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Original papers

Long-term results of combined treatment of colorectal cancer

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Colorectal cancer is one of the leading causes of worldwide cancer mortality. Its incidence in Eastern Europe has been growing systematically with the changes in life style adopted from the West.
Material and method. The analysis was based on a prospective study of 1332 patients operated on for primary colorectal cancer at the 1st Department of General and GI Surgery in Cracow, Poland, between the years 1984 and 2000. The same study protocol was applied to all patients included in the study.
Results. In the group of 1332 operated patients, 1262 underwent resective operations, and in the remaining 70 cases palliative procedures, such as intestinal by-pass, colostomy or explorative surgery without tumor removal were performed. 96.3% and 93.2% resective procedures were performed in the colon and the rectal cancer group, respectively.
Five-year survival rates after resection were as follows ($p<0.001$): 86.3% for stage I colorectal cancer, 68.7% for stage II, 47.5% for stage III, and 7% for stage IV.
Chemotherapy administered to patients with colorectal cancer prolonged both survival and the recurrence-free period. The results were statistically significant in the groups with stage II ($p=0.04$) and III ($p=0.05$) colon cancer. In stage IV colon cancer systemic chemotherapy prolonged patient survival, but failed to achieve statistical significance.
In stage II and III rectal cancer, systemic chemotherapy prolonged patient survival , however statistically significant differences were found for stage III rectal cancer acc. to UICC/AJCC. In both colon and rectal cancers chemotherapy had no effect on the recurrence-free period.
Conclusion. We conclude that extended lymphadenectomy and multivisceral resection is extremely important for the curative outcome, also one cannot deny the importance of careful planning of the extent of colorectal surgery, including decisions concerning the endpoints. Combined treatment of colorectal cancer improves long term results.

Key words: colorectal cancer, colon cancer, rectal cancer, combined treatment

Colorectal cancer is one of the leading causes of mortality due to malignancies worldwide. Its incidence in Eastern Europe has been growing systematically, along with the changes in life style adopted from the West. According to the estimates, 1 out of 20 persons from Western Europe will develop colorectal cancer, which accounts for about 200 000 new cases and 110000 deaths *per annum* [1, 2]. Unfortunately, only 50% of patients benefit from surgery – due to the advanced stage of tumor at the time of cancer diagnosis.

The 10-year survival rates for colorectal cancer reported by the German Colorectal Cancer Group and by the investigators from Scotland ranged from 20-63% in patients undergoing resection. Significant differences in survival point to the important role of surgeon's experience and quality assurance [3-5]. The last decade has brought new management strategies to the treatment of colorectal cancer, such as early diagnosis, improved surgical standards, and the introduction of new models of adjuvant chemo- and radiotherapy. Chemotherapy significantly improves 5-year survival rates and the quality of life in stage III colorectal cancer patients [6]. The ongoing debates address the question of the role of chemotherapy in stage II colorectal cancer and the use of adjuvant chemotherapy [7].

The aim of this study was to analyze the prognostic factors of colorectal cancer.

Material and method

The analysis was performed on a group of 1332 patients with histopathologically confirmed primary site colorectal cancer operated in a single institution between the years 1984 and 2000. The same study protocol was applied to all patients enrolled in the study, and all of them were observed prospectively. The group consisted of 576 women and 756 men, aged between 20 and 92 years. Of these 679 patients had a diagnosis of rectal cancer, 620 – of colon cancer and in 33 cases we had confirmed synchronic multifocal cancer in both localizations (Table I).

The stage of colorectal cancer was assessed according to the TNM – UICC/AJCC system. The same pathologist performed all histopathological examinations. Synchronic multifocal cancer was classified according to the stage of the most advanced lesion (Table II).

Curative resection (no residual tumor) was defined as R0; R1 defined resections in which, microscopically, features of the

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Table I. Localization of colorectal cancer

	n	Localization of CRC colon	Rectum	(multifocal) colon and rectum
Men	756	359 (47.5%)	373 (49.3%)	24 (3.2%)
Women	576	261 (45.3%)	306 (53.1%)	9 (1.6%)
Total	1332	620 (46.5%)	679 (51.0%)	33 (2.5%)

residual tumor were left and R2 – resections with macroscopically discernible residual tumor.

All patients enrolled in the study were regularly followed-up every 3-6 months until death. Follow-up was performed according to the accepted study protocol, which included physical examination, colorectal endoscopy, abdominal ultrasonography and chest X-ray examinations. The obtained results were used to calculate long-term survival and to assess recurrence-free time (Table III).

Surgery

Preoperative preparation of patients included large intestine cleansing with osmotic agents, gastrointestinal tract decontamination, and antibiotic prophylaxis. The tumor was removed *en block* with the mesentery and the regional lymph nodes. For left side colon tumors high (close to aorta) ligation of the inferior mesenteric artery was performed.

Rectal cancer patients underwent either total mesorectal excision (TME) or total transverse mesorectal excision (TTME) with segmental sigmoid resection and ligation of the inferior mesenteric artery. Between 1992 and 2000, the "extended lymphadenectomy" (common iliac artery, periaortal, inferior caval vein lymph nodes up to the lower border of the duodenal wall) was performed for rectal cancer. For the colorectal anastomosis either stapling or hand sutures were used.

Adjuvant therapy

The applied models of chemotherapy for colorectal cancer were modified basing on both own observations and on the results reported by other authors (Figure 1).

We used systemic chemotherapy in 684 eligible patients with colon cancer, stage II, III, and IV according to UICC/AJCC.

Between 1984 and 1991, the patients were randomized either to receive chemotherapy or to a no-chemotherapy group (altogether 222 cases). In the subsequent period between 1992 and 2000 all eligible patients were randomized to receive different types of chemotherapy. In the entire study group only 37 patients, who were not eligible or refused to give their consent did not receive chemotherapy (Figure 1).

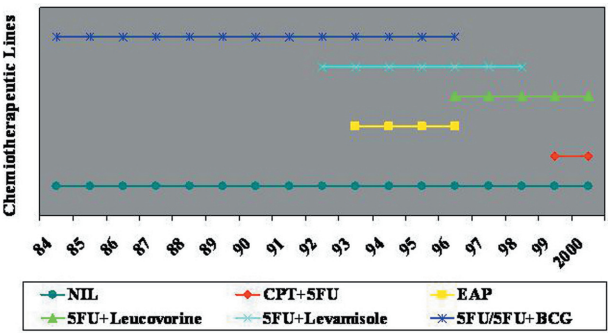

Figure 1. Chemotherapy models in colorectal cancer

Statistical analysis

Data was processed using descriptive statistic methods, and the distributions of the analyzed variables were summarized in tables and curves. Survival rates were presented acc. to the Kaplan-Meier method and comparative analyses were conducted using

Table II. Staging of colorectal cancer (UICC/AJCC) acc to localization

Localization	N		Stage UICC/AJCC I		II		III		IV	
Colon	620	111	(17.9%)	212	(34.2%)	160	(25.8%)	137	(22.1%)
Rectum	679	153	(22.5%)	176	(25.9%)	230	(33.9%)	120	(17.7%)
Multifocal colon and rectum	33	6	(18.2%)	10	(30.3%)	11	(33.3%)	6	(18.2%)
Total	1332	270	(20.3%)	398	(29.9%)	401	(30.1%)	263	(19.7%)

Table III. Study protocol of colorectal cancer diagnostics and treatment

Preoperative diagnostics	Rectoscopy, colonoscopy, USG Manomethry, ERUS (rectal cancer), histopathology Psychological examination
Surgical treatment	Resection or palliative surgical treatment
Combined treatment	Chemotherapy Radiotherapy (preoperative) Radiochemotherapy
Follow up	Physical examination (every 3 months) Abdominal ultrasonography (every 6 months) Chest X-ray , colonoscopy (every 12 months) Rectoscopy, ERUS, histopatholoy – as an option (every 12 months)

the log-rank test. Also, multivariate statistical methods were used with Cox's proportional hazard model to correlate the analyzed variables with the survival times.

Results

Of the1332 operated patients, 1262 underwent resection or amputation (curative /R0/ or palliative /R1/R2/), and in the remaining 70 cases we performed non-resective procedures, such as intestinal by-pass, permanent colostomy without tumor removal or explorative surgery without tumor removal. The resection rate was 96.3% for colon cancer and 93.2% for rectal cancer.

Multivisceral resections were performed in 95 (7.1%) patients with T4 colon cancer invading other organs. Multivisceral resections were more common in patients with primary colon cancer (11.9%) than with rectal cancer (4.3%). Involved organs included the small intestine, the reproductive organs in female patients and the stomach.

Regardless of the resection type and tumor staging, the radicality of surgery was assessed clinically and verified pathologically using the R-classification of Hermanek. Microscopically and macroscopically radical resections were performed in 907 (68.1%) patients – 429 (69.2%) with colon cancer and 451 (66.4%) with rectal cancer (Figure 2).

Macroscopically radical, but microscopically non-radical (R1) resections were performed in 163 patients (12.2%), and palliative (R2) resections in 262 patients (19.7%). In the latter group residual cancer was left beyond the removed organ, or it had metastasized to distant organs or caused peritoneal dissemination.

Although other authors have reported a correlation between tumor localization (colon vs. rectum) and long-term treatment results, we did not observe such a phenomenon. Long-term survival rates for the colon cancer patients were higher (57.5%), as compared to rectal cancer (55.5%), however they failed to achieve statistical significance (Figure 3).

Synchronous cancer in the colon and rectum was detected in 33 (2.55%) colon cancer patients. There was a larger group of 128 (10.15%) patients with detected colon polyps besides the primary cancer. Polyps were removed endoscopically or the patients underwent full-thickness rectal wall resection or intestinal resection, depending on the result of histopathological examination.

The most important prognostic factor determining therapeutic outcome was the cancer stage, classified according to the widely accepted UICC/AJCC system. The use of the same staging system allowed to compare our results with the results reported by other authors. Five-year survival rates demonstrated significant differences between the stage groups ($p<0.001$), and they were: 86.3% for stage I colorectal cancer, 68.7% for stage II, 47.5% for stage III, and 7% for stage IV (Figure 4).

The prognostic role of colorectal cancer staging was confirmed in the multivariate analysis. The most important determinant of survival was the presence of distant metastases (B=0.724 – strongest of all analyzed). Less powerful, but also significant, was the local stage of tumor (B=0.457). Among the anatomopathologic factors we found two important, though less powerful – grading (Table IV) and the presence of nodal metastases (B=0.069) (Table V).

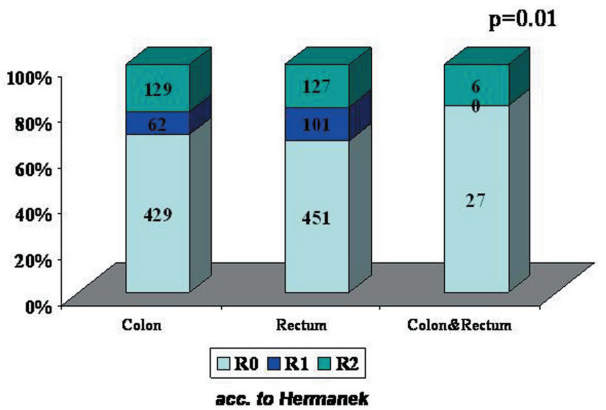

Figure 2. Radicality of surgery verified pathologically using the R-classification of Hermanek

Table IV. Grading of colorectal cancer

	n	Grading G 1	G 2	G 3
Men	756	596 (78.8%)	129 (17.1%)	31 (4.1%)
Women	576	443 (76.9%)	115 (20.0%)	18 (3.2%)
Total	1332	1039 (78.0%)	244 (18.3%)	49 (3.7%)

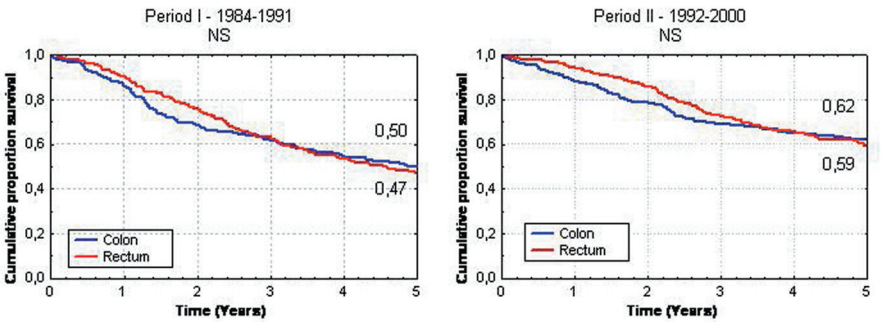

Figure 3. 5-year survival in colon and rectal cancer acc. to extended lymphadenectomy (D 3) in the 2nd period

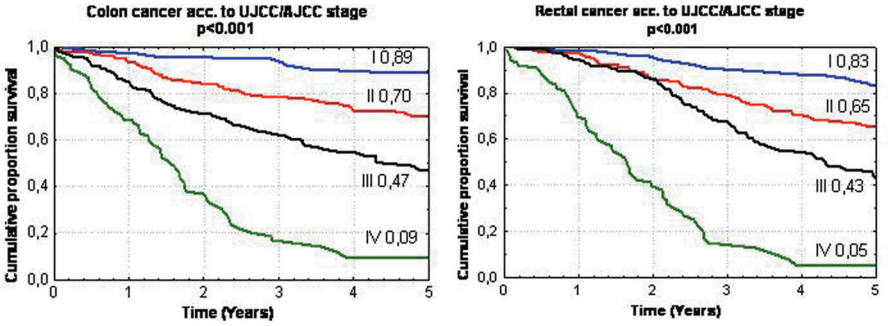

Figure 4. 5-year survival in colorectal cancer acc to the UICC/AJCC stage

Table V. Prognostic factors in long term results of colorectal cancer treatment Cox's analysis p<0.0001

Factor	B	p
M (UICC/AJCC)	0.724845	0.000013
Extended lymphadenectomy (D3)	0.670740	0.000000
R (residual disease)	0.516972	0.000000
T (UICC/AJCC)	0.457743	0.000000
Chemotherapy	0.216628	0.044021
Metastatic lymph nodes	0.069224	0.000000
Number of resected lymph nodes	0.047083	0.000000

In the analyzed patients the extent of lymphadenectomy had a confirmed effect on the long-term results. The mean number of resected lymph nodes increased from 8.62 in the years 1984-1991 to 19.17 in the years 1991-2000. The patients subjected to extended lymphadenectomy achieved longer survival (p<0.001) in both the colon and the rectal cancer groups. The same association was observed for the ratio of resected positive nodes vs. the total number of resected lymph nodes, where a higher rate negatively influenced survival prognosis.

Chemotherapy administered to colorectal patients prolonged long-term survival and recurrence-free time. The results were statistically significant in stage II (p=0.04) and stage III (p=0.05) colon cancer. In stage IV colon cancer systemic chemotherapy prolonged patient survival but failed to achieve statistical significance. In stage II and III rectal cancer, systemic chemotherapy prolonged long-term survival. In both colon and rectal cancer chemotherapy had no effect on the recurrence-free period (Figures 5, 6).

Discussion

The incidence of colorectal cancer has been increasing worldwide, with no significant improvements observed in the long-term treatment results.

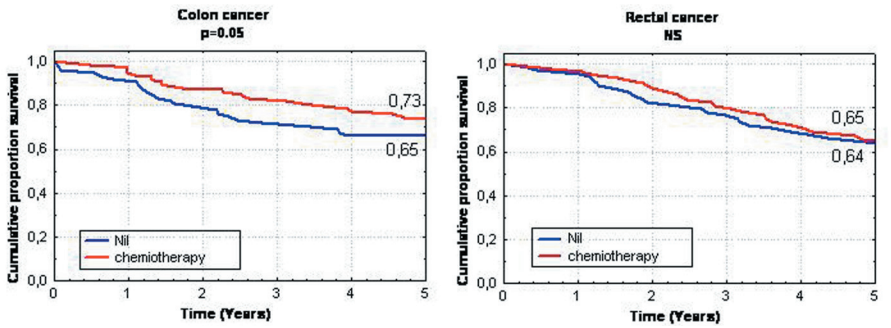

Figure 5. 5-year survival acc. to systemic chemotherapy in stage II UICC/AJCC

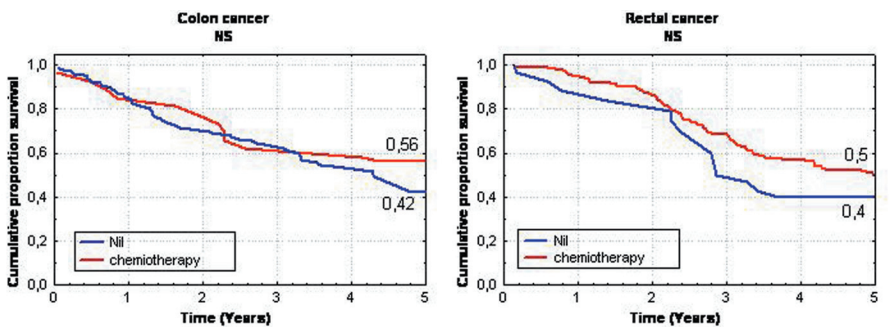

Figure 6. 5-year survival acc. to systemic chemotherapy in stage III UICC/AJCC

It is especially surprising in view of the quite extensive knowledge regarding colorectal cancer pathogenesis, long-term course of the disease, and the availability of the various employed surgical techniques [8].

Our prospective analysis of prognostic factors in colorectal cancer was based on the results of surgical treatment of patients operated in a single institution.

The same study protocol was applied in all cases and histopathological examinations were performed by the same experienced pathologist to avoid interpretation bias.

Until now, none of the medical centers in Poland has opened a multicenter debate to set the guidelines for the management of colorectal cancer, i.e. to follow the example of the Royal College of Surgeons of England [9] or the American Society of Clinical Oncology [10]. Treatment results of colorectal cancer in Poland are worse than those reported in other European Union countries or in the US. Despite the long-term experience with the treatment of this disease there are still controversies as to the surgical techniques, combined treatment or the extent of surgery from minimally invasive to aggressive methods.

In the long-term studies launched in 1984 in our Department, aimed at evaluating the correlations between the surgical techniques and long-term colorectal cancer treatment results we collected data which has allowed us to draw conclusions as to the standards of colorectal cancer treatment. A long period of observation and a large study group allows to perform a reliable evaluation of the changing results related to the applied treatment models [11].

One of the most urgent problems in oncology is the early detection of cancer. The stage of the disease at the time of diagnosis and at the beginning of therapy determines the final outcome [12]. At the time of diagnosis only 50% of colorectal cancer patients can undergo curative resections, while the remaining 50% will not benefit from radical surgery. The differences in the long-term survival figures necessitate the launch of adequate colorectal cancer prevention programs and the introduction of screening procedures capable of detecting colorectal cancer at an early stage, or even at the precancerous stage.

As for today the treatment results of stage I colorectal cancer are satisfying, with 5-year survival ranging from 95 to 98% [13]. However, the diagnosis of colorectal cancer at such an early stage is possible in the course of screening examinations or due to a better understanding of preventive measures by practitioners, who will refer patients for diagnostic tests. In many countries worldwide the high incidence of colorectal cancer has resulted in the launch of screening programs with strong recommendations to cover the entire populace over 50 years of age, if they report with clinical symptoms or have a family history of cancer [14].

Beginning wit the year 1984, all colorectal cancer patients treated at our institution had undergone pre- or intraoperative colonoscopy to confirm the diagnosis, tumor localization, and to detect synchronous lesions. In 5.3% of cases the diagnosis of synchronous lesions changed the surgical tactics and extended resection.

Tumor localization within the colon is an independent prognostic determinant of the therapeutic outcome. The course of disease in colon cancer patients is different than in the case of rectal cancer. Colon cancer patients develop distant metastases and systemic spread occurs more frequently than local recurrence, while rectal cancer accounts for more regional recurrences [15, 16]. The relationship between survival and tumor localization related to the pelvic peritoneum remains controversial [17]. Despite the confirmed influence of tumor localization on long-term treatment results, we have failed to find statistically significant differences regarding this issue. Though 5-year survival of colon cancer patients were higher, reaching 57.5%, no statistical significance was found on comparison with rectal cancer (55.5%).

Tumor staging was comparable in both cancer localizations, as was the number of R0 radical resections, i.e. 66% for colon cancer and 62% for rectal cancer.

The strongest prognostic factor for long-term survival and colorectal cancer recurrence-free time is the tumor stage [18]. Our results are comparable with those reported by other authors. Shelton and Wong report 5-year survival in 74% of stage I colon cancer, 63% in stage II, 46% in stage III and 6% in stage IV [19] – in our study group this corresponds to 89.7% patients with stage I disease, 70.5% in stage II, 48% in stage III and 9% in stage IV. According to the same authors 5-year survival for rectal cancer was 72% for stage I, 54% for stage II, 39% for stage III, and 7% for stage IV, while in our study group we have observed 84.2% for stage I , 66% for stage II, 43% for stage III, and 4% for stage IV.

The strongest determinant of survival in colorectal cancer patients was the presence of distant metastases (M feature), then the local tumor stage (T feature), and lymph nodes metastases (N). In stage III colorectal cancer the presence of lymph node metastases was more significant than the local tumor stage (B=0.116) independently of the primary tumor localization. In stage IV colorectal cancer, of all the anatomopathologic factors only the M feature had prognostic value. Our results correlate with those reported in the literature [20].

Lymph node metastases have a negative effect on the long-term results [21-23]. Significantly more lymph node metastases are observed in patients with tumors penetrating through the *muscularis propria* of the intestinal wall. In these cases both the metastases and the intestinal wall infiltrations are independent prognostic factors [24-26]. Long-term survival prognosis is usually associated with the number of metastatic lymph nodes. The comparative analyses of 5-year survival in 1016 patients with and without metastases reported by Hermanek have reflected statistically significant differences for 5-year survival – reaching 69% for the N0 group, 48% for N1 and 33% for N2 [16].

We found lymph nodes metastases in 401 (30.1%) of the operated patients. The number of positive lymph nodes was an independent prognostic factor of survival

and of the recurrence-free time ($p<0.003$ and $p<0.007$). However, the number of positive lymph nodes and their relation to the number of all resected lymph nodes (colon cancer $p<0.01$, rectal cancer $p<0.003$) was even more significant for survival, which points to the important role of lymphadenectomy, especially in stage III colorectal cancer.

Hojo et al. [27] found the differences in the survival of patients with lymph nodes metastases N1 of 50-55%, and from 22-28% for N2 colorectal cancer patients that is sufficient argument for the extended lymphadenectomy.

According to Hermanek radical resection with simultaneous destruction of distant metastases to liver or adjacent organs using cryo- or thermoablation methods offers results identical with those of radical R0 resection. We have also observed, that such treatment improves the long-term results in stage IV colorectal cancer [28-30].

Extended lymphadenectomy has a significant prognostic value. Although the improved long-term survivals observed after extended lymphadenectomy, which have been presented by the Japanese authors are encouraging, still the observations of Enker et al. show similar long-term survivals and rates of recurrence using standard lymphadenectomy [31]. The benefits of oncological resection are still under discussion. In the analyzed group of patients we have observed a direct correlation between extended lymphadenectomy and survival in colon cancer patients by 11.6% and in rectal cancer by 14.5% ($p<0.001$).

Standard treatment in colorectal surgery combines surgery with chemo- and radiotherapy. In colon surgery systemic chemotherapy already has an established role. According to the NIH Consensus Conference, NCCTG, ECOG, and IMPACT [32] the most relevant chemotherapeutic issue in regard to the outcome is the choice of the apt chemotherapy model. According to Cunningham and Findlay chemotherapy significantly prolongs survival in colon cancer patients, and its role cannot, from now on, be denied. Slevin postulates "No more nihilism in adjuvant chemotherapy in colon cancer" [33, 34].

The analysis of prognostic factors in colorectal cancer would not be complete without mentioning quality assurance. The decisions made by the surgeons and their skills have extreme influence on the therapeutic outcome. Until the extent of the surgery or the need for *en block* resection with adequate tissue margins becomes a standard, the extent of lymphadenectomy, a significant part of colorectal cancer surgery, will be still controversial.

We conclude that extended lymphadenectomy is extremely important for the curative outcome, apart from the undeniable importance of careful planning of the extent of colorectal surgery, including decisions concerning the endpoints.

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