Chapter VII

The addition of low-dose leucovorin to the combination of 5-fluorouracil-levamisole does not improve survival in the adjuvant treatment of Dukes’ C colon cancer.


And the participating surgeons and medical oncologists of the IKN-colontrial Group (see appendix)

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Annals of oncology 11:1-6, 2000
Abstract

Purpose: To assess the effect of the addition of Leucovorin to the combination of 5-Fluorouracil(5-FU)-Levamisole on recurrence risk and overall survival in patients after a resection with curative intent of a Dukes’ C colon cancer.

Patients and Methods: Five hundred patients with Dukes’ C colon cancer were randomly assigned to adjuvant treatment for one year with 5-fluorouracil (450mg/m$^2$ i.v. weekly) and levamisole (150mg p.o. every 2 weeks), the C-group, or with Leucovorin (20mg/m$^2$ i.v.), 5-Fluorouracil and levamisole, the L-group. The median follow-up for patients still alive is 36 months. Four patients were ineligible because of advanced disease at the time of randomisation.

Results: Sixty percent of the patients have completed all courses of chemotherapy. Of the remaining 40% of the patients who did not complete one-year treatment with chemotherapy, 46% discontinued because of toxic and/or emotional reasons. They were equally divided over both treatment groups. The addition of leucovorin increased toxicity (especially mucositis and conjunctivitis) without a significant increase in treatment withdrawal. Five-year disease-free interval (C-group: 49%, L-group: 46%; Log-rank test, $P=0.86$) and overall survival (C-group: 55%, L-group: 59%, log-rank test: $P=0.96$) were very similar in both treatment groups.

Conclusion: The addition of low dose Leucovorin to the combination of 5-fluorouracil and levamisole in a 12-month adjuvant therapy for curatively resected Dukes’ C colon cancer patients does not improve disease-free interval nor overall survival. The addition of leucovorin to the combination of 5-FU-levamisole increases toxicity. Therefore leucovorin-5-FU-levamisole is not recommended in a 12 month adjuvant regimen of Dukes’ C colon cancer.

Introduction

In the Netherlands the incidence of death related colon cancer is second only to lung cancer in men and to breast cancer in women. The publication of the group of Moertel in 1990 was the first one to document that adjuvant treatment with 5-fluorouracil (5-FU) and levamisole (lev) in patients with Dukes’ C colon cancer proved to be effective.¹ A sceptical attitude was
expressed by some European clinicians, but it was generally concluded that this intensive
treatment ought to be considered as standard treatment for Dukes’ C colon cancer, especially
after a final report published in 1995 confirmed the initial favourable results.\textsuperscript{2} Adjuvant
treatment with 5-FU and levamisole reduces the risk of cancer recurrence with 41 percent and
the overall death rate with 33 percent as reported in the intergroup study.\textsuperscript{1} The combination
of 5-FU and levamisole was developed empirically and evidence of an interaction between 5-
FU and levamisole is scarce.

Leucovorin has been shown to enhance the therapeutic effect of 5-FU by inhibition of
thymidilate synthase. The evidence for a synergistic action between 5-FU and leucovorin is
established in many studies.\textsuperscript{3,4} The addition of leucovorin to 5-FU was highly significantly
beneficial over a single-agent 5-FU in terms of tumor response in patients with advanced
colorectal cancer.\textsuperscript{5-7} Generally, tumor response rate improves from 11% to 23% with the
addition of leucovorin to 5-FU. However there is a lack in survival difference between 5-FU
alone and the combination of 5-FU-leucovorin in patients with advanced disease, which might
be due to a large number of non-responders and cross-overs.\textsuperscript{4} Although overall survival may
not be affected in advanced colorectal cancer, the addition of leucovorin to 5-FU might
improve survival in curatively resected Dukes’ C colon cancer. Therefore the addition of
leucovorin to the combination of 5-FU and levamisole might be more effective than the
combination of 5-FU and levamisole alone.

Based on this information we conducted a multi-centre, randomized trial comparing 5-FU and
levamisole to the combination of leucovorin, 5-FU and levamisole in a 12-month adjuvant
treatment regime in patients after curative resection of a Dukes’ C colon cancer.

**Methods**

This trial was initiated by the Comprehensive Cancer Centre North Netherlands and supported
by the Comprehensive Cancer Centres East and South Netherlands. It involved 37
participating hospitals and started in January 1991. Enrolment was completed in December
1997. The protocol was approved by the ethical committees of the participating hospitals.

**Patient selection**

All patients were required to have a curative resection of a Dukes’ C adenocarcinoma of the
colon before participation in this study. No macroscopic or microscopic evidence of residual
disease was allowed. Patients with rectal cancers were excluded. Patients were considered eligible if their age was between 18 and 75. Other exclusion criteria were: WHO performance scale of 1 or higher, other malignancies except for superficial skin cancer or in situ carcinoma of the cervix, patients operated for perforated colon cancer, any indication for metastases elsewhere in the body, abnormal liver tests, high serum BUN or creatinine (> 140mmol/l), low leucocyte count (<3x10^9/l) or low platelet count (<100x10^9/l). Further exclusion criteria were familial polyposis coli syndrome and ulcerative colitis. Eligibility was determined by the oncologists and surgeons, initially checked by data managers and later on verified by review of the operative reports, the pathology reports and the study forms. Informed consent was obtained from all participating patients.

Stratification and Randomization Procedures

Patients were stratified by number of involved lymph nodes (< 4 or ≥ 4 nodes) and by participating hospital. After stratification they were randomly assigned to either adjuvant therapy with 5-FU and levamisole (C-group) or to leucovorin, 5-FU and levamisole (L-group).

Surgical treatment

The surgical resection was performed according to the treatment guidelines of the collaborating Comprehensive Cancer Centres. The resection margins were carefully reviewed by studying the pathological and surgical reports. Cecum cancer and cancer of the ascending colon were treated by a right hemicolecctomy including the right branch of the middle colic artery. A tumor in the right hepatic flexure was resected with an extended right hemicolecctomy including the main branch of the middle colic artery. A colon transversum carcinoma was resected by a transversectomy including the greater omentum. A tumor in the splenic flexure was resected by an extended left hemicolecctomy including the left branch of the middle colic artery. A tumor in the descending colon was resected by a left hemicolecctomy including the left colic artery. Finally a sigmoid tumor was resected by a sigmoid resection including the main branch of the inferior mesenteric artery.

Chemotherapy

Patients started treatment with chemotherapy within 6 weeks after surgery receiving 5-FU by rapid intravenous infusion (450 mg/m^2) daily for 5 consecutive days followed one month later
The addition of leucovorin to 5FU/Levamisole in Dukes C colon cancer

by weekly injections for 48 weeks. Levamisole was given orally in a dose of 3x50mg per day for three days and this was repeated every 2 weeks for 48 weeks. Patients assigned to the leucovorin group received leucovorin in a dose of 20mg/m^2 i.v. one hour before the administration of 5-FU.

Toxicity and Dose Reduction

Toxicity of chemotherapy was determined in accordance to the WHO scales (I-IV) of diarrhoea, stomatitis, nausea, alopecia, neurological disturbances, conjunctivitis and bleeding. Any other type of toxicity was noted separately. Expected toxicity reactions were: stomatitis, diarrhoea, nausea, vomiting, alopecia, and conjunctivitis. Reasons to reduce dosage were: severe leucopenia, thrombocytopenia, stomatitis and diarrhoea. According to our protocol, dose reduction for 5-FU and/or leucovorin of 25% had to be carried out when leucopenia (<3.0x10^9/l) or thrombocytopenia (<100x10^9/l) developed. In case of more serious leucopenia (<2.0x10^9/l) and/or thrombocytopenia (<50x10^9/l) weekly treatment was stopped until side effects subsided. Further treatment with 5-FU was deferred when serious stomatitis or diarrhoea (> 5 times a day) developed. Neurologic symptoms like ataxia, emotional instability and vertigo could be reason to reduce the 5-FU dose. Persistent toxicity attributed to levamisole could lead to temporary discontinuation of levamisole.

Follow-up

Patients were evaluated every three months for the first year, every 6 months the second year and yearly thereafter, for a total of 5 year. Carcino embryonic antigen (CEA) and ultrasonography of the liver were performed on every visit. Routine chest X-ray was performed every 6 months. Colonoscopy or occasionally barium enema were performed after 2 and 5 years. Follow-up visits during chemotherapy were evaluated by the attending physician and consisted of interim-history taking, physical examination, haematological and blood chemistry testing.

Statistical Analysis

Disease-free interval and overall survival data were illustrated using the Kaplan-Meier curves and the log rank test was used to compare these curves. Starting point for these calculations was the time of randomisation. For overall survival, death was the event and alive at last follow-up was a censored observation. For disease-free interval the occurrence of a relapse
was the event while all other situations were considered as censoring. A relapse was defined as a radiological, histological, cytological or clinical evidence for recurrent disease. For the design considerations we expected a five-year survival of 55% in the control arm. To detect improvements of five-year survival of 70% in the L-arm 200 patients per group were required (levels of significance 0.05 two-sided; power 0.90).

**Results**

A total of 500 patients were entered in this study. Four patients were considered ineligible because of a disease more advanced than allowed by the protocol, one was assigned to the 5-FU-levamisole arm and 3 to the leucovorin-5-FU-levamisole arm. These patients were excluded from analysis, leaving a total of 496 patients for the final statistical analysis (Figure1).

The median follow-up time for patients alive is 36 months. Patient and tumor characteristics are presented in Table 1, treatment and outcome characteristics in Table 2. There were no significant differences between both groups regarding the number of lymph nodes, tumor grade, differentiation and depth of invasion.

**Overall survival**

One hundred fifty-three patients died of whom thirteen (13 of 496; 2.6%) of non-cancer related causes, six in the 5-FU-levamisole arm and seven in the leucovorin-5-FU-levamisole arm. Six patients died of myocardial infarction, three in the 5-FU-levamisole arm and three in the leucovorin-5-FU-levamisole arm. Two hundred five patients developed recurrent disease (C-group: 103, L-group: 102) of whom 141 died (C-group: 72, L-group: 69). Two hundred eighty patients are alive without recurrent disease. Overall survival was similar in both arms 55% in the 5-FU-levamisole arm (78 events in 247 patients) and 59% in the leucovorin-5-FU-levamisole arm (76 events in 249 patients; Figure 2, log-rank test: P=0.96).

**Subset analysis**

The number of lymph nodes was the only factor that significantly influenced survival (P<0.01). Treatment with leucovorin-5-FU-levamisole had no advantage in tumors with ≥ 4 positive lymph nodes (log rank test: P=0.51) nor in tumors with < 4 positive lymph nodes (log rank test: p=0.57). Patients younger than 60 years did not have a survival advantage with
leucovorin (log-rank test: \( p=0.74 \)) nor did patients older than 60 years (log-rank test: \( p=0.83 \)). Other factors such as sex, tumor location, tumor differentiation, depth of invasion did not show any survival advantage in the L-arm.

**Disease-free Interval**

Disease-free interval is plotted in Figure 3. At a follow-up period of 60 months, 59 patients were still at risk. One hundred three patients (42\%) in the 5-FU-levamisole arm and 102 patients (41\%) in the leucovorin-5-FU-levamisole arm developed recurrent disease. The five-year disease-free interval is 49\% in the 5-FU-levamisole arm and 46\% in the leucovorin-5-FU-levamisole arm (log-rank test: \( p=0.86 \)). Seventy-two patients (29\%) in the 5FU-levamisole arm and 69 patients (28\%) patients in the leucovorin-5FU-levamisole arm died of recurrent disease.

**Site of first recurrence**

First site of recurrence is presented in Figure 4. Most frequent site of recurrence was the liver (36\%). Type of chemotherapy had no influence on the site of first recurrence (Chi-square test: \( p=0.36 \)).

**Treatment Compliance**

Sixty-one percent of the 5-FU-levamisole arm and 60\% of the leucovorin-5-FU-levamisole arm completed all courses of chemotherapy. Overall 40\% of the patients did not complete the full chemotherapy scheme. Of those patients who did not complete chemotherapy 47.7\% of the 5-FU-levamisole discontinued treatment because of toxic and/or emotional reasons versus 53.8\% in the leucovorin-5-FU-levamisole arm (Chi-Square test: \( p=0.417 \)). Patients who stopped because of toxic reasons, emotional reasons or refusal of further treatment went off-study after an average of 5.7 months.

**Toxicity**

Nausea was the most frequently noted gastrointestinal side effect (78\%). Nearly 27\% of the patients had WHO grade 3-4 nausea or vomiting during chemotherapy without significant differences between both treatment arms. Seven percent of the patients in the C-arm and fifteen percent in the L-arm complained of severe diarrhoea (Chi-square test: \( p=0.06 \)). Twelve percent of the patients noticed mucositis grade 3-4 especially in the leucovorin-5-FU-
levamisole (C-group: 0.9%, L-group: 11.1%; Chi-Square test: p<0.001). Severe leucopenia was rarely (<3%) a clinical problem and mostly manageable after dose reduction or temporary discontinuation. No differences between the treatment arms could be found. Severe thrombopenia was also rarely seen (<2%) but led to treatment discontinuation in two cases.

A significant high incidence of conjunctivitis occurred in the leucovorin-5-FU-levamisole (C-group: 22% vs. L-group 45%, Chi-Square test: p<0.001). In some cases this side effect was permanent and diminished the quality of life substantially. Typical toxicity related to the use of levamisole was change of taste and smell. Sixteen percent of the patients noted anosmia, a foul smell or metallic taste. Although no patient stopped chemotherapy because of this reason, these side effects influenced the general well being of patients substantially. Remarkably, patients receiving leucovorin-5-FU-levamisole noted these side effects more frequently than patients receiving 5-FU-levamisole, although the difference was not significant (C-group: 11% vs. L-group: 20%; Chi-Square test: p=0.07).

Cutaneous lesions, varying from erythema to ulceration, were seen in 24% of the patients and did not differ between both treatment arms. One patient in the L-group suffered from a fixed drug eruption, probably due to levamisole, and discontinued therapy after 7 months. The handfoot syndrome was seen in 12% of the patients. It developed in 9% of patients in the C-group and in 15% of those in the L-group, which did not differ significantly. Alopecia was seen more frequently in the leucovorin-5-FU-levamisole group (C-group: 16% vs. L-group: 34%; Chi-Square test: p=0.008).

Figure 1. Overall data of 50 included patients with Dukes’C colon cancer
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Figure 2: Overall survival. The plot is carries out to 60 months when 67 patients were still at risk.

Figure 3: Disease-free Interval. The plot is carried out to 60 months when 58 patients were still at risk.
Table 1: Patient and tumor characteristics, numbers are given as percentage of total

<table>
<thead>
<tr>
<th></th>
<th>N=249</th>
<th>N=247</th>
<th>5-FU+Levamisole</th>
<th>Leucovorin+5-FU+Levamisole</th>
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<tr>
<td>Age (average in years)</td>
<td>58</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sex (male)</td>
<td>54</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right colon</td>
<td>35</td>
<td>44.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>transversum</td>
<td>3.3</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>left colon</td>
<td>10.4</td>
<td>9.8</td>
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<td></td>
</tr>
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<td>sigmoid</td>
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<td>41.9</td>
<td></td>
<td></td>
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<td>&lt;4</td>
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<td>yes</td>
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<td>5.1</td>
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<tr>
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<tr>
<td>good</td>
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<td>16.1</td>
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<tr>
<td>moderate</td>
<td>60.7</td>
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<tr>
<td>poor</td>
<td>23.6</td>
<td>25.9</td>
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<tr>
<td>Depth of invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mucosa</td>
<td>1.8</td>
<td>2.1</td>
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<td></td>
</tr>
<tr>
<td>muscularis</td>
<td>9.3</td>
<td>10.2</td>
<td></td>
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<tr>
<td>serosa</td>
<td>88.9</td>
<td>87.7</td>
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</table>
The addition of leucovorin to 5FU/Levamisole in Dukes C colon cancer

Table 2: Treatment and outcome characteristics (numbers are given as percentage of total).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>5-FU+Levamisole</th>
<th>Leucovorin+ 5-FU-Levamisole</th>
</tr>
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<tbody>
<tr>
<td>N=247</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Total</td>
<td>31.5</td>
</tr>
<tr>
<td></td>
<td>With tumor</td>
<td>29.1</td>
</tr>
<tr>
<td></td>
<td>Without tumor</td>
<td>2.4</td>
</tr>
<tr>
<td>Alive</td>
<td>68.5</td>
<td>69.5</td>
</tr>
<tr>
<td>Recurrences</td>
<td>Total</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>during chemotherapy</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>After partial chemotherapy</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>after completion</td>
<td>19</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Completed</td>
<td>61</td>
</tr>
<tr>
<td>Did not complete</td>
<td>Death</td>
<td>0</td>
</tr>
<tr>
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<td>Recurrence</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Toxicity</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Psychological/refusal</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>7</td>
</tr>
</tbody>
</table>

Discussion

The results of this study indicated that the addition of low-dose leucovorin to the standard combination of 5-FU and levamisole in the adjuvant treatment of Dukes’ C colon cancer for a period of 12 months is not worthwhile. This addition gave more toxicity but had no influence on treatment withdrawal. Survival in both arms of our study is comparable to that shown by Moertel’s treatment arm.¹ The assumed increase in survival by adding leucovorin was based on the results of early controlled trials.⁵,⁶,⁸-¹⁴ These studies have demonstrated improved tumor response rates in patients with advanced colorectal cancer in the combination of 5-FU and leucovorin (16%-48%), given in various dosage schedules compared to single-agent 5-FU (5%-18%). Besides these substantial objective response rates, the 5-FU-leucovorin regimens were also associated with survival benefit in some of these trials.⁸,⁹,¹² This therapeutic benefit was especially observed in the combination with low-dose leucovorin and in patients with non-measurable metastatic disease. The present study confirms the results of O’Connell’s study that the addition of low-dose leucovorin is not beneficial to the combination of 5-FU-levamisole. In his four-arm study, evaluating the addition of low-dose leucovorin to the
standard treatment of 5-FU-levamisole in a 6 or 12 months regime, he concluded that the 12 months regime was not more effective when low dose leucovorin was added to the standard treatment of 5-FU and levamisole. Information on the optimal duration of treatment has also been acquired. O’Connell et al observed that patients treated during a period of six months with the combination of leucovorin-5-FU-levamisole had a 10% increase in five-year survival compared to patients treated with 5-FU-levamisole alone. This survival difference was absent in patients treated for 12 months. The recently published NCTTG trial reported 317 patients with stage II or III colon cancer treated with 425mg/m$^2$ 5-FU plus 20mg leucovorin (for five days, every four weeks during a period of six months) or observation only. This study showed an advantage for the treatment group both in disease-free survival and overall survival. These studies showed a beneficial effect of 5-FU based adjuvant chemotherapy with a treatment duration of six months only.

Another still unanswered item concerns the optimum doses and administration of leucovorin. In the present study we used low dose leucovorin (20mg/m$^2$i.v.), because the literature known until 1991 showed that results with acceptable toxicity could be obtained with the low-dose regimes. In 1996, Haller described the interim results of a six arm trial (INT-0089 trial) of 3759 patients with stage II and III colon cancer comparing; (a) 5-FU plus high-dose leucovorin versus 5-FU/low-dose leucovorin, (b) 5-FU-levamisole versus 5-FU/high-dose leucovorin and (c) 5-FU/low-dose leucovorin versus 5-FU/low-dose leucovorin and levamisole. A surgery alone group was terminated after the publication of Moertel. Results indicated that there was no substantial benefit from either dosage of leucovorin although it seemed to be that low-dose leucovorin was slightly better. Furthermore, there appeared to be no additional benefit of levamisole but definitive results have to be awaited.

Goldberg showed that other forms of leucovorin (L-Leucovorin i.v., oral (d,l)-leucovorin or (d,l)-leucovorin i.v.) did not have a treatment advantage, although this study involved only patients with advanced disease. Scheithauer et al. reported in 1998, 196 patients with stage III colon cancer treated with adjuvant chemotherapy, in which the study group consisted of patients Dukes’C colon cancer treated adjuvantly with 5-FU-leucovorin both intravenously and intraperitoneally. This combination led to a 43% reduction in mortality compared to a group treated with 5-FU-levamisole for six months. Recently Tepper reported a large trial of 1696 patients with high risk rectal cancer treated with adjuvant radiotherapy combined with; (a) 5-FU;(b) 5-FU-levamisole;(c) 5-FU-leucovorin or (d) 5-FU-levamisole-leucovorin.
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There was no statistically significant advantage to any of the treatment regimens compared with bolus 5-FU alone suggesting that 5-FU is the only really effective agent. The toxicity of the leucovorin-5-FU-levamisole combination in our study is substantial. Especially gastrointestinal, mucocutaneous toxicity and conjunctivitis (with in some cases permanent fibrosis of the lacrimal ducts) disqualifies the triple combination. Toxicity in this combination is recognisable as typically leucovorin amplified 5-FU toxicity, especially with regard to mucositis. That a synergy occurs between the toxicity of levamisole and that of leucovorin in the combination is suggested for the changes in smell and taste and might be considered for the lacrimal gland toxicity. In view of the small differences in survival between the various adjuvant regimes, the optimal adjuvant treatment may be determined by its toxicity profile and treatment duration, as indicated by Haller.17

Conclusions

The addition of low-dose leucovorin to the combination of 5-FU and levamisole does not improve five-year disease-free interval and overall survival in curatively resected Dukes’ C colon cancer patients treated adjuvantly for 12 months, but substantially adds to the toxicity of the regimen. Therefore, leucovorin-5-FU-levamisole is not recommended in a 12-month adjuvant treatment regime of Dukes’ C colon cancer.

Appendix

Participating hospitals and principal investigator(s): Wilhelmina Hospital Assen: Heikens/Blok; University Hospital Groningen: Bleeker/ Plukker/Verschueren/Mulder; “Ziekenhuis Gelderse Vallei” Bennekom: Scheele/Brouwers; “Maasziekenhuis” Boxmeer: Liem/Bork; “Ignatius”Hospital Breda: Nuytinck/Ras; Hospital “het Atrium” Brunssum: vd Bijl/Wals; Streekziekenhuis Coevorden: Maier/Runhaar; Daniel den Hoed Hospital Rotterdam: Rakic/Stoter; Delfzicht Hospital Delfzijl: Kouwenhoven/Roenhorst; Groot Ziekenhasthus Den Bosch: Willekens/Burghouts; Leyenburg Hospital Den Haag; ; Slingerland “Hospital” Doetinchem: van Lammeren/Kateman; Hospital “Sionsberg” Dokkum: van Hillo/Cremer; Hospital “Nij Smellinghe” Drachten/Voesten/Numan; IJsselmeer Hospital Emmeloord:Hanssen/de Koninck; Schepen Ziekenhuis Emmen: vd Zouwen/de Haan; St. Anna Hospital Geldrop: Heyl/Smeets; St. Jansdal Harderwijk: Beck/v Nierop; Hospital “Oranjuegoord” Harlingen: Heevel/van Houte; Hospital “de Tjongerschans” Heerenveen: Bijlsma/Tel; “Bethesda” Hospital Hoogeveen: van de Broek/Wichers; Martini Hospital Groningen:Oeseburg/Bong/Piersma; Medical Center Leeuwarden:Roy van Zuidewijn/van Veelen; Meppel: Jansen- de Varebeke/de Korte; Canisius Hospital Nijmegen: Bruggink/Oosten/ Turnhout; Radboud Hospital Nijmegen: Wobbes/Wagener; Sint Anna Hospital Oss; Luning/Schade; Schieland Hospital Schiedam: Schaftenaar/Braun; Antonius Hospital Zuid-West Friesland Sneek: v Driel/Verkuijl; Refaja Hospital Stadskanaal: Plantinga/Smilde; “Tweesteden Ziekenhuis” Tilburg: Roukema/Dolman; St. Joseph Hospital Veldhoven: den Butter/Vreugdenhill; “Het Ziekenhuis” Velp; Gobardhan/vd Berg; Sint Elisabeth Ziekenhuis Venray:vd Pol/Nio; Sint Lucas Hospital Winschoten: Chin-A-Paw/Staal; “Streek ziekenhuis” Zevenaar: van Wijk/Meiboom; Sophia Hospital Zwolle; v Rooyen/Coenen.
Aknowledgements:

This study was supported with a grant from the Netherlands Cancer Foundation (KWF-CKVO; IKN trial 90-11). The authors would like to thank Mrs. Thea Scholtens and Mr. A. Scheper for their enormous help in collecting the data. We also thank all participating surgeons and medical oncologists for their effort.

References


Prospectively randomized North Central Cancer Treatment Group trial of intensive-
course Fluorouracil combined with the L-isomer of intravenous Leucovorin, oral 
leucovorin, or intravenous leucovorin for the treatment of advanced colorectal cancer. 

Combined intravenous and intraperitoneal chemotherapy with fluorouracil + leucovorin 
vs fluorouracil + levamisole for adjuvant therapy of resected colon carcinoma. 

Adjuvant posoperative fluorouracil-modulated chemotherapy combined with pelvic 