Treatment and complications in elderly stage III colon cancer patients in the Netherlands

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Background: We evaluated which patient factors were associated with treatment tolerance and outcome in elderly colon cancer patients.

Design: Population-based data from five regions included in the Netherlands Cancer Registry were used. Patients with resected stage III colon cancer aged ≥75 years diagnosed in 1997–2004 who received adjuvant chemotherapy (N = 216) were included as well as a random sample (N = 341) of patients who only underwent surgery.

Results: The most common motives for withholding adjuvant chemotherapy were a combination of high age, co-morbidity and poor performance status (PS, 43%) or refusal by the patient or family (17%). In 57% of patients receiving chemotherapy, adaptations were made in treatment regimens. Patients who received adjuvant chemotherapy developed more complications (52%) than those with surgery alone (41%). For the selection of patients who had survived the first year after surgery, receiving adjuvant chemotherapy resulted in better 5-year overall survival (52% versus 34%), even after adjustment for differences in age, co-morbidity and PS.

Conclusion: Despite high toxicity rates and adjustments in treatment regimens, elderly patients who received chemotherapy seemed to have a better survival. Prospective studies are needed for evaluating which patient characteristics predict the risks and benefits of adjuvant chemotherapy in elderly colon cancer patients.

Key words: adjuvant chemotherapy, colon cancer, elderly, recurrence, survival, toxicity

introduction

In the Netherlands, colon cancer is the third most common cancer in males and second most common cancer in females, with almost 8000 new cases and almost 3900 deaths in 2010 (source: Statistics Netherlands), of whom more than half were aged >75 years (source: Statistics Netherlands).

Since the mid-1980s, improvement in colon cancer survival has been achieved among patients with lymph node-positive disease, in particular due to advances in adjuvant treatment [1, 2]. The benefit of adjuvant treatment with 5-fluorouracil (5-FU)-based chemotherapy for younger stage III colon cancer patients is well established [3], in more recent years in combination with oxaliplatin [4]. An equal benefit was reported for selected elderly patients with stage III colon cancer with 5-FU-based chemotherapy [5, 6]. For oxaliplatin-containing chemotherapy, the benefit for elderly patients was less clear and higher toxicity levels were reported [7, 8].

According to the evidence-based national Dutch clinical practice guidelines, adjuvant chemotherapy is nowadays recommended for stage III colon cancer. In case of high age and/or co-morbidity, monotherapy with capecitabine or oral uracil and tegafur plus leucovorin can be chosen instead of combination chemotherapy (www.oncoline.nl). A recent Dutch national study showed an increase in adjuvant chemotherapy administration from 19% in 1989–1993 to almost 80% in 2004–2006 in colon cancer patients aged <75 years [9]. However, for patients aged ≥75 years, a much smaller proportion of patients received adjuvant chemotherapy: only 23% in 2007–2009 [10].

Population-based studies have shown that many elderly patients with stage III colon cancer do not receive adjuvant chemotherapy [9, 11, 12]. Likely explanations why elderly patients receive less adjuvant chemotherapy are frailty, poor functional status or the presence of co-morbidities that may lead to more toxicity [13, 14]. In addition, higher postoperative mortality and morbidity rates are also reasons for withholding adjuvant chemotherapy [15, 16]. In addition, elderly seem less willing to accept possible side-effects associated with adjuvant treatment compared with younger patients and are concerned...
about a negative influence of adjuvant chemotherapy on the quality of life [17, 18].

In this study, we evaluated which patient factors were associated with receiving adjuvant chemotherapy, treatment tolerance and outcome in elderly stage III colon cancer patients.

Methods

data collection

Population-based data from five regional Dutch cancer registries were used, covering a population of around nine million inhabitants. These registries reflect the national population and record data on patients newly diagnosed with cancer in all hospitals in their region. Trained registrars routinely collect data on patient and tumour characteristics like date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3) (Fritz), histology, stage [Tumour Lymph Node Metastasis (TNM) classification] (UICC), grade and primary treatment, directly from the medical records. For the present study, patients aged ≥75 years with resected primary colon cancer stage III (C18.0-C18.9) diagnosed in the period 1997–2004 were included. Patients diagnosed at autopsy were excluded. For each regional cancer registry, all patients aged ≥75 years who underwent resection for colon cancer and received adjuvant chemotherapy were included (total N = 369). As most patients aged ≥75 years did not receive adjuvant chemotherapy in the included period (85–90%), a random sample of a similar number of patients who did not receive adjuvant chemotherapy was selected (N = 375). Unfortunately, part of the medical records could not be retrieved or were incomplete, leaving 216 patients who received adjuvant chemotherapy and 341 patients who only underwent surgery. Age was classified as 75–79, 80–84, and ≥85 years. Stage was based on the pathological TNM classification. The vital status of all patients was obtained actively on a regular basis from the automated database of the municipal registries.

Additional data on co-morbidity according to the Adult Co-morbidity Evaluation 27 (ACE-27) classification [19], World Health Organization (WHO) performance status (PS), living alone, living independently, detailed information on the type of treatment, number of cycles, motive for no chemotherapy, adaptations and underlying motives, grade 3 or 4 toxicity according to the Common Toxicity Criteria (version 2003) and date of recurrence were gathered from the medical records (from the departments of surgery as well as from the departments of medical oncology).

The ACE-27 index is a validated 27-item co-morbidity index for patients with cancer. These co-morbid conditions were gathered from the medical records; each condition was graded to severity and classified [17, 18]. Additional data on co-morbidity according to the Adult Co-morbidity Evaluation 27 (ACE-27) classification [19], World Health Organization (WHO) performance status (PS), living alone, living independently, detailed information on the type of treatment, number of cycles, motive for no chemotherapy, adaptations and underlying motives, grade 3 or 4 toxicity according to the Common Toxicity Criteria (version 2003) and date of recurrence were gathered from the medical records (from the departments of surgery as well as from the departments of medical oncology).

The differences between subgroups were tested using chi-square tests. Motives for suboptimal treatment and treatment adaptations were described. Toxicity and recurrence rates were described according to the treatment group.

The time to recurrence was defined as the time from diagnosis to date of recurrence. Survival time was defined as the time from diagnosis to death or 1 January 2010 for the patients who were still alive. The differences in survival between the two treatment groups were analysed separately for the first year after diagnosis (because this is especially defined by treatment-related mortality and co-morbidity) and 5-year survival for those who had survived the first year (because this might reflect the effect of adjuvant chemotherapy on recurrence/progression). Crude 5-year survival was calculated and a log-rank test was carried out to compare survival proportions. A multivariable proportional hazards regression analysis was used to discriminate independent risk factors for death of patients who survived the first year after diagnosis (SAS system 9.2, SAS Institute, Cary, NC). The P values of <0.05 were considered statistically significant.

Results

treatment and completion

The median age of the study population was 78 years in the adjuvant chemotherapy group and 82 years in the group who did not receive adjuvant chemotherapy. Three quarters of all patients suffered from co-morbidity at the time of diagnosis. The most common co-morbid conditions were cardiovascular disease (67%), diabetes mellitus (16%) and pulmonary disease (10%). Of those with known PS, 94% had a good PS in the adjuvant chemotherapy group and 82 years in the group who did not receive adjuvant chemotherapy. Three quarters of all patients suffered from co-morbidity at the time of diagnosis. The most common co-morbid conditions were cardiovascular disease (67%), diabetes mellitus (16%) and pulmonary disease (10%). Of those with known PS, 94% had a good PS in the adjuvant chemotherapy group and 82 years in the group who did not receive adjuvant chemotherapy. However, the PS was often missing (27% in the adjuvant chemotherapy group versus 35% in the group not receiving adjuvant chemotherapy) (Table 1).

Nine percent of elderly patients with stage III colon cancer underwent emergency surgery. These patients experienced...
more treatment-related complications compared with the patients who underwent elective surgery (59% versus 38%) and 51 patients (9%) underwent re-operation.

The large majority of patients receiving chemotherapy received 5-FU / leucovorin (87%); 4% received capecitabine monotherapy and only 1% received combination chemotherapy containing capecitabine and oxaliplatin.

The most common motives for not receiving chemotherapy for those who had survived at least 30 days after surgery were a combination of high age, co-morbidity and poor PS (43%) or refusal by the patient or family (17%). In 8% of patients, a wait-and-see policy was followed and 2% of patients did not receive adjuvant chemotherapy because of short life expectancy. The motive for not receiving adjuvant chemotherapy was unknown in 28% of the patients.

In 57% of patients receiving chemotherapy, at least one adaptation was made in dose (18%), number of cycles (28%), type of chemotherapy (3%) or time between courses of chemotherapy (23%). The dose of chemotherapy was reduced before the start of treatment in five patients (3%). Adaptations were not significantly associated with age or co-morbidity.

toxicity

Over half (52%) of the patients who received adjuvant chemotherapy developed any toxicity during treatment versus 41% of patients who did not receive adjuvant chemotherapy (Table 2). In the adjuvant chemotherapy group, more gastrointestinal toxicity (13% versus 1%) occurred; only 3% of patients developed haematological toxicity. Seven percent of patients not receiving adjuvant chemotherapy had died due to (postoperative) complications, mainly in the first year after surgery, whereas this was almost zero among those receiving adjuvant chemotherapy. Besides, among patients who did not receive adjuvant chemotherapy more wound infections were seen (8% versus 4% in the adjuvant chemotherapy group).

Table 2. Toxicity in colon cancer patients aged ≥75 years according to adjuvant chemotherapy administration (N = 557)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>No adjuvant chemotherapy (N = 341)</th>
<th>Adjuvant chemotherapy (N = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>None</td>
<td>200 59</td>
<td>104 48</td>
</tr>
<tr>
<td>Hematological</td>
<td>3 1</td>
<td>7 3</td>
</tr>
<tr>
<td>Wound infection</td>
<td>27 8</td>
<td>8 4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 1</td>
<td>2 1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 1</td>
<td>5 2</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>4 1</td>
<td>27 13</td>
</tr>
<tr>
<td>Abdominal</td>
<td>9 3</td>
<td>8 4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>18 5</td>
<td>7 3</td>
</tr>
<tr>
<td>Trombo-embolism</td>
<td>5 1</td>
<td>5 2</td>
</tr>
<tr>
<td>Neurological</td>
<td>12 4</td>
<td>8 4</td>
</tr>
<tr>
<td>Other</td>
<td>19 6</td>
<td>19 9</td>
</tr>
<tr>
<td>Death</td>
<td>24 7</td>
<td>1 0</td>
</tr>
<tr>
<td>Unknown</td>
<td>13 4</td>
<td>15 7</td>
</tr>
</tbody>
</table>

In patients who received adjuvant chemotherapy, toxicity was not influenced by age and co-morbidity (data not shown).

treatment outcome

Of all 517 patients with stage III colon cancer who had survived at least 30 days after surgery, 211 patients (41%) developed recurrence of disease, independently of chemotherapy administration (Table 3). The median time to recurrence was 420 days (4–2629 days); there was no significant difference between both the treatment groups.

For patients not receiving adjuvant chemotherapy, mortality in the first year after surgery was relatively high (12%, 16% and 33% after 30 days, 90 days and 1 year, respectively). For those receiving adjuvant chemotherapy, these rates were 0%, 0.1% and 6%, respectively.

Five-year survival for the selection of patients who had survived the first year after surgery remained significantly better for patients who received adjuvant chemotherapy (52% versus 34%, P < 0.0001; Figure 1). This effect remained significant after adjustment for differences in age, co-morbidity and PS [hazard ratio, HR = 0.73 (95% confidence interval (CI) = 0.55–0.98). Other independent negative prognostic

![Table 3. Local and distant recurrence in colon cancer patients who survived at least 30 days after surgery according to adjuvant chemotherapy administration (N = 517)](table3)

![Figure 1. Overall survival in patients with stage III colon cancer aged ≥75 years who had a survival of at least 1 year after diagnosis, according to adjuvant chemotherapy administration (N = 428) (P < 0.0001); CT: chemotherapy.](figure1)
factors in multivariate survival analysis were high age (>80 years) and severe co-morbidity (Table 4).

**discussion**

The results of this study have shown that the most common motives for withholding adjuvant chemotherapy were a combination of high age, co-morbidity and poor PS or refusal by the patient or family. Although only relatively fit patients were selected for adjuvant chemotherapy, over half of the patients receiving chemotherapy could not complete the full treatment, and more gastrointestinal complications occurred. Receiving adjuvant chemotherapy resulted in better 5-year overall survival, even after excluding the patients who had died within 1 year after diagnosis and after adjustment for differences in age, co-morbidity and PS.

Previous studies have shown that elderly colon cancer patients often received less adjuvant chemotherapy compared with younger patients [20–22]. Although adjuvant chemotherapy is increasingly administered in elderly colon cancer patients in the last decade, elderly patients aged ≥75 years still infrequently received adjuvant treatment in 2004–2006 (19%) [12]. Our study has shown that major motives for withholding adjuvant treatment included the presence of co-morbidities, poor PS, high age and patient preferences. Previous studies have shown that elderly patients are more concerned about the negative influences on the quality of life caused by adjuvant chemotherapy and they seem less willing to accept possible side-effects caused by adjuvant treatment, resulting in more refusal by patients to receive adjuvant treatment [17, 18]. As recommended by experts of the International Society for Geriatric Oncology (SIOG), the therapeutic decisions with regard to the choice and duration of adjuvant therapy should be reached jointly by patient and physician, taking into account individual preferences and coexistent co-morbidities [23].

Confirmed by our results, some other population-based studies have also shown that adjuvant chemotherapy has an independent prognostic impact in elderly patients with colon cancer [24, 25]. In a meta-analysis of randomized trials, smaller survival differences were found between adjuvant chemotherapy and surgery alone and overall survival was higher in both the groups compared with our results (the 5-year overall survival was 71% for those who received adjuvant therapy, when compared with 64% for those untreated) [26]. The difference in overall survival is probably caused by the inclusion of only relatively fit elderly patients in clinical trials and the inclusion of patients with stage II colon cancer in this meta-analysis.

Due to the population-based nature of our data, we do not know to what extent the positive prognostic impact was caused by selection of the ‘fitter’ patients for adjuvant chemotherapy or other factors not included in our analysis. Since our study was retrospective, we could only partly adjust for differences in patient characteristics (age, gender, co-morbidity, and PS).

The recurrence rate in our study was 41% and did not differ between patients receiving and those not receiving adjuvant chemotherapy. Our recurrence rate was slightly higher than in previous studies that reported recurrence rates of 33% and 31% [27, 28]. However, these studies were not specifically designed for the elderly and included mostly younger patients. In our study, no difference in the recurrence rate was found between both the patient groups, although this might be biased due to more unknown data on the recurrence rate and less active follow-up of patients not receiving adjuvant chemotherapy.

In our study, the large majority of patients were treated with 5-FU/leucovorin, since this was the standard adjuvant treatment for stage III colon cancer in the Netherlands until 2004 (www.oncoline.nl). The randomized, controlled trials have shown that the addition of oxaliplatin has a positive effect on survival and the addition of oxaliplatin to 5-FU/leucovorin became the standard treatment for colon cancer patients in the Netherlands in 2004 (www.oncoline.nl) and was, therefore, only applied at the end of our study. The addition of oxaliplatin is likely to improve survival [29], also in the elderly [30], although the addition of oxaliplatin offers only a small incremental benefit [31] and it may enhance toxicity. Since only relatively fit elderly are included in clinical trials, the effect of adding oxaliplatin to the treatment of elderly with stage III colon cancer in everyday clinical practice should, therefore, be investigated in future studies.

Our study shows that patients who received adjuvant chemotherapy belonged to a selected, relatively fit group.

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**Table 4.** Overall survival (crude and multivariable) for stage III resected colon cancer patients aged ≥75 years diagnosed between 1997 and 2004 who survived 1 year after diagnosis (N = 428)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>N</th>
<th>Crude 5-year survival (%)</th>
<th>Adjusted hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>428</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>227</td>
<td>34**</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>201</td>
<td>52</td>
<td>0.73 (0.55–0.98)*</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>266</td>
<td>49**</td>
<td>1.0</td>
</tr>
<tr>
<td>80–84</td>
<td>100</td>
<td>35</td>
<td>1.39 (1.02–1.89)*</td>
</tr>
<tr>
<td>≥85</td>
<td>62</td>
<td>29</td>
<td>1.64 (1.13–2.39)*</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>184</td>
<td>42</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>244</td>
<td>43</td>
<td>0.90 (0.70–1.15)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>114</td>
<td>52</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild</td>
<td>129</td>
<td>41</td>
<td>1.19 (0.87–1.62)</td>
</tr>
<tr>
<td>Moderate</td>
<td>108</td>
<td>43</td>
<td>1.01 (0.78–1.53)</td>
</tr>
<tr>
<td>Severe</td>
<td>68</td>
<td>32</td>
<td>1.54 (1.07–2.22)*</td>
</tr>
<tr>
<td>Performance status (PS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>259</td>
<td>46</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate/poor</td>
<td>46</td>
<td>35</td>
<td>1.05 (0.71–1.55)</td>
</tr>
<tr>
<td>Unknown</td>
<td>123</td>
<td>38</td>
<td>1.16 (0.88–1.53)</td>
</tr>
<tr>
<td>Period of diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997–2000</td>
<td>168</td>
<td>42</td>
<td>1.16 (0.88–1.53)</td>
</tr>
<tr>
<td>2001–2004</td>
<td>260</td>
<td>43</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Adjusted for all variables listed.

**P < 0.0001.

**P < 0.05.
Those who did not receive adjuvant chemotherapy had a worse PS and more co-morbidity compared with patients who received adjuvant chemotherapy. In the group without adjuvant chemotherapy, 7% of patients died due to postoperative complications, mainly in the first year after surgery, while this was almost none in the adjuvant chemotherapy group. Besides, significantly more wound infections occurred in these patients than in the adjuvant treatment group. Wound infection itself and dying before the start of adjuvant chemotherapy are likely underlying reasons why these patients did not receive adjuvant chemotherapy.

In our study, mortality and morbidity in the first year after surgery were indeed relatively high in the group not receiving adjuvant chemotherapy. This is probably related to the selection of fit patients without postoperative complications for adjuvant chemotherapy. In a large population-based study with data of 9379 patients with stage I-III colorectal cancer, Dekker et al. showed mortality rates of 23% 1 year after surgery for elderly patients >75 years. In the latter study, 97% of these patients received only surgery without adjuvant chemotherapy. They also concluded that elderly colorectal cancer patients who survive the first year have the same cancer-related survival as younger patients and that decreased survival in the elderly is mainly due to the differences in early mortality [32].

In our study, by selecting patients who had survived the first year after diagnosis, we tried to partly overcome the selection bias caused by selecting relatively fit patients for adjuvant chemotherapy. Even for patients who had already survived the first year after diagnosis, 5-year survival was significantly better for patients receiving adjuvant chemotherapy and this difference remained after adjustment for differences in age, co-morbidity and PS. This difference is expected to be partly due to the beneficial effect of chemotherapy, although selection bias of the fittest patients could not completely be adjusted for.

Although only relatively fit elderly were selected for chemotherapy, still 52% developed any grade 3 or 4 complications. Treatment adaptations were needed in more than half of all patients receiving adjuvant chemotherapy. These adaptations were often related to toxicity. Toxicity can influence the quality of life, which is an important and relevant factor for elderly patients. As patients age, physiological changes in body function occur, which may interfere with cancer treatment, e.g., decreased bone marrow reserve, decreasing renal function, liver size, cytochrome P450 function and accumulation of body fat. These changes can influence pharmacokinetic processes and can lead to potentially harmful consequences [34, 35]. In our study, especially more gastrointestinal toxicity was seen, and relatively few haematological side-effects (3%). Other studies have reported significantly more haematological toxicity in elderly with stage III colon cancer who received adjuvant chemotherapy [36]. Although toxicity is expected to occur more frequently in elderly, only 3% of patients in our study received dose reduction before the start of chemotherapy.

This descriptive study gives insights into motives for treatment decisions, adaptations of treatment, toxicity and treatment outcome in elderly patients with stage III colon cancer in everyday clinical practice. However, selection of the fittest patients for adjuvant chemotherapy plays a role, because of the retrospective, observational nature of this study. Although we tried to overcome this problem by selecting patients who survived the first year after diagnosis and by adjustment for differences in age, co-morbidity, and PS, we could not completely overcome this selection problem.

Another limitation is the fact that not all characteristics could be retrieved from medical records and some variables like PS were often missing. Unknown PS was included as a separate category in multivariable survival analyses. This might have caused some bias. In addition, we tried to make a clear distinction between toxicity related to the surgery, adjuvant therapy or co-morbidity. Unfortunately, we could not make this distinction, because often it is not clear whether morbidity after treatment for colon cancer in the elderly is related to surgery, adjuvant chemotherapy or co-morbidity.

In conclusion, although over half of all elderly patients with stage III colon cancer who were selected for adjuvant chemotherapy could not complete the full treatment, those who received adjuvant chemotherapy seemed to have a better survival, even after adjustment for differences in age, co-morbidity and PS. Prospective studies are needed for evaluating the predictive value of patient characteristics for risks and benefits of treatment. In this way, a more balanced treatment decision can be made.

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funding
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disclosure
The authors have declared no conflicts of interest.

references


