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Adjuvant treatment of colorectal cancer (current expert opinion derived from the Third International Conference: Perspectives in Colorectal Cancer, Dublin, 2001)

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Abstract

This article summarises the progress that has been made in the adjuvant treatment of colorectal cancer over the last decade. In view of the consequent improvements in recurrence rates and in overall survival, the development of effective adjuvant treatments for colorectal cancer is considered as one of the most important to be made in clinical oncology over the last decade. Treatment recommendations based on evidence-based data and on expert opinions are summarised in this manuscript. However, a consensus cannot be reached on all aspects of treatment because of data that is currently emerging that will influence clinical practice and because of the many ongoing clinical trials. Those involved in the treatment of colorectal cancer should therefore be encouraged to continue to provide optimal patient care and to participate in well designed clinical trials in order to increase the evidence upon which they can base their clinical judgements and in order to make further progress.

Keywords: Colon cancer; Rectal cancer; Adjuvant chemotherapy; Adjuvant radiotherapy

1. Introduction

Colorectal cancer is common in economically developed countries, particularly in Europe, North America and Australia, and is one of the leading causes of cancer-related deaths in the Western world. Every year, colorectal cancer is responsible for an estimated 400 000 deaths worldwide. Approximately 60 000 people die from colorectal adenocarcinoma among the 150 000 new cases which are diagnosed in Europe each year.

Seventy per cent of patients with colorectal cancer present with apparently localised disease. In these patients, surgery can be curative, but relapses after complete resection are frequent. Many trials including

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adjuvant treatment have therefore been performed with the aim of decreasing the recurrence rate and increasing the survival of patients with colorectal cancer. In view of the high incidence of colorectal cancer, an effective adjuvant treatment will have a large impact on the absolute survival rates from this disease.

Colorectal cancer is not uniformly fatal and there are large differences in survival depending on the stage of the disease. The pathological stage is currently the most important determinant of prognosis. The classification system described by Dukes in 1930 is still widely used. However, the original Dukes' system no longer fulfils the requirements of modern tumour staging, as it fails to take into account distant metastases, the number of lymph nodes involved, and carcinomas limited to the submucosa. Therefore, the TNM classification of the American Joint Committee on Cancer (AJCC) is currently recommended for daily routine and in clinical trials. The prognosis depends on the stage at which the tumour is diagnosed. In patients with a stage I tumour (pT1 or pT2N0M0), the 5-year survival exceeds 90%. In patients with a stage II tumour (pT3 or pT4N0M0) (Dukes' B), the survival is variable. In patients with a pT3N0M0 tumour, the 5-year survival is approximately 70%, while in those with a pT4N0M0 tumour, the 5-year survival is only approximately 30%. One of the most important prognostic factors in stage II colon cancer is the number of lymph nodes analysed. Twelve lymph nodes are required in the International Union against cancer (UICC) recommendations. In patients with stage III tumours ($pT_{any}N+M0$) (Dukes' C), the 5-year survival is 30–50%. In patients with metastatic colorectal cancer (stage IV), the 5-year survival is $<5\%$ (Table 1).

This article reports on the conclusions of an expert discussion on the adjuvant treatment of colorectal cancer. The expert discussion was organised during the Third International Conference on Perspectives in Colorectal Cancer, which was organised in June 2001 in Dublin, Ireland. Well-known opinion leaders and experts from different nationalities participated in this discussion. In preparation for this expert discussion, a detailed survey and questionnaire was sent to all of the experts and the questions and answers were discussed during the meeting. This article reports their evidence-based conclusions and advises on the adjuvant treatment of colorectal cancer proposed by these experts.

Table 1
Prognosis of colorectal cancer in relation to staging

UICC-stage	TNM classification	5-Year survival (%)
Stage I	pT1N0M0 pT2N0M0	>90
Stage II	pT3N0M0 pT4N0M0	70 30
Stage III	$pT_{any}N+M0$	30–50
Stage IV	$pT_{any}N_{any}M+$	<5

UICC, The International Union against cancer.

2. Stage III colon cancer

There has been a general consensus that adjuvant treatment is indicated in stage III colon cancer. Different regimens of 5-fluorouracil (5-FU)/folinic acid (FA = leucovorin) are utilised. The Mayo Clinic regimen (5 days/every 4 weeks) and the Roswell Park regimen (weekly for 6 consecutive weeks followed by 2 weeks of rest) are considered to be standard options. Based on data in advanced disease, infusional 5-FU/FA regimens are also proposed as adjuvant treatments by some experts, but results from clinical trials are needed. The duration of an adjuvant treatment is 6–8 months, depending on the regimens. The treatment should be started as soon as possible after surgery, usually within 6–8 weeks. There is an uncertain loss of efficacy after 8–12 weeks. There is no upper age limit for treatment, but elderly, unfit patients should be followed more closely.

2.1. Supporting evidence

The intergroup trial (INT-0035) was the first large-scale study to demonstrate a significant effect of a post-operative adjuvant treatment in patients with stage III colon cancer. This trial randomised 1296 patients with stage II and III cancer (929 with stage III cancer) to one of three arms: (a) surgery alone, (b) surgery plus 12 months of levamisole, or (c) surgery plus 12 months of 5-FU plus levamisole. The study showed a 15% absolute reduction ($\pm 40\%$ relative reduction) in the risk of recurrence and a 16% absolute reduction (33% relative reduction) in the overall death rate with a combination of surgery plus 5-FU/levamisole in patients with stage III colon cancer [1,2]. Levamisole alone had no impact on the disease-free and overall survival.

Since the combination of 5-FU and FA has proved to be superior to 5-FU alone in patients with advanced colorectal cancer, a number of studies have confirmed the efficacy of 5-FU modulated by FA as adjuvant treatment, when compared with no postoperative treatment control arm [3]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol C-03 indicated a disease-free (73% versus 64%) and overall (84% versus 77%) survival advantage for the 5-FU/FA combination when compared with MOF (methyl-CCNU, oncovin, 5-FU) at 3 years for patients with Dukes' stage B and C colon cancers [4]. The control arm in this study (MOF) had previously shown a borderline survival

advantage over surgery alone in the adjuvant setting. The Canadian and European consortium trial (IMPACT) is a common analysis of three trials which compared adjuvant treatment with high-dose 5-FU and FA with no treatment in nearly 1500 patients; they demonstrated a 22% relative risk reduction in mortality at 3 years in Dukes' C patients [5]. A similar in design, but smaller, Italian study showed a 39% reduction in mortality for the same group of patients [6]. With a median follow-up duration at 72 months, an intergroup study indicated that patients who received a combination of 5-FU and low dose FA over 6 months experienced a significant improvement in the time to relapse ($P < 0.01$) and survival ($P = 0.02$) compared with control patients treated with surgery alone. Based on indirect comparisons of these trials with 5-FU/levamisole and 5-FU/FA, it was therefore suggested that both regimens could be equally effective.

More recently, the results of three large adjuvant American trials have been presented in which several thousands of patients have been treated (Table 2). In a large, randomised study by the North Central Cancer Treatment Group (NCCTG) and the National Cancer Institute of Canada (NCIC), it was shown that there was no additional benefit associated with administration of a full year of chemotherapy compared with just 6 months of treatment with the same regimen [7]. In the same study, it is shown that, if only 6 months of chemotherapy was administered, patient survival was significantly inferior with the 5-FU plus levamisole regimen compared with the three-drug regimen of 5-FU plus levamisole plus leucovorin [7]. At the 1998 American Society of Clinical Oncologists (ASCO) meeting, the intergroup reported that there was no additional benefit from the addition of levamisole when 5-FU/FA is given, and moreover 6–8 months of treatment with 5-FU/FA was as efficient as 12 months of 5-FU/levamisole (INT-0089) [8]. The NSABP C-04 study showed similar results for 1 year of treatment with 5-FU/levamisole, 5-FU/FA and 5-FU/FA/levamisole [9] (Table 2). Taking into account the increased toxicity of the three-drug combination (5-FU/FA/levamisole) compared with the combination of 5-FU/FA, it has been accepted that treatment with 5-FU/FA for 6–8 months is the standard treatment for Dukes' C (stage III) colon carcinoma [10–12]. The largest study ever done in this setting by the Quasar has recently confirmed these results and demonstrated that low dose of FA was as effective as high dose [13]. There was no difference in the NSABP C-O4 and in the Quasar trials between the weekly and monthly regimens of 5-FU/FA [9,13].

Two regimens of 5-FU/FA are generally used in the USA: weekly FA (500 mg/m^2) plus 5-FU (500 mg/m^2) during 6 weeks followed by 2 weeks of rest for four cycles (Roswell Park Regimen) or the 'NCTTG/Mayo Clinic Regimen': FA (20 mg/m^2) + 5-FU (425 mg/m^2) days 1–5 repeated every 4–5 weeks for 6–7 months. In Europe, the Mayo Clinic regimen is usually utilised as the standard regimen. Several new ongoing studies are evaluating the role of other 5-FU regimens as adjuvant treatments: infusional 5-FU, infusional 5-FU/FA and shorter duration (3 months). It has been shown that infusional 5-FU ± FA regimens are more efficient in terms of response rate and time to tumour progression (TTP) than bolus 5-FU ± FA regimens in patients with advanced colorectal cancer [14–18]. Despite greater technical requirements, the tolerance of infusional 5-FU regimens is better than that of bolus regimens in patients with advanced colorectal cancer [16]. Preliminary results of two studies have shown the feasibility

Table 2

Trial	Regimen	Patients (*n*)	5-year disease-free survival rate (%)	5-year overall survival rate (%)
NCCTG-NCIC [7]	5-FU/levamisole (6 months)	230	58	60
	5-FU/FA (Mayo Clinic regimen) + levamisole (6 months)	225	63	70
	5-FU/levamisole (1 year)	228	63	68
	5-FU/FA (Mayo Clinic regimen) + levamisole (1 year)	232	57	63
INT 0089 [8]	5-FU/levamisole (1 year)	833	56	63
	5-FU/FA weekly (8 months)	946	59	65
	5-FU/FA (Mayo Clinic regimen) (6 months)	953	60	66
	5-FU/FA (Mayo Clinic regimen) + levamisole (6 months)	827	60	67
NSABP C-04 [9]	5-FU/levamisole (1 year)	691	60	70
	5-FU/FA weekly (1 year)	691	65	74
	5-FU/FA weekly + levamisole (1 year)	696	64	73

5-FU, 5-fluorouracil; FA, folinic acid; NCCTG, North Central Cancer Treatment Group; NCIC, National Cancer Institute of Canada; INT, Intergroup; NSABP, National Surgical Adjuvant Breast and Bowel Project.

of infusional regimens and a different toxicity pattern compared with bolus regimens in the adjuvant treatment of colon cancer. The preliminary results demonstrated an identical disease-free survival and overall survival [19,20].

The topoisomerase I inhibitor, irinotecan (CPT-11), and the diaminocyclohexane platinum derivative, oxaliplatin, are two new drugs that are active in advanced colon cancer which hold promise as potentially effective drugs in early colon cancers. Large phase III trials are at present ongoing to evaluate the role of irinotecan and of oxaliplatin in combination with 5-FU/FA in the adjuvant treatment of stage II and III colon cancers. The oral fluoropyrimidines, capecitabine and uracil/ftorafur (UFT) + FA, are also presently under evaluation as adjuvant treatment for colon cancer.

3. Stage II colon cancer

The panel of experts did not recommend routine treatment of all stage II patients. The preference of the experts was to treat patients in clinical trials.

However, many patients with stage II colon cancer are presently treated with chemotherapy, although data from prospective randomised trials are lacking. Selection is often done on additional risk factors for recurrence. It is possible to define high-risk populations for recurrence. However, no consensus was reached on a common definition of a high-risk stage II colon cancer population. Several factors may be important: T_4 tumour, perineural invasion, venous invasion, lymphatic vessel invasion, poor tumour differentiation, tumour soiling or perforation and colonic obstruction at presentation. Based on available prospective data, however, it is not possible to define a high-risk population that benefits from adjuvant treatments.

Molecular markers are important and data are emerging on their prognostic value. However, treatment decisions should not be based on these molecular markers at present. The most relevant molecular markers at present appear to be microsatellite instability (MSI) and thymidylate synthase (TS) expression.

Future trials should therefore focus on demonstrating a benefit of chemotherapy in stage II colon cancer, on selecting patients at a higher risk and on the demonstration of the value of clinical, pathological and molecular predictive markers for recurrence.

3.1. Supporting evidence

The question whether stage II (Dukes' B) cancer patients should be treated with adjuvant chemotherapy remains controversial. Most of the published trials on adjuvant treatment of colon cancer include stage II, as well as stage III, colon cancers. Data from large prospective trials only that allow definitive conclusions to be drawn on the role of adjuvant treatment in stage II colon cancer are still lacking. The INT-0035 trial, which compared 5-FU/levamisole plus surgery to surgery alone, showed a similar reduction in the rate of recurrence (32%) in stage II as was observed in stage III colon cancers. No benefit in overall survival was shown, perhaps because of the relative low statistical power of this study [1,2].

The International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) investigators, by combining five separate trials in which patients were randomised to postoperative 5-FU and FA in a meta-analysis or to no further therapy concluded that their analysis does not support the routine use of 5-FU + FA in patients with B2 colon cancer. The 5-year overall survival was 80 and 82% and the disease-free survival 73 and 76% for controls and for 5-FU/FA-treated patients, respectively [21].

However, the NSABP group, after combining data from four of the group's trials including stage B and C colon cancer patients, reported that patients with Dukes' B colon cancer likely benefit from adjuvant chemotherapy. The relative reduction in mortality, recurrence or disease-free survival was, in most instances, in these NSABP trials as great or greater for Dukes' B than for Dukes' C patients. The mortality reduction was 30% for Dukes' B patients and this occurred irrespective of the presence or absence of adverse prognostic factors [22]. These conclusions were, however, criticised based due to the retrospective nature of the data and to the use of relative rather than absolute improvements in survival [23,24]. This NSABP meta-analysis also put together different regimens with different control arms.

It is likely, therefore, that only a subgroup of stage II patients really benefits from postoperative treatment [10,11,18,23,24]. The value of molecular prognostic factors such as aneuploidy, expression of p53 or p21, MSI, overexpression of, and absence of expression of the deleted-in-colorectal cancer gene (*DCC*) are currently under investigation for stratifying patients for adjuvant treatment. Clinical and pathological prognostic factors such as young age, perforation or occlusion as presenting symptoms, the presence of a T_4N_0 tumour, and the presence of perineural, venous or lymphatic invasion can currently be used to identify patients at a higher risk for recurrence and may be able to select suitable stage II patients for adjuvant treatment outside of a clinical trial.

4. Colon cancer: miscellaneous aspects

Every effort should be made to examine at least 12 lymph nodes for accurate staging. Laparotomy remains

the standard type of surgery until randomised ongoing trials show a superiority for one or another aspect from laparoscopic surgery.

There is no place in clinical practice (outside of clinical trials) for active specific immune therapy, for treatment using the monoclonal antibody against the 17–1A antigen or for portal vein infusion.

Adjuvant treatment is not routinely recommended after resection of liver metastases, but may benefit selected patients. Further trials are needed.

4.1. Supporting evidence

The concept of using vaccines to induce specific immunity against carcinomas has been actively pursued over the last two decades. Early attempts to induce tumour regression in cancer patients by inducing tumour-specific immunity with autologous or allogeneic tumour cell vaccines were not successful. A European trial showed a longer recurrence-free period and a risk reduction for recurrence, but no survival advantage for active specific immunotherapy (ASI) with an autologous tumour cell Bacillus Calmette Guerin (BCG) vaccine as adjuvant treatment for stage II colon cancer [25]. An Eastern Cooperative Oncology Group (ECOG) trial, however, did not show a clinical benefit in patients with stage II and III colon cancers [26].

Monoclonal antibodies have also been developed as immunotherapy. The murine monoclonal antibody against the 17–1A antigen, edrecolomab, reduced mortality by 32% and the relapse rate by 23% in Dukes' C colon cancer patients [27] in a small randomised study with a median follow-up of 7 years.

A large randomised trial in 2761 patients did not show a difference in the recurrence rate and survival of patients treated with edrecolomab + 5-FU/FA compared with 5-FU/FA and has shown inferior results for edrecolomab alone compared with 5-FU/FA [28]. A trial from the US comparing 5-FU/FA to 5FU/FA + edrecolomab has been completed. Results are pending.

Several randomised trials have studied the effect of an intraportal infusion of chemotherapy (usually a combination of 5-FU and mitomycin) administered for several days immediately after the operation. The rationale of this treatment was that colorectal cancer recurrences are often seen in the liver. Initially, some positive results were reported showing a lower hepatic recurrence rate. However, these results could not always be confirmed. A meta-analysis of 10 trials of adjuvant postoperative intraportal chemotherapy was performed. A small, but statistically significant, improvement in survival was found (relative risk (RR): 0.89; 95% confidence interval (CI) 0.84–0.94) [29]. However, the incidence of liver metastases was not significantly lower in this meta-analysis. The reason for this finding is not clear. This might suggest a systemic effect of intraportal chemotherapy, that may be attributed to the early postoperative administration of chemotherapy. In addition, the largest randomised trial that was published after the meta-analysis could not show any effect of intraportal adjuvant chemotherapy (EORTC) [30]. Thus, intraportal chemotherapy does not have an important role to play and its systematic use in clinical practice cannot be advised.

Adjuvant systemic chemotherapy administered after resection of liver metastases from colorectal cancer to reduce the risk of recurrence has been assessed both in retrospective and in a few prospective comparative studies. Until recently, none had clearly shown effectiveness. A large intergroup study was closed due to insufficient recruitment, as many investigators believed that patients should be treated anyway with systemic 5-FU/FA. A randomised study of intra-arterial 5-FU/FA after resection of liver metastases versus surgery alone did not show a significant difference in median survival (34.5 months for chemotherapy versus 40.8 months for the control group) [31]. Two studies using adjuvant hepatic arterial infusion with or without systemic chemotherapy after resection of liver metastases have been presented recently. One study demonstrated a significant improvement in 3-year recurrence-free survival compared with surgery alone (58 versus 34%; $P = 0.039$) [32]. The other study compared hepatic arterial infusion of FUDR in combination with 5-FU/FA intravenously (i.v.) versus 5-FU/FA i.v. alone after resection of liver metastases. The 2-year survival was significantly better for patients treated with a combined approach (86% versus 72%; $P < 0.05$). However, the 5-year survival rate was not significantly different (61 versus 49%) [33,34]. These results are encouraging for the future, but significant toxicity, costs and patient and centre selection prohibit this treatment from becoming standard treatment, particularly in Europe [35]. Preoperative chemotherapy in resectable liver metastases is under investigation.

5. Rectal cancer

The definition of rectal cancer in clinical practice remains controversial. The definition for clinical practice is not always identical to the anatomical definition. The most frequently used definition in clinical practice is a tumour that is localised at or below the peritoneal reflection during surgery. The most difficult and challenging concept is the definition of rectal cancer in patients not yet operated upon, in view of the decision of a neoadjuvant preoperative treatment. Rectal cancer is usually defined as a cancer that has its lower border within 12–15 cm from the anal verge evaluated by rigid rectoscopy.

Adequate preoperative staging includes clinical examination and examination by endoscopic ultrasound

and computerised tomography (CT)-scan. High quality magnetic resonance imaging (MRI) has an emerging role.

Rectal cancer surgery needs experienced and dedicated surgeons, as the outcome is directly correlated with the experience of the surgeon. In all tumours, a circumferential resection is required. In mid- and lower rectal cancers, standard surgery is total mesorectal excision (TME). An adjuvant treatment regimen cannot compensate for suboptimal surgery.

Neoadjuvant and/or adjuvant treatment is indicated in T3–4N0 and $T_{all}N+$ rectal cancers. Postoperative radiotherapy alone and postoperative chemotherapy alone are not valid options. Different strategies can be proposed: (a) preoperative radiotherapy (short course: 5×5 Gy); (b) preoperative radiotherapy (long course: 1.8–2 Gy/fraction, total dose of 45–50.4 Gy during 5 weeks)±5-FU-based chemotherapy; (c) postoperative radiotherapy (45 Gy in fractions of 1.8 Gy + boost of 5.4 Gy) plus chemotherapy with 5-FU/FA.

5.1. Supporting evidence

Locoregional failure is clinically more important in patients with rectal cancer than in patients with colon cancer. Distant metastases are also seen in approximately 25% of patients. The aims of (neo-)adjuvant therapy before or after resection of rectal cancer are to improve local tumour control, to decrease distant metastases and to improve survival. Postoperative radiotherapy alone decreases slightly the local relapse rate, but does not improve the survival. It is also generally accepted that postoperative chemotherapy alone does not increase survival, although one trial did show a survival difference [36,37]. Two American and a Norwegian study have shown that a combined modality approach with chemoradiotherapy after surgery provides a significant benefit in local and distant recurrences and an increased survival compared with either surgery alone, postoperative chemotherapy or postoperative radiotherapy [38–40]. However, the picture is not entirely clear and the superiority of postoperative chemoradiotherapy over either modality alone has been questioned [41,42]. In another trial, continuously administered 5-FU during radiotherapy demonstrated a further significant effect on distant metastases and survival in comparison to a 5-FU concurrent bolus scheme [43]. The main advantage of postoperative treatment is the optimal selection of patients based on surgical observations and pathological specimen analysis.

Europeans have generally turned towards preoperative radiotherapy. North American investigators are also evaluating preoperative radiotherapy. Several types of radiotherapy regimens are used in the preoperative setting including: short-regimen of radiotherapy (5×5 Gy), surgery being planned immediately after radiotherapy, and a conventional long-course radiation (1.8–2 Gy/fraction: total 45–50.4 Gy), surgery being planned after a 4–6 weeks interval. The potential advantages of a preoperative approach over a postoperative one are: a decreased tumour seeding during operation, less acute and late toxicity, increased efficacy of radiotherapy and for patients who receive a conventional long course of radiotherapy an increased rate of sphincter preservation [44]. It is accepted that long-course radiation regimens can down-size a rectal cancer, whereas short-course radiation regimens do not induce down-sizing of the tumour. The long-course radiation regimens might therefore be more suitable for more locally advanced cancers.

Several large randomised trials have tested preoperative radiotherapy in comparison to surgery alone and have demonstrated a lower local recurrence rate, but no improved survival in most of the trials with preoperative radiation alone [45]. The Swedish trial, however, has shown an advantage in overall survival, as well as in locoregional recurrence, with the short-course preoperative radiation regimen (5×5 Gy) [46]. The Dutch Colorectal Cancer Group has shown that the addition of a short-course radiation to optimal surgery (total mesorectal excision) still reduces the risk of local recurrence in all stages of rectal cancer: 2.4% versus 8.1% in the surgery alone group ($P<0.001$), but did not improve the 2-year survival [47].

Two randomised trials are testing preoperative versus postoperative conventional long-course radiation plus chemotherapy and the final results are pending.

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