

# Should the Benefit of Adjuvant Chemotherapy in Colon Cancer Be Re-Evaluated?

Lars A. Pålman, *Uppsala University, Uppsala, Sweden*

Werner M. Hohenberger and Klaus Matzel, *Universitätsklinikums Erlangen, Erlangen, Germany*

Kenichi Sugihara, *Tokyo Medical and Dental University, Tokyo, Japan*

Philip Quirke, *St James's University Hospital, Leeds, United Kingdom*

Bengt Glimelius, *Uppsala University, Uppsala, Sweden*

Because favorable effects on survival were seen in randomized trials conducted during the 1980s, adjuvant chemotherapy in colon cancer was established as routine therapy in stage III disease in the United States in 1990.<sup>1</sup> Follow-up trials in the United States, Asia, and Europe<sup>2,3</sup> soon meant that it became recommended therapy worldwide, not only in stage III but in stage II disease as well, if risk factors for recurrence were present. Additional trials established the combination of a fluoropyrimidine and oxaliplatin as reference treatment for patients with stage II disease with risk factors who are fit for therapy and for those with stage III disease.<sup>4-6</sup> The addition of oxaliplatin in the treatment of elderly patients has been questioned.<sup>7</sup> Here we present arguments questioning not only the addition of oxaliplatin in the treatment of some younger patients as well but also the offering of adjuvant chemotherapy at all to some of these patients.

Medical care continuously develops, and as a consequence, treatment results improve. This development has also been seen in colon (and rectal) cancer, and the improvements actually challenge the established benefit of adjuvant chemotherapy in colon (and rectal) cancer. We question whether the risk of recurrence is sufficiently high for most patients with stage II disease, even when risk factors are present, and for some patients with stage III disease in the presence of high-quality, modern, multidisciplinary team care to motivate adjuvant chemotherapy.

In colorectal cancer, there has been a marked change during the past decades regarding surgery. It started with the total mesorectal excision (TME) technique for rectal cancer.<sup>8</sup> This technique has now spread around the world; the majority of surgeons have learned how to operate effectively on rectal cancer, and many centers report low local recurrence rates. Population-based data from national quality registers also show that the local recurrence rate can today reach approximately 5%,<sup>9,10</sup> equaling the rates achieved in dedicated centers.<sup>8,11-13</sup> Surgery for colon cancer may also be about to change, with complete mesocolic excision dissection and the concept of central ligation.<sup>14</sup> These techniques have started to spread among surgeons, and population data already indicate that there may be an overall survival benefit, in addition to improvements reflecting stage migration, if colonic surgery is performed in accordance with such procedures.<sup>15-19</sup>

Preoperative staging of colorectal cancer has also improved, and up-to-date contrast-enhanced computed tomography of the

thorax and abdomen, completed with ultrasonography or magnetic resonance imaging with contrast agents in the case of equivocal liver lesions or positron emission tomography-computed tomography in the case of equivocal findings outside the liver, has also resulted in fewer recurrences in those undergoing surgery (ie, the target patients for adjuvant therapy). The scenario has changed from fewer metachronous to more synchronous metastases. Furthermore, although pathologists cannot reduce recurrence risks per se, better pathologic staging results in lower stage-specific recurrence rates, often referred to as stage migration.

The rectal cancer radiotherapy story illustrates the same kind of problem the medical community is facing when one or several aspects of multidisciplinary care are improved. The story is well known from literature. The reduction in local recurrence rates seen after preoperative radiotherapy<sup>20</sup> was questioned when surgery was improved (ie, when TME was introduced). The two trials then initiated—the Dutch–Swedish TME trial and the Medical Research Council CR07 trial in the United Kingdom,<sup>21,22</sup> in which preoperative radiotherapy using the 5 × 5 Gy schedule was tested against selective postoperative (chemo)radiotherapy—showed that preoperative radiotherapy significantly reduced local recurrence rates. Actually, the relative reduction may have been slightly larger with TME (hazard ratio, 0.38; absolute difference, 11% v 4%) than with the older, suboptimal surgery (hazard ratio, 0.46; absolute difference, 27% v 13%). The overall survival gain seen previously in the Swedish Rectal Cancer Trial<sup>23</sup> could not be reproduced; the absolute gain in local recurrences was likely too small to show up in the trials in which TME was used.

The gains from postoperative chemoradiotherapy in local recurrence rates and survival<sup>24</sup> have not been tested using TME. In a German trial testing pre- versus postoperative chemoradiotherapy, it was shown that preoperative chemoradiotherapy was better than postoperative in reducing the local recurrence rate, approximately 10% after postoperative treatment versus 7% after preoperative irradiation. The TME technique was used for most patients in the trial, but no difference in survival could be seen even after long-term follow-up.<sup>25</sup>

On the basis of this knowledge, there is an ongoing debate over whether radiotherapy is needed in the majority of rectal cancers because of the low recurrence rates seen today without

radiotherapy and the adverse effects of irradiation. The so-called number needed to harm, in addition to the number needed to treat, has become an important issue of discussion. The question to be raised is whether it is necessary to lower the limited risk of local recurrence even further (by approximately 60%) by adding radiotherapy.

All trials that have tested chemotherapy versus surgery alone were conducted in an era when surgery was far from optimal; classic hemicolectomies were not always performed, and the complete mesocolic excision technique was not used. In addition, preoperative staging and postoperative pathology were suboptimal according to present standards. The recurrence risks in patients undergoing radical surgery (stage I to III disease) are thus likely much lower today than they were when those trials were conducted. Today, many centers can report survival figures clearly better than those seen both with and without chemotherapy in the older trials. In many cancer registries in Europe, patients with stage I or II colon cancer have a 5-year survival rate greater than 90%; for patients with stage III disease, this rate is approximately 80%<sup>14</sup> (in Swedish, Danish, and Dutch colorectal cancer registries). The adjuvant chemotherapy administered according to recommendations contributes to these results, and it is impossible to know from modern series what the recurrence risk overall and in each stage would be if no adjuvant chemotherapy were administered. A Nordic group made an attempt to find out the recurrence risk on the basis of a systematic literature review of modern series, where the quality of care (including staging, surgery, and pathology) would be reasonably high.<sup>26</sup> It was not possible to quantify the risk, but evidence indicated that the risk was considerably lower than in the past, potentially lower than 10% to 15% in many groups of patients who would be considered for adjuvant chemotherapy according to most guidelines (eg, those with stage II disease with risk factors like pT4, < 12 nodes, poor differentiation, or vascular and nerve invasion). There was a clear lack of studies reporting recurrence figures with modern quality of care.

Analogous to the experience in rectal cancer, the relative gains from adjuvant chemotherapy using a fluoropyrimidine alone in colon cancer are likely (at least) to be the same as in the older trials. In stage II disease, these gains range from 20% to 25% on the basis of a Cochrane analysis and other systematic overviews.<sup>27</sup> In stage III disease, they are less well described but anticipated to be higher (30% to 35%).<sup>28</sup> Let us assume that the relative gains average 30% in stage II and III disease combined. If 100 patients are treated with adjuvant fluoropyrimidine alone, and the absolute risk of recurrence is, for example, 20%, six patients will not experience recurrence. Similarly, if the absolute risk of recurrence is 40%, 12 recurrences will be prevented in 100 treated patients. The addition of oxaliplatin further reduces the risk by 18% to 20%, at least in stage III disease and potentially also in stage II disease with risk factors. Again, if 100 patients are treated, and the absolute risk figures after surgery alone are as we have described (ie, 20% and 40%, respectively), an additional three (from 20 recurrences down to 14 with a fluoropyrimidine alone and down to approximately 11 with the combination) and six recurrences (from 40 down to 28 and approximately 22), respectively, will be prevented. Today, with optimized staging, surgery, and pathology, if the absolute risks of recurrence after surgery alone in the particular stages of disease are

not 20% and 40% but instead 10% and 20%, respectively, the absolute gains are then three and six with a fluoropyrimidine alone and are further reduced by one to two with the addition of oxaliplatin per 100 treated patients. Today, the standard of care at most centers is fluorouracil or capecitabine combined with oxaliplatin (eg, FOLFOX [fluorouracil, leucovorin, and oxaliplatin] or CAPOX [capecitabine plus oxaliplatin] regimen) for all patients with stage III disease and many patients with stage II disease, if risk factors for recurrence are present. Because toxicity resulting from oxaliplatin treatment is not negligible, with sometimes persistent neuropathy,<sup>29</sup> many patients with a low risk of recurrence will be harmed for little gain.

The present guidelines for adjuvant chemotherapy in stage II colon cancer with and without risk factors and in stage III disease are based on recurrence risks from the past. They are much lower today, although we do not know precisely how much lower. The reasons are mainly better surgery and better preoperative staging, where many patients with metastatic disease have been “converted” to synchronous from metachronous disease. Even if the relative gains from administering adjuvant chemotherapy with or without oxaliplatin are the same as those shown in the trials (with the higher absolute risk figures), the absolute gains are less than they were, and they may be too low to recommend therapy. It is not realistic to conduct a new surgery-alone trial in the groups of greatest interest (ie, those with anticipated recurrence risks of 10% to 20%, or most patients with stage II and many with stage III disease), as was done for radiotherapy in rectal cancer. Rather, it is important to properly analyze risk figures in large unselected populations where the quality of care is known and with an attempt to control for the effects of adjuvant chemotherapy administered to different proportions of patients. The number needed to treat is high, and thus, many patients will unnecessarily be harmed. Today, we must re-evaluate the need for administering routine adjuvant chemotherapy to many patients with colon cancer when they are receiving high-quality multidisciplinary care. Furthermore, a much more differentiated stratification than simply grouping patients into stages II (with risk factors) and III (A, B, and C) is required; some patients with stage III disease have a much lower risk of recurrence than some patients with stage II. For example (also an example of the amount of information needed in routine care), we do not believe that an otherwise fit 60-year-old patient, who has undergone adequate staging and surgery, with left-sided pT3b, N1 (1 positive, 28 sampled), no vessel (v-) or nerve (N-) involvement, and low V malignancy grade colon cancer has a sufficiently high recurrence risk to recommend adjuvant chemotherapy, certainly not with oxaliplatin. If his or her preoperative carcinoembryonic antigen level is very low or only moderately elevated (eg, < 10) and normalizes postoperatively, the risk of recurrence is likely less than 10%; the absolute benefit of adjuvant combination chemotherapy for this patient is low (four per 100 patients treated) compared with the morbidity associated with receiving the two chemotherapy agents during 6 months (or maybe 3 months in the future). Improving multidisciplinary care to meet modern standards should lead to a reduction in the use of adjuvant therapy in everyday practice.

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**Lars A. Pählman**

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**Werner M. Hohenberger**

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**Klaus Matzel**

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