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Research Paper

Incomplete 5-FU based adjuvant chemotherapy in patients with stage III colon cancer significantly prolongs overall survival

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ABSTRACT

Purpose: Adjuvant chemotherapy is considered standard of care in patients with stage III colon cancer. Because of different reasons in many patients not all chemotherapy cycles are completed or chemotherapy is completely withheld.
Methods: We analyzed the data of 215 consecutive patients with UICC stage III colon cancer between 01/1997 and 01/2010. Incomplete adjuvant chemotherapy was defined as completion of less than 2/3 of the planned chemotherapy cycles.
Results: Of 104 patients with adjuvant therapy, 46 patients had incomplete chemotherapy. We were able to show a statistically significant survival advantage concerning disease-free 5-year-survival between patients with incomplete and without chemotherapy (76% vs. 53%, (p = 0,003). This superior effect was even more pronounced with regard to overall 5-year-survival with 82% vs. 57% (p = 0,001). No statistically significant differences were shown between complete and incomplete adjuvant chemotherapy.
Conclusions: Although our study was not randomized we were able to show a highly statistically significant survival advantage of incomplete adjuvant chemotherapy in patients with UICC stage III colon cancer. If side effects of chemotherapy are tolerable for the patient, temporary limitations of the individual quality of life are outweighed by the survival advantage even if therapy is not completed.

1. Introduction

With an incidence of 13% colorectal cancer is the second most frequent carcinoma with also the second highest cancer associated mortality of 13% in Europe [1,2]. In the past 25 years the carcinoma had a continuously growing incidence of up to 34% in males and 26% in females [3]. Absolute survival increased to 78% in large population based studies [4,5].

Current national and international guidelines recommend adjuvant chemotherapy in patients with colon cancer UICC stage III [6–8].

Although there is level I evidence for adjuvant chemotherapy in stage III the clinical experience is different: a large number of patients only receive incomplete or even no adjuvant therapy at all. Causes for incomplete treatment included physical frailty, toxicity and a lack of social and psychological support. In the present study we did an analysis of the data of all patients with colon cancer UICC stage III that had R_0-resection in the department of surgery of a maximum care provider for about 1, 5 million citizens. The main focus of the study was on long-term survival and the influence on survival of incomplete adjuvant therapy.

2. Material and methods

2.1. Patients

Between January 1997 and January 2010 a total of 237 patients had curative resection with stage III colon cancer. Only R_0-resected patients with radical lymphadenectomy, complete mesocolic resection and the removal of more than 12 lymph nodes were included in the statistical analysis. We did not include data of patients with rectal cancer or hereditary cancers. With regard to the localization of the cancers there was a higher prevalence of cancers of the left colon (Table 1). Statistical analysis revealed that there

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Table 1
Primary carcinomas.

Primary carcinoma n (%)	Total n = 215	No CTx n = 111	Incomplete CTx n = 46	Complete CTx n = 58
Caecum	34 (15,8)	20 (18,0)	4 (8,7)	10 (17,2)
Colon ascendens	23 (10,7)	16 (14,4)	2 (4,3)	5 (8,6)
Hepatic flexure	25 (11,6)	13 (11,7)	7 (15,2)	5 (8,6)
Colon transversum	12 (5,6)	5 (4,5)	2 (4,3)	5 (8,6)
Splenic flexure	14 (6,5)	9 (8,1)	3 (6,5)	2 (3,4)
Colon descendens	17 (7,9)	11 (9,9)	2 (4,3)	4 (6,9)
Sigmoid Colon	86 (40)	37 (33,3)	22 (47,8)	27 (46,6)

was no difference in survival between the different cancer localizations. The study was carried out in accordance with the Declaration of Helsinki. All patients gave informed consent before inclusion into the study.

2.2. Methods

The data was compiled in a prospective tumor registry of the department of surgery. This study is a retrospective data analysis. Data was analyzed after allocation of the patients to three prespecified groups: complete adjuvant chemotherapy, incomplete adjuvant chemotherapy (less than 2/3 of the planned cycles) and no adjuvant chemotherapy. The Tables 2 and 3 show general demographic data and data on the different chemotherapy regimens. We wanted to investigate on the question if patients with incomplete adjuvant chemotherapy had better overall and disease-free survival compared to patients with no adjuvant chemotherapy.

The statistical analysis was done with SPSS (Windows Version 22). The statistical significance regarding the distribution of variables within the patient cohort was analyzed with the Chi-Square test (Pearson). We defined a p-value of less than 0,05 to be statistically significant. Long-term survival was calculated with the use of the Kaplan-Meier method. The log rank test was used to compare survival distributions ($p < 0,05$ = statistically significant).

3. Results

3.1. General patient data

Between 01/1997 and 01/2010 a total of 791 patients had oncologic resection of colon cancer. In 237 patients (43%) a stage III carcinoma was found. Stage IIIb had the highest prevalence (n = 162) followed by stages IIIc (n = 46) and IIIa (n = 29). The median age of the patients was 64 ± 22 (31–93) years. The subgroup-analysis of mortality between UICC stages IIIa-c did not show any statistically significant differences.

A total of 130 (55%) patients were male, while 107 (45%) were female. Less than half of the patients (n = 104; 48%) of the overall cohort received adjuvant chemotherapy. Among these patients with any adjuvant therapy only 58 patients had complete adjuvant therapy, which accounts for only 27% of patients with completion of adjuvant therapy. The median interval between operation and initiation of adjuvant chemotherapy was 4,5 weeks. In Table 4 the reasons for incomplete chemotherapy or no adjuvant therapy at all are presented.

We excluded 15 patients from the statistical analysis because of perioperative mortality and further 7 patients that only had palliative resection. Thus 215 patients met the inclusion criteria and were included in the statistical analysis.

3.2. Reasons for missing adjuvant chemotherapy

A bad performance status and severe comorbidities were the main reasons that patients did not have any adjuvant chemotherapy (45%). Another reason with high prevalence was patient refusal from chemotherapy (34%). Most patients opted against adjuvant therapy because of advanced age, bad social and/or psychological support and personal reasons (Table 4). In the patient group with incomplete adjuvant chemotherapy therapy associated toxicities were the main reasons for incomplete therapy (67%). Table 5 shows the toxicities classified according to the WHO-classification (grade I-IV) and the average number of cycles of the different chemotherapies. We did not observe any differences concerning the average number of cycles.

Different from patients with incomplete chemotherapy we observed no adverse events in 21 patients (36%) in the group of patients with complete chemotherapy. Also in the comparison of toxicities grade II-IV between the groups the prevalence of adverse events was significantly higher in the group with incomplete chemotherapy. This was especially the case for grade III and IV toxicities that were most often associated with dose reductions or modifications of the chemotherapy cycles or termination of chemotherapy (7% vs. 41%). This difference was statistically

Table 2
Chemotherapy protocols.

Protocol	Drugs and cycles
Capecitabine mono	Capecitabine (Xeloda) 2 × 1250 mg/m^2 p.o. days 1–14, every 3 weeks total: 8 cycles
Folfox 4	Folinic acid 200mg/m2 as 2h infusion, days 1 and 2 + bolus 5-FU (400 mg/m^2), followed by 5-FU 600 mg/m^2 as 22h infusion days 1 and 2 + Oxaliplatin 85 mg/m^2 as 2h-infusion, days 1 and 15), total: 12 cycles/6 months
Folfox 6	Oxaliplatin 85 mg/m^2 i.v. and folinic acid 400 mg/m^2 as 2h infusion + bolus 5-FU 400 mg/m^2 followed by 5-FU 2400 mg/m^2 i.v. for 46 h every 2 weeks total: 12 cycles/6 months
5-FU/LV (Mayo)	bolus 5-FU 425 mg/m^2/d i.v days 1–5 and bolus folinic acid 20 mg/m^2/d i.v. days 1–5 4 weeks no chemotherapy total: 6 cycles
Moertel protocol	bolus 5-FU 450 mg/m^2 i.v. days 1–5, 4 weeks no chemotherapy followed by once weekly bolus 5-FU 450 mg/m^2 i.v. for 48 weeks Levamisole p.o. 50 mg every 8h for days 1–3 every 2 weeks for 1 year