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Colorectal Cancer: The Challenge

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Colorectal cancer is a common cancer and a common cause of death. The incidence varies widely and is highest in industrialised Western countries. Surgery remains the mainstay of treatment of localised tumours and, in addition, may also play a role in some patients with local recurrence and/or isolated liver or lung metastases. Chemotherapy is required to improve the results of surgery and to treat patients with disseminated disease. For more than 30 years, 5-fluorouracil (5-FU) has been the only active agent in advanced colorectal cancer with an overall response rate of less than 15%. Biomodulation of 5-FU with leucovorin has led to a substantial increase in the response rate, but only a modest benefit in survival. Improvement in palliative effects has also been observed. In adjuvant treatment after curative surgery, 5-FU with levamisole or leucovorin has shown approximately a 10% absolute increase in survival, compared with controls. Despite this progress, there is evidence that an important proportion of colorectal cancer patients remains untreated. New treatments, such as the direct and specific thymidylate synthase inhibitors (e.g. 'Tomudex'™—raltitrexed, previously known as ZD1694) in first-line therapy, or CPT-11 or oxaliplatin, along with increased referral and a more consistent treatment approach could improve the outcome of patients with advanced colorectal cancer.

Key words: colorectal cancer, chemotherapy, 5-fluorouracil, leucovorin
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INTRODUCTION

COLORECTAL CANCER is both a common cancer and a common cause of cancer death. Mortality from colorectal cancer in the U.S.A. ranks third behind lung and prostate cancer in men, and lung and breast cancer in women [1]. Significant progress has been made with surgery, adjuvant chemotherapy and the addition of radiotherapy for rectal cancer. Moreover, even in disseminated disease, the data indicate that not only can survival be prolonged, but a better quality of life can also be obtained in comparison with untreated patients.

Epidemiology

The world-wide incidence of colorectal cancer varies widely between countries and races: high incidence is seen in industrialised Western countries such as Northern and Western Europe, United Kingdom and Canada; lower rates are seen in Asia and Africa. Within countries, the incidence is higher in urban areas compared with rural areas. In the U.S.A, almost 150 000 new cases of colorectal cancer are diagnosed annually and approximately 57 000 patients die from their disease each year (Table 1) [1]. The world-wide incidence has remained stable over the last 30 years, although there has been an increase in actual numbers owing to an expansion in the population size [2].

Although the aetiology of colorectal cancer is not fully understood, many risk factors have been identified: a first degree relative with colon cancer [3], a medical history of chronic inflammatory bowel disease [4] and a history of cigarette smoking [5] are all associated with an increased risk of colorectal cancer. Perhaps the most important environmental factor is diet, particularly fat intake [6]. A positive correlation between the incidence of colon cancer and total fat intake has been demonstrated, an association clearly highlighted in Japan where diet has undergone a dramatic change over the last 50 years: fat intake has increased from 10% to 25% of total energy intake, accompanied by a striking rise in mortality from colon cancer [6].

Table 1. Reported deaths for main cancer sites by sex in the U.S.A., 1991

	Males	Females
All cancers	272 380	242 277
Lung	91 690	52 068
Prostate	33 564	—
Breast	—	43 583
Colon and rectum	28 178	29 017
Ovary	—	13 247
Pancreas	12 375	13 161
Leukaemia	10 194	—

Source: National Center for Health Statistics: Vital Statistics of the United States, 1991. Washington DC, Public Health Service, 1994.

Table 2. Influence of the stage of the disease on postoperative prognosis in colorectal cancer [7]

Surgical stage	5-year survival rate (%)	
	1940s and 1950s	1960s and 1970s
A (T1)	80	> 90
B1 (T2N0)	60	85
B2 (T3N0)	45	70–75
C (T1-T3N1-2)	15–30	45–60

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Prognosis

Colorectal cancer is an important disease in terms of impact on society and healthcare services [7]. The 5-year survival rates have, however, improved in both men and women over the last 50 years [1, 7]. When comparing the survival rates by disease stage over four decades, an increase of approximately 30% is observed (Table 2). This is more apparent if the overall 5-year survival rates for colon and rectal cancer are examined, decade by decade, from the 1960s to the late 1980s: an increase in survival from 43% to 61% for colon cancer and from 38% to 58% for rectal cancer is seen [1]. The increased survival rates translate into a decrease in mortality from colorectal cancer over the last 50 years, which is more marked in women than men [1]. As no active adjuvant treatment was available during this period, it can be speculated that the increase may be due to earlier diagnosis and/or improvement in operative techniques and peri-operative care.

TREATMENT

Surgery is the only potentially curative therapy for colorectal cancer and remains the first line treatment for patients with localised disease. The prognosis of patients following surgery depends on the tumour stage; for those patients with lymph node involvement, the overall 5-year survival is less than 40% [8]. Adjuvant chemotherapy, therefore, plays an important role in such patients. In advanced disease, palliative chemotherapy and supportive care are the mainstay of treatment. Despite numerous clinical trials investigating a variety of chemotherapeutic regimens, only modest survival benefits have been reported [9, 10]. However, selected liver and lung metastases and some locally recurrent cancers may still be resected to achieve a cure in a small subset of patients.

Chemotherapy for advanced disease

For many years, 5-fluorouracil (5-FU) was the only available treatment for advanced colorectal cancer. Reported response rates ranged from between 0 and 87% [11], reflecting the methodological inconsistencies between reported trials. Differences in patient selection, such as disease stage and performance status, and the lack of standard methods for assessing the response, may explain these discrepancies.

In the most recent studies, 5-FU was given weekly or during 5 consecutive days, every 4 or 5 weeks. At dose intensities of 525–550 mg/m^2/week, response rates in the range of 12–17% were observed, with a median survival time of less than 1 year [12, 13]. Some data suggest that the response rate is directly related to the dose intensity [14].

Administration schedules. In order to improve this poor response rate, modifications in the route and schedule of 5-FU administration have been investigated. As colorectal cancer is a slow-growing cancer with less than 3% of cells actively dividing at one time, and the plasma half-life of 5-FU is short [15], a major limitation of bolus administration is the small fraction of cells that are susceptible to chemotherapy. This can be overcome by administering 5-FU as a continuous infusion which has been made feasible by advances in pump technology and can now be given on an outpatient basis. Continuous infusion has been given over various time periods: 24 h once-weekly [16], 48 h bi-weekly [17], 5 consecutive days monthly [18] or indefinitely [19]. Although the delivered dose intensities were significantly higher (2000 mg/m^2 compared with 525–550 mg/m^2 for the bolus administration), the toxicity profile was favourable, with less mucositis and myelotoxicity: palmar–plantar erythrodysesthesia became the most frequently observed event and encephalopathia the dose-limiting toxicity. Comparison of daily bolus injections (for 5 consecutive days, repeated at 5-week intervals) with continuous infusion (for at least 10 weeks), showed significantly greater response rates with continuous administration (7% and 30%, respectively; $P < 0.0001$) [19]. However, despite a fourfold difference in objective response rate, no survival advantage could be seen. Other randomised studies have reported similar results with response rates in the range of 25–35%, but again no survival advantage could be demonstrated [20, 21]. Additional cost associated with the use of pump devices may limit the widespread use of this schedule.

Hepatic artery infusion (HAI) is another approach to trying to increase the efficacy of 5-FU or of its analogue, floxuridine, in patients with hepatic metastases. Administration via this route results in high hepatic extraction and drug concentration with theoretically less systemic exposure. Early investigations used external pumps which were associated with arterial thrombosis and catheter dislocation. The development of implantable infusion devices has renewed the interest for this mode of administration. Five prospective randomised trials comparing HAI with systemic therapy have been reported [22–26]. All five trials demonstrated a significantly greater response rate with HAI compared with systemic therapy, with a mean response rate of 51% versus 16%, respectively [27]. The overall effect on survival is difficult to evaluate because two trials allowed non-responders in the systemic arm to cross over to the HAI arm [22, 23]. However, two studies reported increased 2-year survival rates [24, 26], and the two studies which permitted crossover also demonstrated a survival advantage in patients who received HAI both initially or after the crossover. A meta-analysis of these trials showed a statistically significant survival advantage for HAI compared with *ad libitum* control, but not compared with intravenous chemotherapy [28]. Toxicity with HAI can be significant; the most frequently reported events are chemical hepatitis, biliary sclerosis, duodenal ulceration and haemorrhage.

Combination chemotherapy. Attempts to improve efficacy by combining 5-FU with other chemotherapeutic agents, such as methyl-CCNU or cisplatin, have failed to demonstrate either improved response rates or increased survival [18, 29–32]. Combination therapy was also associated with increased toxicity and, therefore, such combinations are not recommended for routine clinical use.

Biomodulation. The most effective treatment strategy to improve the outcome has been the biomodulation of 5-FU with various agents, amongst which leucovorin, methotrexate and

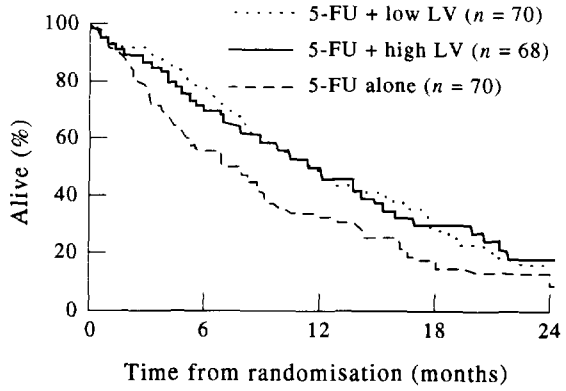

Figure 1. Survival of patients treated with 5-FU alone, 5-FU plus high-dose leucovorin (LV), or 5-FU plus low-dose leucovorin. Reprinted by permission from Poon MA, *et al.*, *J Clin Oncol* 1989, Vol. 7, pp. 1407–1418.

interferon alpha are the most investigated. Of these, the most extensively used modulator is leucovorin. Leucovorin acts by forming a ternary complex with the enzyme thymidylate synthase and the active metabolite of 5-FU, fluorodeoxyuridine monophosphate, which increases and prolongs the competitive inhibition of thymidylate synthase.

To date, 13 randomised trials have been reported comparing 5-FU plus leucovorin with 5-FU monotherapy in patients with advanced colorectal cancer [12, 13, 31, 33–42]. Two studies demonstrated a survival advantage [31, 36] and 10 reported increased response rates with 5-FU plus leucovorin [13, 31, 33, 34, 36–41]. High- or low-dose leucovorin appear equally effective [31] (Figure 1). A meta-analysis of nine randomised trials, incorporating 1831 patients, has shown a highly significant benefit over single-agent 5-FU in terms of tumour response rate (23% vs 11%) but no survival benefit could be demonstrated [43] probably due to second-line treatment.

Many schedules employing 5-FU plus leucovorin have been investigated, but no regimen has been established as being superior to the others [31]. In a comparison of two commonly used regimens—5 consecutive days of 5-FU plus low-dose leucovorin or weekly 5-FU plus high-dose leucovorin—no difference in response rate, survival rate or palliative effect could be demonstrated [44]. However, significant differences were apparent in the toxicity profiles; leucopenia and stomatitis were the major toxicities in the intensive course, whereas diarrhoea was the most frequently reported event with the weekly regimen. The latter regimen had an additional requirement for hospitalisation to manage toxicity, resulting in a higher financial cost.

There is some evidence to indicate that 5-FU plus methotrexate is more effective than 5-FU alone and may confer a survival advantage [31, 45], although this combination has not been extensively studied. Improved response rates are seen if methotrexate is given prior to 5-FU but the variable response rates reported in the literature may reflect differences in doses and schedules. A recent meta-analysis has compared the combination of methotrexate and 5-FU ± leucovorin with 5-FU alone and has demonstrated an improved response rate and increase in overall survival of the combination [46].

The use of interferon alpha in combination with 5-FU has been investigated [47, 48]. No significant survival advantage has been demonstrated and excessive neurotoxicity has been reported [47, 48]. This combination is therefore not used in clinical practice.

Adjuvant chemotherapy

Three studies have shown a benefit in survival for adjuvant therapy. The results of a randomised trial of 5-FU plus levamisole have been reported in patients with stage III colorectal cancer. Combination therapy reduced the recurrence rate by 40% ($P < 0.0001$) and the mortality rate by 33% ($P < 0.001$) compared with no treatment [49]. Levamisole alone was not superior to the control arm. The advantage of treatment was still apparent after an 8-year follow-up period [8].

Trials of adjuvant 5-FU bolus weekly plus 500 mg/m^2 leucovorin in patients with Dukes' stage B and C cancer have reported increased survival and a significantly prolonged disease-free interval, compared with the combination chemotherapy lomustine, vincristine and 5-FU (MOP) ($P < 0.005$) [50]. After a 3-year follow-up, the patients receiving 5-FU plus leucovorin had a 30% reduction in treatment failure and a 32% reduction in mortality rate, compared with the MOP-treated patients. A pooled analysis of three randomised trials of 5-FU bolus with leucovorin 200 mg/m^2 over 5 consecutive days monthly for 6 months versus surgery alone, also showed a survival benefit with chemotherapy [51]: the mortality rate was reduced by 22% in the treated group ($P < 0.05$).

New strategies

New therapeutic strategies in the treatment of advanced colorectal cancer, such as thymidylate synthase inhibitors, topoisomerase I inhibitors and oxaliplatin, are currently being developed. Thymidylate synthase inhibitors are the most widely studied as first line therapy and offer therapeutic activity similar to the most effective 5-FU regimens but with less toxicity. Their potential advantage as compared with the 5-FU regimens is a more convenient dosing schedule.

TREATING ADVANCED COLORECTAL CANCER: THE CHALLENGE

In addition to the increased response rates obtained with the modulated 5-FU regimens [31, 43], a 3–4 month increase in median survival time has been documented compared with 5-FU alone [31, 36]. A 6-month median survival advantage has also been demonstrated with chemotherapy compared with supportive care alone [9] and with early intervention versus late treatment [10]. Furthermore, recently published data suggest that palliative chemotherapy is cost-effective in comparison with supportive care alone [52].

Importantly, palliative effects and improvement in quality of life have been demonstrated following chemotherapy in patients with advanced disease [31, 53]. Poon and associates

Table 3. Percentage of improvement with various palliative treatments

	5-FU	5-FU/ methotrexate	5-FU/ leucovorin (high dose)	5-FU/ leucovorin (low dose)
Improved performance status	13	31	34	33
Weight gain	14	20	25	31
Symptomatic improvement	34	56	40	69

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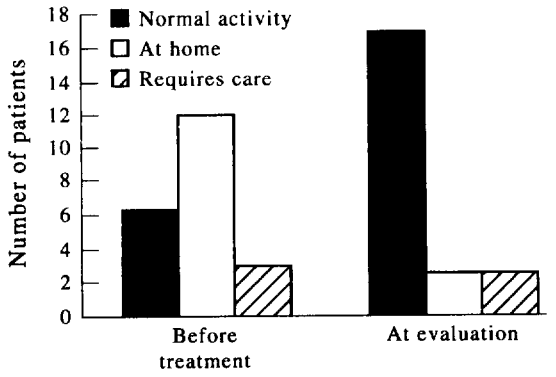

Figure 2. Improvement in performance status with 5-FU in patients with advanced colorectal cancer. Reprinted by permission of Karger, Basel from Hansen RM, *et al.*, *Oncology* 1989, Vol. 46, pp. 245–250.

[31] demonstrated that treatment with 5-FU and leucovorin significantly improved performance status, body weight and tumour-related symptoms ($P < 0.05$) compared with 5-FU alone (Table 3). It has been clearly shown that patients have an improved performance status in terms of resumption of normal activity after treatment compared with their status at the first evaluation [54] (Figure 2).

Despite this clear demonstration of the benefits from chemotherapy for patients with advanced colorectal cancer, an international survey of oncology specialists suggested that approximately 40% of patients are not being appropriately referred for treatment [55] and current management of advanced disease is not always consistent. Referral rates are variable between hospitals and between different countries and it is difficult to estimate how often treatment is offered, what dosages are used and the level of patient compliance. It can be expected that clinicians with little experience of the disease may use inadequate doses, leading to a decreased activity of treatment. In other areas, such as breast cancer, a clear correlation exists between compliance to treatment and survival. Patient referral to centres which see large numbers of patients and the use of a multidisciplinary approach improves the overall quality of care and survival [56]. There is no clear treatment consensus in the management of colorectal cancer, and the treatment a patient receives largely depends on where they are seen. It is estimated that less than 1% of the patients enter into randomised clinical trials [57] despite their apparent willingness to receive chemotherapy [58].

Further improvement in the management of patients with this common and important disease is vital. Patients are probably undertreated and increased referral, a more consistent approach to treatment and a multidisciplinary approach could be expected to lead to a better outcome for patients with advanced colorectal cancer. In addition, new drugs, such as the new, direct and specific thymidylate synthase inhibitors (e.g. 'Tomudex'™*—raltitrexed) in first line therapy as well as CPT-11 or oxaliplatin presently studied in second line treatment, could further improve the therapeutic options in the very near future.

* 'Tomudex' is a trademark, the property of Zeneca Limited.

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