Adjuvant therapy for stage II colon cancer: an elephant in the living room?

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At present, standard adjuvant treatment for patients with stage III colon cancer after surgical resection is represented by 6 months of chemotherapy based on 5-fluorouracil/leucovorin regimens. Even elderly patients enjoy the benefit of chemotherapy in terms of superior overall survival with no detrimental effects on quality of life. More questionable is the role of adjuvant chemotherapy for stage II colon cancer patients, the standard of care for whom is surgical resection alone. Although a majority of patients will be cured with resection, a significant minority will ultimately relapse, suggesting the need to identify patients who may benefit from adjuvant therapy. Putative prognostic markers for stage II patients, as well as the state-of-the-art of the adjuvant treatment in this setting, are reviewed in this paper.

Key words: adjuvant therapy, Dukes’ B stage II colon cancer

Introduction

Results obtained by adjuvant treatment of colon cancer over the past 20 years are one of the most important advances in modern oncology. Thousands of lives are saved by adjuvant chemotherapy every year, lives that otherwise would be lost to recurrent cancer. This is evident for patients with positive lymph nodes (stage III), while the benefit of adjuvant treatment is still debatable in stage II colon cancer. In 2004, in the USA, 106,370 cases of colon carcinoma are expected and at least 32,000 will be stage II [1, 2]. This high percentage of patients is characterized by a prognosis that could vary from 60% to 80% survival at 5 years, as shown in Table 1.

Therefore, between 6,400 and 12,800 of these stage II patients will eventually die from their disease. Of the many difficulties in deciding whether or not to treat stage II colon cancer patients with adjuvant therapy, two are particularly important. The first is the fact that most adjuvant trials conducted so far have contained an insufficient number of stage II patients to achieve any significant difference in survival. The second is that the intrinsic overall prognosis of stage II patients is quite good, with the vast majority of patients never developing a recurrence. So, in an attempt to detect a 10% survival gain by any adjuvant treatment with 90% power, >10,000 patients would be needed in a randomized trial.

We therefore need to identify prognostic markers capable of establishing which stage II patients will suffer from recurrences and which could benefit from adjuvant treatment. It should be noted that practically all the ‘negative’ prognostic factors that we will look at have never been confirmed on a prospective basis. Furthermore, even given the negative prognostic value of some of these factors, adjuvant treatment will not necessarily improve the prognosis of these patients.

We now look at the known data regarding the efficacy of adjuvant therapy and summarize the data regarding past and more recent prognostic factors.

Adjuvant chemotherapy

The results from the INT-0035 trial, a 7-year median follow-up study of 318 patients with stage II colorectal cancer (mainly patients with poor risk status: T4, perforation, obstruction) showed a decreased recurrence of 31% in patients treated with 5-fluorouracil (5-FU)+levamisole compared with surgery alone [3]. However, overall survival (OS) did not significantly differ between the two approaches. This study is frequently quoted as a definitive trial demonstrating the lack of benefit of adjuvant treatment in stage II colon cancer. However, the study was too underpowered to be able to detect reductions in recurrence of <50%. No further large-scale clinical trials have independently demonstrated any clinical benefit in terms of OS for adjuvant treatment of stage II patients. On the other hand, the only ‘positive’ single trial reported so far in stage II colon cancer was published in 2001 by Taal and Van Tinteren [4]. In their experience, 12 months of 5-FU+levamisole provided an OS benefit over surgery alone (78% versus 70%, median follow-up 4.9 years).
The International Multi-center Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators compared the effect of 6 months of chemotherapy with 5-FU and leucovorin (LV) versus surgery alone in 1016 patients with Dukes’ B colon cancer treated in five different trials. The absolute risk reduction for treated patients was 3% for 5-year disease-free survival (DFS) and 2% for 5-year OS, which was not statistically significant. On the basis of these results, routine use of chemotherapy for stage II colon cancer was not recommended [5, 6].

Conversely, the NSABP group performed a pooled analysis of outcome data from four of their trials (C-01 to C-04) with >1500 stage II patients. They compared outcomes for all patients treated on the superior treatment arms of the four trials examining different strategies and/or schedule with those patients treated in the inferior treatment arms, whether these included treatment or observation alone (Table 2). A mortality reduction of 30% was observed for adjuvant therapy. This benefit was also present in poor prognosis patients, such as T4 and obstructed/perforated patients [7, 8].

It should be noted that only trials C-01 and C-02 had a true control group (surgery alone). Four different chemotherapy regimens with therapy duration ranging from 7 days to 18 months were studied. Various criticisms were made of the NSABP analysis, in particular of the heterogeneity of the analyzed studies and of the non-orthodox statistical method used [9, 10]. As shown in Table 2, the major advantages for stage II patients seem related to the portal vein infusion trial (C-02, 12% absolute mortality reduction), a technique now largely abandoned, and to 5-FU/LV when compared with MOF (C-03, 8% absolute mortality reduction). This latter difference could be partially explained by the increased incidence of second primary tumors in the MOF arm versus 5-FU/LV arm (25 versus 11) [11]. The remaining differences, which are 3% and 4% absolute mortality reduction for trials C-01 and C-04, respectively, do not seem very different from the IMPACT results.

A more recently published systematic review on adjuvant therapy for stage II colon cancer analyzed survival data available for 4187 patients with stage II disease across 18 trials. The mortality RR was 0.87 (95% CI 0.75–1.01) for the treated patients [12].

The statistician point of view as to the difficulties and pitfalls of the analysis of adjuvant studies and the meta-analysis of stage II patients has been analyzed in depth elsewhere [13].

An indirect method of evaluating the usefulness of adjuvant therapy was made by Schrag et al. A group of 3725 patients with resected stage II colon cancer was studied evaluating the SEER-Medicare data (Table 3). Thirty-one per cent had received adjuvant therapy. At 5 years, 74% of the treated patients were alive compared with 72% of those not treated. No significant difference has come to light for the subgroup of patients with poor prognostic features (T4, obstructed/perforated) [14]. These data, even if they are not from a randomized trial, would indicate that generally only very few patients received adjuvant therapy and that a non-treated control group might be considered for future trials. At the 2003

<table>
<thead>
<tr>
<th>Table 1. Tumor–node–metastasis (TNM) staging system and prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNM stage</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee in Cancer

Table 2. The NSABP meta-analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>‘Inferior arm’</th>
<th>No. of patients</th>
<th>5-year OS (%)</th>
<th>‘Superior arm’</th>
<th>No. of patients</th>
<th>5-year OS (%)</th>
<th>P value</th>
<th>Absolute survival difference (%)</th>
<th>Reduction of cumulative odds of death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-01</td>
<td>Surgery</td>
<td>166</td>
<td>72</td>
<td>MOF</td>
<td>150</td>
<td>75</td>
<td>0.73</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>C-02</td>
<td>Surgery</td>
<td>201</td>
<td>76</td>
<td>PVI</td>
<td>188</td>
<td>88</td>
<td>0.005</td>
<td>12</td>
<td>51</td>
</tr>
<tr>
<td>C-03</td>
<td>MOF</td>
<td>141</td>
<td>84</td>
<td>5-FU/LV</td>
<td>149</td>
<td>92</td>
<td>0.03</td>
<td>8</td>
<td>53</td>
</tr>
<tr>
<td>C-04</td>
<td>5-FU/LV</td>
<td>285</td>
<td>81</td>
<td>5-FU/LV</td>
<td>285</td>
<td>85</td>
<td>0.25</td>
<td>4</td>
<td>21</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; LV, leucovorin; MOF, methyl-ccnu, oncovin, fluorouracil; NSABP, National Surgical Adjuvant Breast and Bowel Project; OS, overall survival; PVI, portal vein infusion.

Table 3. Adjuvant therapy of stage II colon cancer: SEER-Medicare data

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Age, years</th>
<th>Years</th>
<th>Patients treated with CT (%)</th>
<th>5-year OS, CT (%)</th>
<th>5-year OS, no CT (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3725</td>
<td>65–74</td>
<td>1992–1996</td>
<td>31</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>No comorbidity</td>
<td>2478</td>
<td>Same</td>
<td>Same</td>
<td>34</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>T4/obstructed or perforated</td>
<td>448</td>
<td>Same</td>
<td>Same</td>
<td>38</td>
<td>62</td>
<td>60</td>
</tr>
</tbody>
</table>

CT, chemotherapy; HR, hazard ratio; OS, overall survival; CI, confidence interval.
Adjuvant immunotherapy

Adjuvant immunotherapy has been less extensively studied than chemotherapy in both stage II and stage III colon cancer. Immunotherapy in the adjuvant setting seems more logical than in metastatic disease, given the minimal tumor burden (even smaller for stage II patients) and a more responsive immune system.

Recent data from three prospective, randomized and controlled clinical trials conducted in stage II–III colon cancer using specific immunotherapy (ASI) look promising [16–18]. A meta-analysis of the three studies all based on Oncovax (irradiated autologous tumor cells mixed with BCG) has recently been carried out [19]. In stage II patients, Oncovax therapy produced an annual odds reduction of relapse of 34% (±18%; P=0.05). OS did not differ between the ASI group and control group. However, disease-specific survival was statistically better in stage II patients receiving four doses of vaccination. Toxicity was virtually absent.

Another immunotherapeutic approach is based on the use of Edrecolomab, a monoclonal antibody that binds to the tumor-associated CO17-1 A antigen [20]. Although preliminary results of a large-scale trial conducted in stage III patients do not seem to confirm the initial enthusiasm about this agent [21], the results of a recently closed trial comparing Edrecolomab monotherapy versus surgery alone, conducted by CALGB, National Cancer Institute of Canada, US Colorectal Intergroup and EORTC (study 157-003), are awaited with keen interest.

Quality of surgery and role of the hospital procedure volume

The role of the quality of surgery in determining the prognosis of patients with rectal cancer has been extensively covered in the scientific literature [22, 23] What is apparently less known is the role of experience and ability of the surgeon to improve colon cancer prognosis. However, there have been certain recent contributions on this subject [24, 25]. Wein et al. have recently suggested that the lack of data available about the quality of surgery could be an important criticism of the NSABP and IMPACT meta-analyses [10]. In a prospective trial with over 1000 colon cancer patients conducted in Germany, the prognostic significance played by different Surgical Departments was evident. After potentially curative surgery for stage II colon cancer, local recurrence rates differed between 1% and 18%, and 5-year survival rate ranged from 36% to 89% [10, 24].

US data suggest that hospital procedure volume may also influence the prognosis of stage II patients (Figure 1). Using SEER-Medicare data, Schrag et al. showed that hospital volume was predictive of survival for patients with stage II disease [26]. These results, as well as another study [27], show that in the USA colon cancer surgery is currently performed in many hospitals with very low case volumes. Prospectively recorded data from a large clinical trial (INT 0089) indicate that patients whose colon cancer was resected at low-volume hospitals experienced a higher risk for long-term mortality, without detectable differences in colon cancer recurrences [28].

Finally, the importance of surgeon case volume as a prognostic factor has been less well explored, but when studied together, hospital volume seems to exert a stronger effect [29]. Globally, the authors suggest that the improved prognosis obtained in high-volume hospitals could be related not only to the skill of the individual surgeon, but also to the fact that there is access to an entire team of health-care professionals (surgeons, anesthesiologists, radiologists, pathologists, etc.) well used to working on a multidisciplinary basis.

Cost-effectiveness analysis

French investigators have compared the effectiveness and cost-effectiveness of various strategies for treating patients with stage II and III colon cancer after surgery, by using a decision analysis model. Their conclusions favor adjuvant treatment (based on 5-FU/LV) for stage II colon cancer patients [30]. However, they could be biased by having substantially overestimated the effectiveness of adjuvant treatment, assuming a quite optimistic 25% reduction in mortality [31].

The toxicity issue

The standard adjuvant therapy, based on the association of 5-FU and LV, is commonly held to be a well-tolerated treatment. Certainly, a not insignificant number of patients develop oral mucositis, neutropenia or clinically relevant diarrhea, according to the regimen utilized [32]. However, we know from prospective data that in stage II patients (as well as in stage III), 6 months of adjuvant chemotherapy with 5-FU/LV are not detrimental to the patients' quality of life [33].

Nevertheless, we must consider that treatment-related deaths are reported in 0.3% to 0.8% of patients treated with 5-FU/LV-based adjuvant treatments [10]. It is clear that even
such a limited mortality rate is relevant if we consider that the potential benefit in terms of survival rate thanks to adjuvant therapy may be ~2%, according to the IMPACT B2 analysis. Furthermore, it should be outlined that we do not know the long-term effect of toxicity and quality of life that new regimens, based on new drugs such as irinotecan and oxaliplatin, in the adjuvant treatment could have. Therefore, particular care should be shown, especially in the light of recent negative experiences in terms of toxic deaths with Tomudex [34] and irinotecan in combination with weekly bolus 5-FU/LV [35].

We should remember, finally, that there are no data related to the long-term effects of new drugs, for example in terms of the potential induction of secondary acute leukemia and myelodysplastic syndromes, a sad lesson already learned by the nitrosoureas-based adjuvant trials of the past [36].

**Prognostic factors of potential interest for stage II patients**

**T stage**

Stage II patients with T4 lesions (direct invasion by tumor into an adjacent organ or perforation of visceral peritoneum) have been shown to have a 5-year survival rate only slightly better than or similar to N1 stage III patients [37]. A worse prognosis for T4N0M0 patients has also been supported by other authors [25, 38]. In addition, pT3 tumors with a depth of invasion >15 mm beyond the outer border of the muscularis propria (pT3d; Table 4) seem at high risk of recurrence [25].

**Tumor location**

There is retrospective evidence that left-sided stage II tumors have a worse prognosis compared with right-sided tumors [25, 39, 40], Gervaz et al. noted that among 126 stage II colorectal cancer patients, 86% of p53 positive tumors were located in the distal colon and rectum [41]. It has also been noted that most tumors with microsatellite instability (MSI) are found in the proximal colon and there are data that would suggest that MSI+ tumors have a better prognosis than MSI– tumors [42]. Therefore, tumor location might be taken into account for group stratification in future trials of adjuvant chemotherapy in stage II patients.

**Obstructing or perforating tumors**

Patients with obstructing or perforating node-negative cancers are known to have survival rates comparable to non-obstructed and non-perforated patients with stage III disease, as suggested by trial INT-0035 results [3]. The negative impact of obstruction on prognosis is also suggested by a recent observational study [43], as well as by many historical observations [44, 45]. When the perforation is associated with bowel obstruction, recurrence rates are even higher, with as few as 19% of patients surviving at 5 years [46].

**Lymph node retrieval rate**

The American Joint Committee on Cancer and TNM Committee of the International Union Against Cancer has stated that a minimum of 12 lymph nodes should be recovered from colon adenocarcinoma specimens in order to perform correct pathological staging. However, other authors claim that an even higher number ranging from 14 to 17 nodes should be obtained for optimal results [47, 48]. An even more provocative report was recently published by Le Voyer et al., suggesting that the higher the number of analyzed nodes, the better the prognosis of stage II patients [49]. The number of lymph nodes collected is dependent on the method of identifying nodes, i.e. a lower number with manual dissection and a higher number with fat-clearing techniques which are more time consuming and expensive [50].

A recent Canadian survey showed that only 25% of the interviewed pathologists identified that a minimum of 12 nodes are necessary for accurate designation of node negativity, raising the question of a suboptimal education strategy [51].

Whatever the technique used, patients with stage II colon cancer with <12 retrieved nodes should probably be considered for adjuvant treatment even outside a clinical trial.

**The role of lymphatic mapping (LM) and sentinel lymphadenectomy (SL)**

LM and SL, originally described for melanoma and breast cancer, are now being investigated in colon cancer. Unlike breast cancer and melanoma, LM/SL do not aim to modify standard surgical procedure in colon cancer. Rather, the rationale is that if the sentinel node (SN), identified and taken during surgery, does not harbor microscopic metastatic disease, then the other regional nodes are unlikely to contain metastatic disease. In addition, a proportion of patients staged as node-negative with conventional pathological procedures are upstaged by means of LM/SL, and could be considered for adjuvant treatment. A fundamental supposition for this reasoning is to know whether the identification of lymph node micro-metastasis affects the prognosis of colon cancer [49]. Many retrospective studies dealing with this subject are reported in

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**Table 4. The pT3 classification**

<table>
<thead>
<tr>
<th>pT3a minimal</th>
<th>Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissues, not &gt;1 mm beyond the outer border of muscularis propria</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT3b slight</td>
<td>Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissues, &gt;1 mm but not &gt;5 mm beyond the outer border of muscularis propria</td>
</tr>
<tr>
<td>pT3c moderate</td>
<td>Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissues, &gt;5 mm but not &gt;15 mm beyond the outer border of muscularis propria</td>
</tr>
<tr>
<td>pT3d extensive</td>
<td>Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissues, &gt;15 mm beyond the outer border of muscularis propria</td>
</tr>
</tbody>
</table>
the literature, with opposite conclusions, as shown in Table 5 [53–64].

These differences could, at least in part, be explained by the different sensitivity of the methods used in identifying the lymph node micro-metastases. Furthermore, only a subset of cancer patients with micro-metastases will develop overt recurrent tumors. It is therefore important to be able to analyze the clonogenic capacity of the neoplastic cells found in the lymph node micro-metastases, as well as the genotypic/phenotypic characteristics and micro-environmental factors that may influence migration, survival and growth of these cells [65, 66].

It should be outlined that isolated tumor cells in mesenteric nodes also seem to predict a worse prognosis in patients with stage II colon cancer, as recently suggested by Bukholm et al. [67]. Saha et al. have pioneered LM and SL in colon cancer. In their pilot study, they demonstrated a 99% rate of SN identification, a 96% rate of accuracy for the SN as an indicator of regional nodal status and a 17% rate of upstaging [68]. In a subsequent multi-institutional study using cytokeratin immunohistochemical staining in combination with reverse transcription-PCR for processing SN, up to 53% of patients whose SN were negative by conventional staging techniques, were found to have micro-metastases [69]. Many other studies were subsequently performed in an attempt to confirm Saha’s results. A summary of these experiences is reported in Table 6 [70–76]. In addition, the LM/SL were recently demonstrated to be feasible also during laparoscopic surgery [75]. Overall, it could be said that this technique holds promise in identifying a subset of stage II patients who may benefit from adjuvant chemotherapy, even if its routine clinical use is still premature, as clearly outlined also by the conflicting results of the first confirmatory trial reported at the 2004 ASCO Meeting by the CALGB [77].

Other pathological findings

Venous invasion, and in particular invasion of extramural veins, seems to be a particularly strong adverse prognostic factor [78, 79]. Vessel counts in combination with the expression of vascular endothelial growth factor may predict outcome for stage II patients [80, 81]. Mucinous histology, poorly differentiated tumors and perineural invasion are also frequently quoted as ‘negative’ prognostic factors for stage II patients [82–84]. However, mucinous differentiation is not proven to be a statistically significant factor independent of histological grade [85].

In addition, considering mucinous tumors, we should add a further cautionary note. This characteristic is a feature of cancers with MSI, which occurs in younger patients and appears to be a marker of improved prognosis. Possibly, the negative effect of mucinous histology might be more significant in older patients. These observations, however, need to be confirmed by solid data derived from multivariate analysis.

Finally, further to the issue of the number of retrieved nodes already discussed, even the size of the lymphnodes seems to be of prognostic value in stage II patients (86).

### Table 5. Nodal micro-metastasis in colorectal cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Technique</th>
<th>Prognostic significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenson [58]</td>
<td>50</td>
<td>IH</td>
<td>Yes</td>
</tr>
<tr>
<td>Jeffers [53]</td>
<td>77</td>
<td>IH</td>
<td>No</td>
</tr>
<tr>
<td>Adell [54]</td>
<td>100</td>
<td>IH</td>
<td>No</td>
</tr>
<tr>
<td>Broll [55]</td>
<td>49</td>
<td>IH</td>
<td>No</td>
</tr>
<tr>
<td>Sasaki [59]</td>
<td>19</td>
<td>IH</td>
<td>Yes</td>
</tr>
<tr>
<td>Liefer [60]</td>
<td>26</td>
<td>RT–PCR</td>
<td>Yes</td>
</tr>
<tr>
<td>Mori [61]</td>
<td>65</td>
<td>RT–PCR</td>
<td>Yes</td>
</tr>
<tr>
<td>Oberg [56]</td>
<td>96</td>
<td>IH</td>
<td>No</td>
</tr>
<tr>
<td>Cagir [62]</td>
<td>21</td>
<td>RT–PCR</td>
<td>Yes</td>
</tr>
<tr>
<td>Nakanishi [57]</td>
<td>44</td>
<td>IH</td>
<td>No</td>
</tr>
<tr>
<td>Clarke [63]</td>
<td>133</td>
<td>IH</td>
<td>Yes</td>
</tr>
<tr>
<td>Rosenberg [64]</td>
<td>85</td>
<td>RT–PCR+IH</td>
<td>Yes</td>
</tr>
</tbody>
</table>

IH, immunohistochemistry; RT–PCR, reverse transcription-analysis.

### Table 6. Lymphatic mapping in colon cancer: selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Success rate (%)</th>
<th>SN +ve (%)</th>
<th>Upstaged patients (%)</th>
<th>False negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saha [68]</td>
<td>117</td>
<td>98</td>
<td>95</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Waters [70]</td>
<td>22</td>
<td>91</td>
<td>30</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Wood [71]</td>
<td>50</td>
<td>94</td>
<td>55</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Codignola [72]</td>
<td>10</td>
<td>100</td>
<td>60</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Esser [73]</td>
<td>31</td>
<td>58</td>
<td>NA</td>
<td>11</td>
<td>NA</td>
</tr>
<tr>
<td>Paramo [74]</td>
<td>35</td>
<td>71</td>
<td>28</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Bilchik [69]</td>
<td>40</td>
<td>100</td>
<td>35</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>Wood [75]</td>
<td>75</td>
<td>96</td>
<td>69</td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>Saha [76]</td>
<td>203</td>
<td>98</td>
<td>37</td>
<td>14</td>
<td>4</td>
</tr>
</tbody>
</table>

SN, sentinel node; NA, not applicable.
Miscellaneous possible prognostic markers

There are considerable retrospective data in the literature that would suggest the negative prognostic value of multiple molecular markers and various laboratory findings. In general, the following are claimed to be associated with a worse prognosis: an elevated pre-surgical CEA value [87], bax expression [88], loss of p27 expression [89], increased mytotic index [90] and low bcl2 expression [91].

On the other hand, k-ras [92] mutations and thymidylate synthase expression [93] seem to be of no potential value in identifying a subset of stage II colon cancer patients with worse prognosis. Furthermore, other factors, such as mutated p53 gene have not given any clear unequivocal results. In fact, a pooled analysis on the p53 overexpression or mutation as a prognostic factor in colorectal cancer conducted in 4416 patients failed to show any positive effect, as was the case for at least four out of seven studies specifically conducted in stage II patients [94].

A detailed analysis of these theoretical prognostic markers is beyond the scope of this review. The interested reader is referred to reviews reported elsewhere [85, 95–98].

Chromosomal abnormalities

Aneuploid tumors have been identified in the past as having a poor prognosis even for stage II tumors [99]. The molecular correlation of aneuploidy is allelic imbalance due to the loss of chromosome arms. When the lost region contains a tumor suppressor gene, cells with this kind of defect can acquire a competitive growth advantage.

Jen et al [100]. retrospectively studied the influence of allelic loss of chromosome 18q on the prognosis of stage II colon cancer. At a median follow-up of 35 months, 83% of the patients without 18q allelic loss were alive, whereas only 58% of patients with 18q allelic loss were still alive [100]. This observation has been confirmed by some studies [101, 102], but not by all [103].

Gryfe et al. have more recently shown that high-frequency MSI in colorectal cancer predicts a favorable outcome even among patients with stage II disease [42]. However, other reports have produced discordant results [104].

More recently, Zhou et al [105] have studied 180 node-negative colorectal cancer patients for imbalances of chromosomes 8p and 18q by a new sophisticated technique called digital single nucleotide polymorphism. Five-year DFS was 100% for patients with no allelic imbalances, whereas it was 58% for those patients with allelic imbalances of both chromosomes (P=0.0001) [105]. However, it is not possible at the moment to foresee what the practical implications of these findings could be. Furthermore, there are no clinical adjuvant therapy studies at present that stratify patients according to these genetic parameters, with the exception of the planned E5202 trial (Figure 2).

Recently, Wang et al., using gene expression profiling technique, have found a 23-gene signature profile in a small number of stage II patients linked with a 13-fold higher risk of relapse. It should be noted that this group of patients with a worse prognosis was characterized also by a clearly suboptimal mean number of examined nodes (8 vs 12). Nevertheless, this is the first study related to a genomic approach for better defined stage II colon cancer prognosis [106].

Conclusions

It is not yet clear whether all patients with stage II colon cancer should be treated with adjuvant therapy. Certain ongoing trials could help us to reach a definitive answer to this problem. In particular, the Quasar study enrolled 3238 patients (71% with colon, cancer 92% with stage II disease), comparing surgery alone with 5-FU/LV. With a median follow-up of 4.2 years, the risk of death of C≥ vs control was 0.88 (95% CI: 0.75-1.05) and recurrence 0.82 (95% CI: 0.70-0.97) as reported in the abstract. During the oral presentation, however, mortality data was reported as significantly in favour of treatment (RR0.83, 95% CI 0.71-0.97, p 0.02) even if this benefit was not confirmed for patients ≥70 years of age [107].

Additional information about the value of adjuvant therapy is also expected by other new trials based on cox-2 inhibitors (Victor study, UK) and combination of CPT-11 and 5-FU/LV (Petacc-04). Both supporters and opponents of adjuvant therapy are however generally agreed that the benefit of the treatment, if any, is today rather modest. Therefore the efforts made to identify which patients could benefit from adjuvant therapy and which could be spared it, are certainly justified. Along with sophisticated markers and genome analyses, an in-depth and perfected use of classical pathology seems to be among the most promising way forward.

In everyday clinical practice, it is likely that stage II patients without T4 tumors, neither occluded nor perforated, with >12 examined lymph nodes (and probably with a negative SN), treated in hospitals that can guarantee a multidisciplinary approach, have a very high surgical cure rate.
However, as for any clinical scenarios in which the evidence-based medicine is not of any particular help, the decision to treat a patient with stage II colon cancer outside a clinical trial must be taken after careful, detailed and frank talk with the patient, clarifying all the pros and cons the choice involves. To give such a patient the possibility to participate in a clinical trial still remains the best available choice.

References


