195 (100.0%)	288 (100.0%)

Discussion and Conclusion

Prognosis of newly diagnosed colorectal cancer (CRC) relies on stage as defined by the UICC-TNM and American Joint Committee on Cancer classifications. The tumor extent, lymph node status, tumor grade and the assessment of lymphatic and venous invasion are still the most important morphological prognostic factors[5]. Although many questions still exist over which patients have benefit from adjuvant treatment, some general principles exist: for stage III (node ??positive) colorectal cancer chemotherapy with fluorouracil and leucovorin has become widely used. For stage II (node ??negative) chemotherapy is rarely used because it is a question of its benefit in these patients. Some authors emphasize that at this stage of chemotherapy is not an advantage, and some notice a small increase in survival rates and reduce relapse rates by using adjuvant chemotherapy with 5-fluorouracil and leucovorin[6–8]. It is generally accepted that there is a cluster of basic histopathological features (T4 tumors, lymphovascular invasion and perineural invasion) that are associated with poor prognosis. About one fifth of the total number of stage II patients recruited to a QUASAR displayed one or more these features[9]. Many previous trials of fluorouracil and folinic acid have included only patients with colon cancer[10]. Therefore, in many clinicians exist a doubt about the benefits of adjuvant chemotherapy for rectal cancer (node ??whether positive or negative). Over decades, 5-fluorouracil (5-FU) was the only cytostatic used in the treatment of CRC. Its using in combination with leucovorin, which enhances its cytotoxic effect, especially in patients with metastatic disease results prolonged survival time in approximately 12 months, which is about twice longer than expected survival with only symptomatic treatment. In recent years, application of two new cytostatic, irinotecan and oxaliplatin, as well as targeted biologic therapy, increased response rate and survival[11–14].

Regarding to the application of chemotherapy, proportional reduction in mortality was greater in the group stage III compared to group stage II, as well as in group with a higher grade in comparison with the group with

low grade and in younger patients than in older age group. There were no differences with regard to the application of chemotherapy and tumor localization. Reducing the return of malignant disease was significantly higher in the group treated with chemotherapy and in patients in stage III in comparison with stage II disease.

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PROCJENA ADJUVANTNE KEMOTERAPIJE U BOLESNIKA S RAKOM DEBELOG CRIJEVA U PRIMORSKO-GORANSKOJ I ISTARSKOJ ŽUPANIJI-DVADESET GODIŠNJA RETROSPEKTIVNA STUDIJA

SAŽETAK

Kolorektalni karcinom je po učestalosti drugi najčešći maligni tumor u razvijenim zemljama, s oko milijun novih slučajeva u svijetu svake godine, praćen visokom stopom smrtnosti. Ispitivali smo stopu preživljavanja i ponovno pojavljivanje (pojava udaljenih metastaza i/ili lokalnih recidiva) bolesnika s rakom debelog crijeva u Primorsko-goranskoj i Istarskoj županiji koji su primali adjuvantnu kemoterapija, u usporedbi s onima koji nisu, u razdoblju od 1980. do 1999. Ova studija obuhvaća 483 pacijenata s rakom debelog crijeva stadija II i III Primorsko-goranske i Istarske županije, koji su bili podvrgnuti resekciji raka debelog crijeva u KBC Rijeka, a zatim se liječeli kemoterapijom (288) ili bez kemoterapije (195). Analizirali smo petogodišnju stopu preživljavanja i recidiva maligne bolesti u skupini liječenoj adjuvantnom kemoterapijom u usporedbi sa skupinom netretiranom kemoterapijom, ovisno o stadiju bolesti, stupnju histološke diferencijacije, dobi i lokalizaciji raka (debelog crijeva ili rektuma). Nakon praćenja od 60 mjeseci umrlo je 44,79% (129/288) bolesnika koji su primali kemoterapiju i 53,33% (104/195) bolesnika koji nisu primili kemoterapiju. Relativni rizik od smrti (iz bilo kojeg uzroka) u skupini liječenoj adjuvantnom kemoterapijom u odnosu na grupu bez kemoterapije je 0,82 ($p<0,008$). Recidiv maligne bolesti u skupini liječenoj adjuvantnom kemoterapijom je iznosio 38,54 (111/288), a u skupini bez kemoterapije 46,15% (90/195). Relativni rizik od recidiva maligne bolesti u skupini s kemoterapijom u odnosu na grupu bez kemoterapije je iznosio 0,78 ($p<0,001$). Nije bilo razlike u učinkovitosti liječenja u odnosu na lokalizaciju tumora, ali postoje razlike u učinkovitosti s obzirom na stanje bolesti, stupanj i dob. Kemoterapija s 5-fluorouracil i leukovorin poboljšava preživljavanje i smanjuje recidiv i pojavu udaljenih metastaza u bolesnika s rakom debelog crijeva stadija II i III.