Is it deleterious to delay the start of adjuvant chemotherapy in colon cancer stage III?

Postoperative chemotherapy using modulated 5-fluorouracil (5-FU) to patients operated for a colon cancer stage III can prevent recurrences in some individuals and thereby improve survival. These gains have been seen in randomised trials published 10–15 years ago. In the trials having a surgery-alone group, the treatment was generally initiated within 35 days, and the maximum number of days allowed was 56 [1–8]. In one trial, patients who did not start treatment within the stipulated 42 days were excluded [8]. In contrast, later trials comparing different regimens have allowed intervals up to 56 days or more [9–12]. In routine practice, this interval is frequently longer than in the trials. The potential importance of this interval was recently discussed [13]. Further, several abstracts at American Society of Clinical Oncology (ASCO) symposia in 2007 presented results from retrospective analyses [14–17]. The relevance of timing of adjuvant chemotherapy can for ethical reasons never be tested in a randomised trial, since a delay beyond what is reasonable for postoperative recovery can only be detrimental.

After the USA consensus statement in 1990, several groups wanted more documentation before acceptance of routine adjuvant therapy for stage III, and randomised trials, including a surgery-alone group, were initiated [6, 9, 18, 19]. In the Nordic countries, discussions led to a pragmatic trial design, so that any results would be relevant for the general population considered for treatment.

From 1991 to 1997, 708 patients with colon cancer stage III were randomly assigned to receive surgery alone (n = 364) or surgery plus chemotherapy (5-FU/leucovorin or 5-FU/leucovorin + levamisole, n = 344). An absolute difference in 5-year survival of 7% favouring the adjuvant group was found [19]. This difference did not reach statistical significance (P = 0.15) but did not differ from the previous surgery-alone trials or from a pooled analysis of seven randomised trials [20]. The study thus supports that a small gain is seen from adjuvant 5-FU-based therapy.

In Sweden, having the most pragmatic design, randomisation and treatment initiation should be as early as possible, or preferably within 49 days. When data were analysed, it was found that one-third of the patients started treatment after 8 weeks (57 days). It was speculated [19] that this delay could be one reason why a clear survival gain was not seen. The overall results of the 494 stage III patients randomised in Sweden were identical to those in the entire Nordic cohort (data not shown). Patient characteristics, time to randomisation and start of adjuvant therapy are presented in Table 1. There was no difference in overall survival according to whether randomisation was carried out within 7 weeks or not. A difference, however, was seen according to when treatment was initiated (Figure 2). Patients who had their treatment initiated beyond 8 weeks appeared to have no gain from the chemotherapy.

The evidence base for gains from adjuvant chemotherapy in colon cancer stage III is at level I, according to ASCO.
guidelines, however, only when the treatment started within 5–6 weeks after the surgery [1–8]. When the relevance of the time interval was explored, no clear influence was found according to whether treatment was initiated within 20 [21] or 28 days [6]. In a British trial, comparing two 5-FU-based schedules, survival was inferior in those who started their treatment beyond 8 weeks [22]. Actually, the survival curves in that trial parallel those presented here. In another study [15], the risk of death was significantly higher (relative hazard = 1.33) among those 69 patients who commenced adjuvant chemotherapy beyond 8 weeks. In contrast, three other studies [14, 16, 17] could not detect any difference according to when treatment started. Actually, in one study, disease-free survival tended to be better in those who started after 56 days [17]. In an analysis of 4382 patients with colon cancer using Surveillance, Epidemiology, and End Results-Medicare data, initiation of chemotherapy >2 months after surgery influenced overall survival whereas initiation >3 months had to be present to influence disease-specific survival. It could not be determined whether the results were because of chemotherapy timing or other associated factors [23].

The question of timing cannot be explored prospectively, and we are left with retrospective analyses. It is obvious that a very long delay (any beneficial effect will of course be lost if waiting until a recurrence has occurred) is deleterious. A delay within reasonable limits, up to 6–7 weeks appears not important, as recently found [24], whereas a delay longer than ~8 weeks can be negative. No definite cut-off is present, but with time, the positive but in absolute terms rather small gain from 6 months of adjuvant chemotherapy becomes smaller and smaller. We argue that all efforts should be made to initiate treatment as early as possible after the surgery and postoperative recovery and, if the delay turns out to be beyond some 8 weeks, the gain may be too small. It is likely that the relations between time to treatment initiation is the same using a combination of 5-FU and oxaliplatin [10], being slightly more effective than 5-FU alone. In breast cancer, a similar retrospective analysis indicated that survival was compromised by delays of >12 weeks after definitive surgery [25].

Table 1. Characteristics of Swedish patients with colon cancer stage III

<table>
<thead>
<tr>
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<th>Surgery</th>
<th>Surgery + CT</th>
<th>Surgery + CT</th>
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<tbody>
<tr>
<td></td>
<td>Treatment start</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 263</td>
<td>n = 231</td>
<td>n = 149</td>
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<tr>
<td>Patient characteristics</td>
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<tr>
<td>Age (median, range)</td>
<td>66 (32–77)</td>
<td>65 (27–75)</td>
<td>65 (29–75)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>140</td>
<td>125</td>
<td>76</td>
</tr>
<tr>
<td>Female</td>
<td>123</td>
<td>106</td>
<td>73</td>
</tr>
<tr>
<td>Time to randomisation (days)</td>
<td>30 (6–126)</td>
<td>34 (5–97)</td>
<td>27 (5–51)</td>
</tr>
<tr>
<td>Time to treatment start (days)</td>
<td>–</td>
<td>50 (10–117)</td>
<td>40 (10–56)</td>
</tr>
</tbody>
</table>

= not relevant.

CT, chemotherapy.

Figure 2. Overall survival according to whether the adjuvant chemotherapy was initiated within 56 days (n = 149) or not (n = 82) in relation to survival in the group randomised to surgery alone. Thirteen patients who did not start adjuvant chemotherapy, although randomised to this, and seven patients who received adjuvant chemotherapy in the surgery-alone group were excluded.

funding

Swedish Cancer Society and the Stockholm Cancer Society.

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doi:10.1093/annonc/mdm582