

Evolution of nonsurgical therapy for colorectal cancer

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SUMMARY

The management of colorectal cancer (CRC) has changed considerably in the past 15 years with the introduction of multiple novel active therapeutic agents. Chemotherapy regimens combining a fluoropyrimidine with either oxaliplatin or irinotecan are standard first-line and second-line therapy for advanced and metastatic disease. The first-line use of these combinations produces tumor response rates of ~50% and a median overall survival of ~20 months. Addition of bevacizumab to first-line treatment and addition of cetuximab to salvage therapy for patients who fail to respond to irinotecan have contributed to further increases in tumor response rates and enhanced progression-free survival. Such approaches have produced only marginal overall survival benefits, however, and entail considerable cost. Adjuvant chemotherapy, delivered after surgical resection of the primary tumor, increases cure rates by ~10% for stage III disease and ~3–4% for stage II disease. Encouraging reductions in local relapse rates have been observed in patients with early rectal cancer who have undergone chemoradiotherapy, and increasingly complex regimens are currently being explored in phase II clinical trials in an attempt to increase both the operability and long-term local control of CRC. The greater the therapeutic choice, the greater the cost (both financial and in terms of toxicity), thus the keener the clinical community becomes to develop biomarkers to select patient populations who will be most likely to benefit from a specific agent.

KEYWORDS biologic therapy, biomarkers, chemotherapy, colorectal cancer, therapeutic monoclonal antibodies

REVIEW CRITERIA

A PubMed search was performed between August 2007 and August 2008 using the term “colorectal cancer” in combination with “chemotherapy”, “biological therapy”, “pharmacogenomic”, “radiotherapy”, and “patient selection”. In addition, the proceedings of the American Society of Clinical Oncology and of the European Society of Medical Oncology 2007 and 2008 annual meetings were searched for relevant abstracts. Appropriate English-language articles and their references were reviewed. We sought to identify, when possible, randomized trials and large series. The reference list was updated in October 2008.

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INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in the Western world.¹ After decades of clinical research dedicated to optimizing clinical care for patients with CRC, median survival for those with advanced disease has increased from approximately 6 months in untreated patients to about 20 months in those treated with sequential combination chemotherapy. In addition, advances in surgery, postoperative care and adjuvant treatment are beginning to translate into real reductions in CRC mortality in the developed world. This Review summarizes the contribution of combination chemotherapy, therapeutic monoclonal antibodies, adjuvant treatment, chemoradiotherapy, and biomarkers to the improved clinical outcomes observed in patients with CRC.

CHEMOTHERAPY FOR ADVANCED COLORECTAL CANCER

The therapeutic mainstay for CRC is 5-fluorouracil (5-FU). This antimetabolite inhibits DNA and RNA synthesis by blocking thymidylate synthase (TS) and by incorporating futile bases into RNA molecules. There is a good clinical and pharmacological rationale for combining 5-FU with leucovorin (LV), as LV stabilizes the ternary complex formed between 5-FU and TS, thus potentiating inhibition of the latter.

Overall, clinical trials comparing 5-FU plus LV chemotherapy with 5-FU alone show that combination therapy doubles tumor response rates; however, the addition of LV has little or no effect on overall survival (OS).

Importantly, in the past decade two new cytotoxic agents have emerged: irinotecan, a topoisomerase I inhibitor; and oxaliplatin, a DNA cross-linking agent. In patients with CRC, both these agents have improved tumor response rates, increased duration of progression-free survival (PFS), and produced some benefit in OS when given in combination with infusional 5-FU plus LV compared with 5-FU plus LV only.^{2–10} Data from many trials including

thousands of patients support first-line and second-line chemotherapy with combinations of 5-FU and LV plus oxaliplatin or irinotecan.

Over the past 10 years, there has been a steady increase in survival for patients with advanced CRC so that median OS is now 18–20 months (Figure 1).¹¹ This increase must, in part, be because of the evolution of novel chemotherapy regimens. It must be recognized, however, that methods of detecting small-volume (<1 cm³) recurrent metastatic disease have improved, and that as a clinical community we have developed an increasing tendency to screen for metastatic disease at regular intervals after primary resection. Consequently, metastatic disease is more frequently detected at a small volume, which will inevitably produce a degree of lead-time bias in our interpretation of the results gleaned from trials of novel chemotherapy regimens compared with studies of historical regimens.

In addition, it is important to remember that the benefits brought about by our increasing tendency to use more-intensive chemotherapy regimens have been achieved at a cost of increased toxic effects. The use of oxaliplatin-containing and irinotecan-containing regimens has doubled the rates of serious neutropenia; oxaliplatin induces neurotoxicity and irinotecan induces alopecia and a significant increase in the incidence of high-grade diarrhea.^{2–10} It is common practice among most clinicians who treat CRC to use combinations of 5-FU plus oxaliplatin or 5-FU plus irinotecan, in either order, for first-line and second-line therapy. There is a compelling rationale to deliver oxaliplatin only in combination with 5-FU plus LV because there are data to indicate that there is true synergy between these two cytotoxic agents (i.e. the combined efficacy of the two drugs is greater than the sum of their constituent single-agent efficacies).¹² This is not the case with irinotecan, however, and whether this drug should be given as a single agent or as part of combination therapy remains contentious, especially for second-line treatment in the advanced disease setting.

Although many clinicians believe that dual combination chemotherapy should always be the standard first-line therapy for advanced CRC, two European studies have questioned this philosophy.^{13,14} Broadly similar in design, these trials compared serial chemotherapy (5-FU plus LV followed by irinotecan) with sequential combination chemotherapy (5-FU

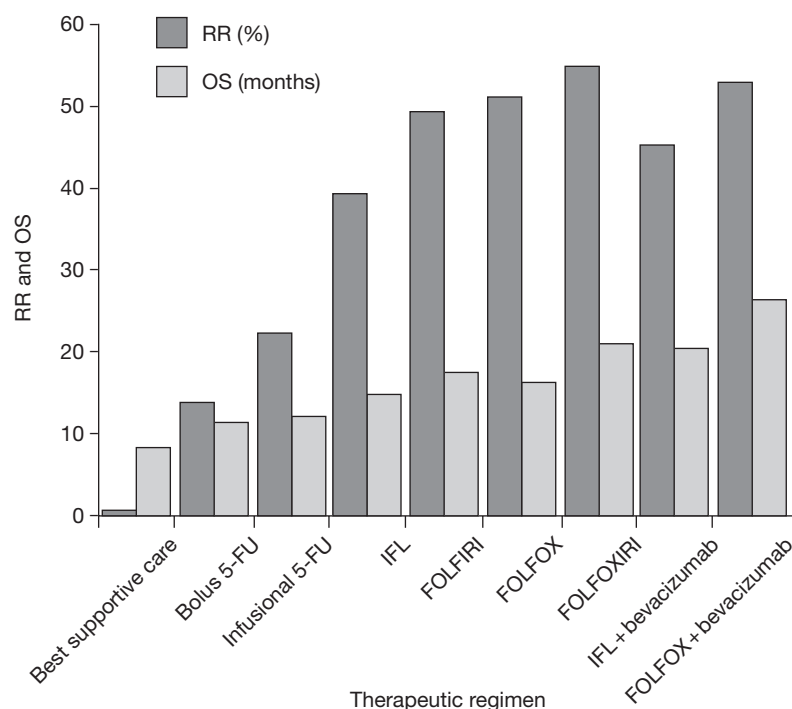


Figure 1 Increasing RRs and OS during the evolution of chemotherapy for advanced colorectal cancer. Best supportive care entails symptomatic treatment only. Abbreviations: 5-FU, 5-fluorouracil; FOLFIRI, 5-fluorouracil plus leucovorin in combination with irinotecan; FOLFOX, 5-fluorouracil plus leucovorin in combination with oxaliplatin; FOLFOXIRI, 5-fluorouracil plus leucovorin, oxaliplatin and irinotecan combination therapy; IFL, irinotecan, leucovorin and 5-fluorouracil; OS, overall survival; RR, response rate.

and LV plus irinotecan or oxaliplatin). In the FOCUS trial,¹³ more than 2,000 patients were randomly allocated to one of the following five treatment groups: initial 5-FU (46 h infusion every 2 weeks) and LV, followed by single-agent irinotecan (30–90 min drip on day 1 of a 3-week cycle) on 5-FU plus LV failure (arm 1); initial 5-FU plus LV, followed by 5-FU plus LV in combination with either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX; arms 2 and 3, respectively) on 5-FU plus LV failure; or initial upfront FOLFIRI or FOLFOX (arms 4 and 5, respectively). When irinotecan and oxaliplatin are given with 5-FU plus LV, these cytotoxic agents are generally administered on the first day of the 2-week cycle. In the CAIRO trial,¹⁴ sequential therapy (capecitabine monotherapy followed by irinotecan monotherapy then finally combination therapy with capecitabine plus oxaliplatin [CAPOX]) was compared with combination therapy (initial therapy with capecitabine plus irinotecan [CAPIRI] followed by therapy with CAPOX). Capecitabine tablets

are generally given for 2 weeks of a 3-week cycle and any additional cytotoxic drugs (e.g. irinotecan or oxaliplatin) are generally administered on the first day of each cycle.

Both trials showed that initial fluoropyrimidine therapy followed by combination chemotherapy on failure of monotherapy provides similar survival benefits to combination chemotherapy administered from the outset.^{13,14} The interpretation of these trial results and their translation into routine clinical practice is an ongoing process. Many experts would agree that these trials support a risk-adapted approach in which a sequential strategy might be used for patients with either less-aggressive cancer or a considerable degree of comorbidity, which precludes the first-line use of a combination regimen. Patients with more-aggressive cancer, and those who are fit enough to endure more-intensive first-line treatment, should receive combination treatment from the outset. This risk-adapted approach would thereby maximize response rates and open up the possibility of using other potentially curative treatment modalities such as resection of liver metastases and radiofrequency ablation, the details of which are outside the scope of this Review.

On the basis of the hypothesis that the most intensive treatment strategy represents the most effective treatment, the Gruppo Oncologico Nord Ovest conducted a phase III study comparing combination therapy with 5-FU plus LV, oxaliplatin and irinotecan (FOLFOXIRI; oxaliplatin and irinotecan on day 1 of a 2-week regimen) with FOLFIRI in 244 patients with previously untreated unresectable metastatic CRC.¹⁵ The primary end point was tumor response. The rates of grade 2–3 peripheral neurotoxic events and grade 3–4 neutropenia were higher in the FOLFOXIRI arm than in the FOLFIRI arm (0% vs 19%; $P < 0.001$ and 28% vs 50%; $P < 0.001$, respectively). The incidence of febrile neutropenia and that of grade 3–4 diarrhea was not significantly different between arms. The proportion of patients who showed a complete response to treatment was similar in the FOLFOXIRI and the FOLFIRI arms (8% vs 6%, respectively) but the partial response rate was greater in the FOLFOXIRI arm (58% vs 35% for FOLFIRI), giving an overall response rate of 66% in the FOLFOXIRI group and 41% in the FOLFIRI group ($P = 0.0002$). The rate of successful secondary-metastasis resection with uninvolved margins (R_0) was greater in the

FOLFOXIRI arm than the FOLFIRI arm among all 244 patients (15% vs 6%; $P = 0.033$) and selectively among patients with liver metastases only (36% vs 12%; $P = 0.017$). PFS and OS were both significantly better in the FOLFOXIRI arm than in the FOLFIRI arm (median PFS 9.8 months vs 6.9 months, hazard ratio [HR] 0.63; $P = 0.0006$ and median OS 22.6 months vs 16.7 months, HR 0.70; $P = 0.032$).¹⁵

The authors concluded that further studies of combination chemotherapy with FOLFOXIRI in the neoadjuvant setting are warranted. It is likely that only within this rather selective setting would the increased level of toxic effects be deemed a clinically acceptable price to pay for the improved response rates.

Fluoropyrimidine selection

5-FU has been used for the treatment of CRC for more than four decades, yet there is still controversy about the optimum 5-FU regimen. Two parameters need to be considered when evaluating 5-FU regimen: dose of 5-FU and duration of exposure. 5-FU is a cycle-specific and phase-specific antineoplastic agent, and prolonged exposure kills a greater fraction of cells than short-term therapy. Prolonged exposure can be achieved either by repeatedly giving high-dose bolus treatment or by administering a continuous infusion of 5-FU at a much lower dose. A variety of 5-FU plus LV regimens exist (both bolus and infusional), but the superiority of one particular regimen has not been established because of a lack of enthusiasm within the oncology community to perform any large-scale trials. Two large trials, however, have shown that capecitabine,¹⁶ an oral prodrug of 5-FU designed to generate the active agent preferentially at the tumor site, is therapeutically equivalent to bolus 5-FU plus LV (Mayo Clinic regimen—5-FU and LV as bolus injections for 5 days every 4 weeks) for first-line therapy in metastatic CRC.^{17,18} After these two trials were performed, approximately 2,000 patients with stage III colon (but not rectal) cancer were treated with adjuvant capecitabine (1,250 mg/m² twice daily on days 1–14 every 3 weeks), and the oral prodrug was shown to have similar efficacy to the Mayo clinic 5-FU plus LV regimen.¹⁹ These data highlighted an obvious development pathway for capecitabine—could this agent replace 5-FU as the fluoropyrimidine backbone of combination therapy with irinotecan and/or oxaliplatin?

A variety of trials have indicated that capecitabine and irinotecan can be combined but that treatment-related diarrhea might cause considerable morbidity.¹⁴ The BICC-C study²⁰ randomly assigned 430 patients to one of the following three chemotherapy regimens: conventional chemotherapy with FOLFIRI; irinotecan, LV and 5-FU (mIFL; all administered on day 1 and day 8 in a 3-weekly regimen); or CAPIRI (irinotecan on day 1 and oral capecitabine twice daily on days 1–14 in a 3-weekly regimen). A second randomization to either an oral cyclooxygenase-2 inhibitor, celecoxib, or placebo was also performed. After a median follow-up of 34 months, median OS was 23.1 months for the FOLFIRI group, 17.6 months for the mIFL group ($P=0.09$), and 18.9 months for the CAPIRI group ($P=0.27$), suggesting that there is no statistically significant difference between the regimens. The overall objective response rates likewise did not differ significantly between the chemotherapy arms (47.2% for FOLFIRI, 43.3% for mIFL and 38.6% for CAPIRI). CAPIRI was associated with the highest rates of severe (grade 3 or 4) nausea (18.4%), vomiting (15.6%), diarrhea (47.5%), dehydration (19.1%), and hand–foot syndrome (9.9%). By contrast, FOLFIRI was associated with the lowest rates of diarrhea (13.9%) and febrile neutropenia (3.6%). Of the patients receiving CAPIRI, 25% discontinued medication during the study because of unacceptable toxic effects.

The EORTC 40015 study²¹ aimed to demonstrate the noninferiority (measured by PFS) of CAPIRI compared with FOLFIRI for first-line treatment of advanced CRC. In addition, this study examined the benefit of adding celecoxib to these regimens. Patients were randomly assigned to receive FOLFIRI or CAPIRI and additionally randomly assigned to receive either placebo or celecoxib (400 mg twice daily orally). The trial was closed early following eight deaths unrelated to disease progression in the 85 patients enrolled (629 planned). Response rates were 22% for CAPIRI plus celecoxib, 48% for CAPIRI plus placebo, 32% for FOLFIRI plus celecoxib, and 46% for FOLFIRI plus placebo. Median PFS and OS were shorter for CAPIRI than for FOLFIRI (PFS 5.9 months vs 9.6 months and OS 14.8 months vs 19.9 months) and were shorter for celecoxib than those on a regimen containing placebo (PFS 6.9 months vs 7.8 months and OS 18.3 months vs 19.9 months). The authors concluded that given the small sample size

following early termination of the study, no definitive conclusions could be drawn in relation to the noninferiority of CAPIRI compared with FOLFIRI. Although CAPIRI was tolerated somewhat better in the CAIRO study¹⁴ than the EORTC 40015 study, further dose refinements and careful selection of the target population will be needed if the use of this regimen is to become more widespread.

The benefits of the CAPOX combination regimen are much clearer. A large factorial trial that recruited almost 2,000 patients showed the equivalence of CAPOX and FOLFOX.²² OS was 19.8 months with CAPOX compared with 19.4 months with FOLFOX (HR 0.99, 97.5% CI 0.88–1.12), with slightly higher rates of diarrhea and hand–foot syndrome and a lower rate of neutropenia in the CAPOX arm than in the FOLFOX arm.²² Given the relative ease of administration of oral capecitabine and the consequent reductions in costs for line insertion, nursing administration and so on, health economic models favor capecitabine as the fluoropyrimidine of choice.²² As mentioned previously, however, there is still debate about the optimum dose of capecitabine, especially in the US, whose citizens seem somewhat more sensitive to the drug than European populations in terms of toxicity.²³

Duration of chemotherapy in advanced disease

The optimum duration of chemotherapy for advanced CRC is still debated. At one extreme, treatment is continued until disease progression or until the patient experiences intolerable toxic effects, with sequential immediate transition from first-line to second-line and then to third-line regimens. The other extreme involves a policy that introduces treatment breaks, which could comprise complete cessation of chemotherapy for 2–3 months or a reduction in drug intensity (e.g. treatment with just infusional 5-FU plus LV for 2–3 months, with subsequent reintroduction of oxaliplatin).

In the CR06B study,²⁴ patients with advanced CRC who had stable or responding disease after 3 months of first-line chemotherapy with infusional 5-FU (with or without LV, depending on regimen) or raltitrexed, a direct inhibitor of TS, were randomly assigned to one of two treatment strategies. The first strategy was to continue treatment until disease progression and the second was to interrupt chemotherapy at this

point after the 3-month assessment, with the intention of restarting the same chemotherapy regimen when disease progression had been documented. Detailed assessments suggested that quality of life was better in patients who received intermittent chemotherapy than in those who received chemotherapy until progression, but OS was unaffected.²⁴

Two French studies also investigated whether chemotherapy should be administered continuously until disease progression or intermittently with prescribed treatment breaks.^{25,26} In the OPTIMOX1 study,²⁵ patients with untreated metastatic CRC were randomly assigned to receive either FOLFOX (with bolus and infusional 5-FU plus LV every 2 weeks on both day 1 and day 2) until disease progression (arm A), or a simplified version of the FOLFOX regimen (with LV and bolus 5-FU only on day 1 followed by a continuous 2-day infusion of 5-FU, administered every 2 weeks for 6 cycles) followed by maintenance chemotherapy without oxaliplatin for 12 cycles and reintroduction of simplified FOLFOX on disease progression (arm B). There were no significant differences between arm A and arm B in terms of response rates, PFS and OS.²⁵ Encouraged by these results, the investigators performed the OPTIMOX2 study.²⁶ In this large, phase II trial, patients were randomly allocated to the OPTIMOX1 arm (6 cycles of simplified FOLFOX followed by infusional 5-FU alone until disease progression, then reintroduction of simplified FOLFOX) or the OPTIMOX2 arm (6 cycles of simplified FOLFOX followed by complete cessation of chemotherapy and reintroduction of simplified FOLFOX before tumor size reached that recorded at baseline).

Median PFS was greater in the OPTIMOX1 arm than the OPTIMOX2 arm (8.7 months vs 6.9 months; $P=0.009$), as was median OS (24.6 months vs 18.9 months; $P=0.05$). The primary end point of the trial, duration of disease control (defined as the sum of PFS after first administration of FOLFOX and PFS after FOLFOX reintroduction), was not significantly different between groups (12.9 months vs 11.7 months).²⁶

Interestingly, the median OS was not reached for patients with good prognostic disease in the OPTIMOX1 arm (as 50% of patients had not died at the time of analysis). Median OS for patients in the OPTIMOX2 arm who had a good prognosis was 28.7 months. Median OS for patients with a poor prognosis was

20.9 months for those in the OPTIMOX1 arm and 14.5 months for patients in the OPTIMOX2 arm.²⁶ Overall, the chemotherapy-free interval was shorter in patients who had a poor prognosis, and the authors suggested that a chemotherapy-free interval should only be recommended in patients with no adverse features and a good performance status.

In the Italian GISCAD study,²⁷ the authors randomly allocated patients with advanced CRC to receive first-line treatment with either FOLFIRI administered intermittently—2 months on and 2 months off (arm A)—or FOLFIRI administered continuously (arm B). A total of 336 patients from 27 centers were included in the trial. No significant difference in median OS was found between arm A and arm B (16.9 months and 17.3 months).²⁷

Overall, these studies are not conclusive with respect to the validity of treatment breaks. Most clinicians—across Europe at least—do adopt the treatment break approach, particularly in patients who show a good partial response to chemotherapy, have no adverse features, and have a good performance status. Similarly, most clinicians are keen to see the development of an orally available low-toxicity drug (perhaps a biologic) that can be used during chemotherapy-free intervals to extend the duration of PFS.

THERAPEUTIC MONOCLONAL ANTIBODIES IN ADVANCED COLORECTAL CANCER

Research into the underlying cell and molecular biology of CRC has identified many of the key factors involved colorectal carcinogenesis and has, therefore, defined a series of potential therapeutic interventions. A number of monoclonal antibodies that target relevant pathways have been assessed in CRC, but the two most widely used agents are bevacizumab (a monoclonal antibody against vascular endothelial growth factor [VEGF]) and cetuximab (an antibody against the epidermal growth factor receptor [EGFR]).

Bevacizumab

The process of angiogenesis has become one of the most widely studied mechanisms in cancer research. In order for a tumor to grow beyond a couple of millimeters in size, and also for micrometastases to become established in the environment in which they become lodged, the angiogenic switch must be activated (Figure 2). Activation of the angiogenic switch leads to the

production of a variety of proangiogenic factors that stimulate the growth and development of new blood vessels at the tumor site, facilitating the delivery of nutrients and oxygen to the tumor and, therefore, enabling tumor growth.

Bevacizumab, a humanized antibody directed against the proangiogenic peptide VEGF,²⁸ has been examined in combination with chemotherapeutic agents (including irinotecan and oxaliplatin) as both first-line and second-line therapy for advanced CRC. Hurwitz *et al.* randomly assigned 813 patients with advanced CRC to receive irinotecan and bolus 5-FU and LV (IFL) plus bevacizumab or IFL plus placebo.²⁹ Response rates, PFS and OS were all significantly better in the IFL plus bevacizumab arm than in the IFL plus placebo arm.²⁹ Specifically, median survival was 20.3 months in the IFL plus bevacizumab group compared with 15.6 months in the IFL plus placebo group (HR for death 0.66; $P < 0.001$) and median PFS was 10.6 months and 6.2 months, respectively (HR for disease progression 0.54; $P < 0.001$). The response rate was 44.8% in the IFL plus bevacizumab arm and 34.8% in the IFL plus placebo arm ($P = 0.004$). Grade 3 hypertension was more common during treatment with IFL plus bevacizumab than during treatment with IFL plus placebo (11.0% vs 2.3%); however, the hypertension was manageable. These early trial data were certainly very encouraging for the use of bevacizumab in patients metastatic CRC.

Subsequently, a total of 1,401 patients with advanced CRC were randomly assigned to receive chemotherapy with CAPOX or chemotherapy with FOLFOX and then to bevacizumab or placebo in a 2 × 2 factorial design.³⁰ Care was taken to ensure that the dose intensity of bevacizumab was the same for both arms. Median PFS and median OS were 9.4 months and 21.3 months, respectively, in the bevacizumab group and 8.0 months and 19.9 months in the placebo group (HR 0.83, 97.5% CI 0.72–0.95; $P = 0.0023$ and HR 0.89, 97.5% CI 0.76–1.03; $P = 0.077$). Response rates were similar in both arms.³⁰ These data suggest that bevacizumab has a much more moderate effect than that observed in the earlier trial by Hurwitz and colleagues. Further detailed analysis, however, revealed that the number of patients who discontinued treatment—predominantly because of chemotherapy associated adverse effects such as neurologic, gastrointestinal and hematologic toxic events—was higher in bevacizumab group

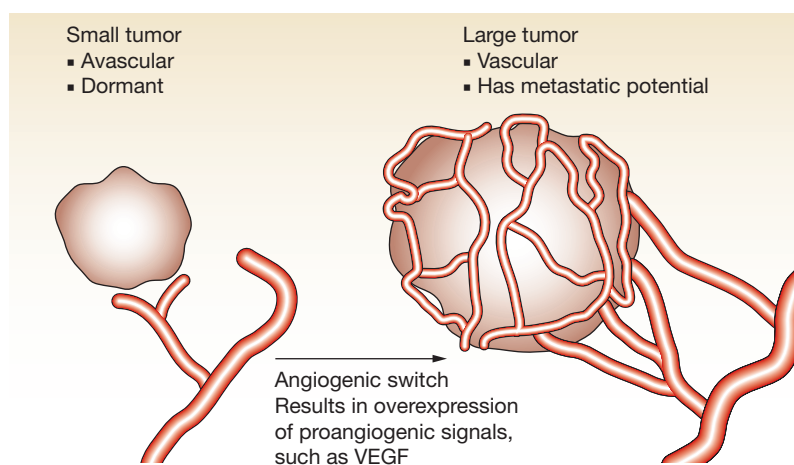


Figure 2 The angiogenic switch in tumors. The turning on of the angiogenic switch by VEGF and other signaling molecules enables small primary tumors to grow and metastasize and distant micrometastases to become established and to develop into functional tumor masses. Adapted from Bergers G and Benjamin LE (2003) *Nat Rev Cancer* **3**: 401–410. Abbreviation: VEGF, vascular endothelial growth factor.

than in the placebo group (30% vs 21%), potentially biasing the results. Analysis of treatment withdrawals showed that despite the protocol permitting treatment continuation until disease progression, only 29% and 47% of bevacizumab and placebo recipients, respectively, were treated until this point. The authors concluded that treatment continuation until disease progression might be necessary in order to optimize the contribution of bevacizumab to outcome. The overall incidence of grade 3 or 4 adverse events (treatment-related or not treatment-related) was 80% in the bevacizumab group and 75% in the placebo group. The most common adverse effects attributed to bevacizumab were thromboembolic events, which occurred in 8% of patients.³⁰

As a consequence of these two trials,^{29,30} bevacizumab is now approved by the FDA and the European Medicines Agency for use in combination with 5-FU-based chemotherapy regimens for first-line and second-line treatment of advanced or metastatic CRC.

Cetuximab

The EGFR is a transmembrane glycoprotein that is often overexpressed in CRC and is involved in signaling pathways that affect cellular growth, differentiation and proliferation, and programmed cell death.^{31,32}

Cetuximab is a monoclonal antibody that binds to and inhibits the EGFR. The agent has been found to be effective alone and in combination

with irinotecan in patients with metastatic CRC who have experienced prior treatment failure with irinotecan-based therapy.^{33,34} In a trial by Cunningham and colleagues,³⁴ 329 patients who had undergone irinotecan therapy within the previous 3 months were randomly allocated to receive either cetuximab in combination with irinotecan or cetuximab alone. The response rate was significantly higher and the median time to disease progression significantly longer in the combination group than in the monotherapy group (22.9% vs 10.8%, $P=0.007$ and 4.1 months vs 1.5 months; $P<0.001$). The efficacy demonstrated by these findings was sufficient to gain cetuximab FDA approval for use in this setting in 2004.^{33,34}

In 2007 Van Cutsem *et al.* reported the results of the CRYSTAL trial,³⁵ in which 1,217 patients with EGFR-expressing metastatic CRC were randomly allocated to receive first-line therapy with either FOLFIRI fortnightly plus cetuximab weekly (group A; $n=608$) or fortnightly FOLFIRI alone (group B; $n=609$). The median PFS was significantly longer and the response rate was significantly higher in group A than group B (8.9 months vs 8.0 months; $P=0.036$ and 46.9% vs 38.7%; $P=0.005$). Although these findings are statistically significant, one might argue that an increase in PFS of 0.9 months is not clinically significant.

In OPUS³⁶—a randomized, phase II study—337 patients with metastatic CRC received first-line therapy with either FOLFOX fortnightly plus cetuximab weekly (group A) or fortnightly FOLFOX alone (group B). The response rate was 45.6% in group A compared with 35.7% in group B (odds ratio 1.65, 95% CI 1.04–2.60; $P=0.063$); however, the median PFS was the same in both arms (7.2 months). The most common grade 3 and 4 adverse events in both group A and group B were neutropenia (27.6% vs 31.5%, respectively), diarrhea (7.1% vs 6.0%, respectively) and leucopenia (7.1% vs 5.4%, respectively); acneiform skin rash was associated with exposure to cetuximab (group A). The authors of the above trials, and other research groups, have postulated that there is a correlation between tumor response and extent of cetuximab-induced skin rash, but the data are not sufficient to warrant dose adaptation to induce skin rash in all patients.

Both the CRYSTAL and the OPUS studies attempted to assess the importance of tumor *KRAS* status in determining response to cetuximab,

and these studies have presented some very interesting results.^{37,38} The rationale for these scientific analyses was based on the knowledge that mutations in *KRAS*, an intermediate in the EGFR signal transduction pathway, define a population of patients who have tumors that depend on EGFR signaling. *KRAS* acts downstream of the EGFR; therefore, it was hypothesized that somatic changes in this gene might be a potential marker to predict lack of response to anti-EGFR therapy.

Indeed, this finding has been borne out in practice. In the CRYSTAL study,³⁷ patients with tumors that expressed wild-type *KRAS* showed a better response to FOLFIRI plus cetuximab than to FOLFIRI alone (response rate 59.3% vs 43.2%; $P=0.0025$), and median PFS in these patients was longer with FOLFIRI plus cetuximab than with FOLFIRI alone (9.9 months vs 8.7 months; $P=0.017$). These findings indicate a statistically significant superior outcome with the addition of cetuximab to FOLFIRI chemotherapy for this group of patients. Among patients with tumors that displayed mutant *KRAS*, response rates for FOLFIRI with and without cetuximab were 36.2% and 40.2% (not significant [NS]) and PFS was 7.6 months and 8.1 months (NS), respectively. It seems that, if anything, there was something of a negative effect of cetuximab in patients who had tumors with mutant *KRAS*, although the differences between the two treatment arms did not reach statistical significance.³⁷

Similarly, further analysis of the OPUS results revealed that the response rate in patients with tumors that expressed wild-type *KRAS* was 60.7% for FOLFOX plus cetuximab and 37% for FOLFOX alone ($P=0.011$). Again, by contrast, the response rate among patients whose tumors expressed mutant *KRAS* was 32.7% for those who received FOLFOX plus cetuximab compared with 48.9% for those who received FOLFOX alone ($P=0.106$). This finding likewise suggests a trend towards a negative effect of the addition of cetuximab to standard chemotherapy in the population with *KRAS* mutations.³⁸ Neither bevacizumab nor cetuximab has been approved by the UK's National Institute of Clinical Excellence³⁹ (<http://www.nice.org.uk>), and so these agents are not routinely available within the UK National Health Service. Perhaps this fact is not surprising given that the cost of bevacizumab is estimated to be as high as UK£80,000–90,000 per quality-adjusted life year gained and the survival benefits shown in the study

by Hurwitz *et al.*²⁹ were not borne out to the same extent when the drug was given in combination with 5-FU-based or oxaliplatin-based chemotherapy.³⁰

There is no doubt that both bevacizumab and cetuximab met their prespecified end points in large, well-designed clinical trials. On the other hand, one might still debate the validity of the moderate-size clinical benefit gained with these agents relative to their cost, unless patients who will benefit can be routinely identified. The compelling data surrounding tumor *KRAS* status provide an avenue for this kind of rational selection of patients for treatment, and these data are the first to show that it is possible to truly select a responding population.

ADVANCES IN ADJUVANT CHEMOTHERAPY

After curative surgical resection, 40–50% of patients with stage III CRC, and 20% of patients with stage II CRC, will experience disease relapse within 5 years.¹ The purpose of adjuvant chemotherapy is to destroy remaining tumor cells or micrometastases that cannot be detected at the time of surgery, consequently reducing the risk of disease recurrence.⁴⁰ Fluoropyrimidine-based adjuvant treatment can increase 5-year survival by 5–12% for patients with stage III disease and by 3–4% for patients with stage II disease.⁴⁰

Stage III disease

Surprisingly, there is no role for irinotecan in the adjuvant therapy setting,^{41,42} but the MOSAIC study⁴³ demonstrated the benefit in terms of disease-free survival (DFS) of adding oxaliplatin to 5-FU and LV in patients with stage III CRC. A total of 2,246 patients with stage II or stage III CRC who had undergone complete resection of a primary tumor were randomly allocated to receive infusional 5-FU plus LV or 5-FU plus LV in combination with oxaliplatin (the FOLFOX regimen) for 6 months. After a median follow-up of 37.9 months, the proportion of patients disease free at 3 years was 78.2% in the FOLFOX arm and 72.9% in the 5-FU plus LV arm ($P=0.002$). When only patients with stage III disease were analyzed, 3-year DFS was 72.2% in the FOLFOX arm and 65.3% in the 5-FU plus LV arm, respectively. Finally, the probability of survival at 3 years was 88.2% in the FOLFOX arm compared with 86.6% in the 5-FU plus LV arm, although this result did not reach statistical significance.⁴³

The NSABP C-07 phase III clinical trial⁴⁴ evaluated the effect of adding oxaliplatin to weekly bolus 5-FU and LV as opposed to adding oxaliplatin to infusional 5-FU plus LV, which is the regimen that is used in FOLFOX and is the most commonly used 5-FU plus LV regimen used in Europe. In total, 2,492 patients with stage II or III CRC who had undergone a potentially curative resection were randomly assigned to receive either 5-FU (intravenous bolus weekly for 6 weeks of an 8-week cycle) plus LV (intravenous weekly for 6 weeks of an 8-week cycle) for 3 cycles (FULV), or the same FULV regimen plus oxaliplatin intravenously administered on weeks 1, 3, and 5 of each 8-week cycle for a total of 3 cycles (FLOX).⁴⁴ At the time of reporting, the median follow-up for patients who were still alive was 42.5 months. The HR for death (FLOX vs FULV) was 0.80 (95% CI 0.69–0.93), which represents a 20% risk reduction in patients who received FLOX ($P<0.004$). The 3-year and 4-year DFS rates were 71.8% and 67.0% for patients on FULV and 76.1% and 73.2% for patients on FLOX, respectively. Grade 3 neurosensory toxic effects were noted in 8.2% of patients receiving FLOX and in 0.7% of those receiving FULV ($P<0.001$). Hospitalization for diarrhea associated with bowel-wall thickening occurred in 5.5% of patients receiving FLOX and in 3.0% of patients receiving FULV ($P<0.01$). The authors concluded that the addition of oxaliplatin to weekly adjuvant chemotherapy with FULV significantly improves DFS in patients with stage II or III CRC.⁴⁴

Many clinicians are gradually moving towards using more-aggressive adjuvant combination chemotherapy for young, fit patients with a poor disease prognosis. Given the neurotoxicity that can be a consequence of long-term oxaliplatin treatment, however, and the marginal OS benefits of its addition to 5-FU or capecitabine, there is still a role for single-agent fluoropyrimidine adjuvant chemotherapy, particularly in the elderly patient population or in patients whose tumors have good prognostic features.

The ongoing UK QUASAR2 study is randomly allocating patients with stage III or high-risk stage II CRC to receive either 6 months of adjuvant chemotherapy with capecitabine alone or 6 months of adjuvant capecitabine plus 12 months of bevacizumab. The results of this study will be very informative in defining the role of biologic therapy in the adjuvant setting and in determining whether a better-tolerated replacement for oxaliplatin exists. Other trials

are also exploring the addition of bevacizumab or cetuximab to already quite intensive combination chemotherapy.

Stage II disease

Controversy has always existed regarding the use of adjuvant chemotherapy in patients with stage II CRC. The QUASAR1 study⁴⁵—in which 3,200 patients with stage II CRC were randomly allocated to receive adjuvant chemotherapy with bolus 5-FU ILV or no adjuvant chemotherapy—has, for the first time, shown a small (3–5%) but statistically significant benefit in terms of 5-year OS with well-tolerated adjuvant chemotherapy. In our practice, younger patients (approximately <70 years old) with stage II disease are more likely to agree to adjuvant chemotherapy, even though the benefits seem marginal, whereas some very elderly patients feel that the general hassle of treatment and potential toxic effects outweigh the small return in terms of survival. This trend is not a hard and fast rule, however, and careful communication outlining the pros and cons for an individual patient is imperative in the decision-making process.

CHEMORADIOTHERAPY FOR RECTAL CANCER

Radiotherapy can significantly reduce local pelvic recurrence of rectal cancer.⁴⁶ Accordingly, there is growing interest in combining radiation and chemotherapy to increase tumor response and operability in order to move towards elimination of postoperative local recurrence.

Once preoperative radiotherapy had been established as worthwhile in patients with stage T3 or T4 rectal tumors,⁴⁶ two randomized trials compared the use of preoperative radiotherapy with chemoradiotherapy.^{47,48} In the FFCD 9203 study,⁴⁷ 733 patients were randomly assigned to receive either preoperative radiotherapy with 45 Gy in 25 fractions over 5 weeks, or the same treatment plus concurrent chemotherapy. Chemotherapy comprised bolus 5-FU ILV daily for 5 days during the first and fifth week of radiotherapy. Grade 3 or 4 toxic events were more frequent in the chemoradiotherapy arm than the radiotherapy arm (11.4% vs 3.6%; $P=0.05$). There was no difference in the likelihood of sphincter preservation. The 5-year incidence of local recurrence was lower with chemoradiotherapy than with radiotherapy alone (8.1% vs 16.5%; $P<0.05$). OS at 5 years in the two groups did not differ.

In the EORTC 22921 trial,⁴⁸ a total of 1,011 patients with stage T3 or T4 resectable rectal cancer were randomly assigned to one of the following four treatment arms: preoperative radiotherapy; preoperative chemotherapy and radiotherapy; preoperative radiotherapy plus postoperative chemotherapy; or preoperative chemoradiotherapy followed by postoperative chemotherapy. Radiotherapy consisted of 45 Gy delivered in 25 fractions over a period of 5 weeks. One course of chemotherapy comprised 5-FU plus LV daily for 5 days. Courses of chemotherapy were administered at 4-week intervals. Two chemotherapy courses were combined with preoperative radiotherapy in the selected groups, and four courses of chemotherapy were delivered postoperatively in the selected groups. The primary end point was OS. The results showed that there was no significant difference in OS or DFS between the groups that received preoperative chemotherapy and those that had postoperative chemotherapy (both NS). In terms of the incidence of local recurrence, however, there was a significant difference between patients who received preoperative radiotherapy alone and the other three treatment groups. The 5-year cumulative incidence rates for local recurrences were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy ($P=0.002$). The authors concluded that chemotherapy, regardless of whether it is administered before or after surgery, confers a significant benefit with respect to local control. This conclusion is perhaps a little surprising given traditional theoretical thinking that only chemotherapy delivered preoperatively in conjunction with (and as a sensitizer to) radiotherapy affects local recurrence rates and that only prolonged postoperative chemotherapy reaps significant benefit in terms of reducing distant metastases.

Each individual group in the EORTC 22921 trial contained relatively small numbers of patients, which might explain why it is difficult to determine any perceptible difference between the groups in terms of survival. The only trial to date that has demonstrated a beneficial effect of postoperative chemotherapy on OS for patients with rectal cancer is the QUASAR1 trial.⁴⁸ This study randomly allocated patients who had an uncertain indication for chemotherapy (30% of whom had rectal cancer) to receive postoperative 5-FU plus LV chemotherapy or no chemotherapy.

At analysis the authors found that adjuvant postoperative chemotherapy did improve survival in the subgroup of patients with rectal cancer.⁴⁸

A phase III trial carried out in Norway and reported in 2008⁴⁹ evaluated the use of chemotherapy in rectal cancers that were not initially resectable. In this study, 207 patients with inoperable disease, either locally-advanced primary rectal cancer or locally-recurrent rectal cancer, were randomly allocated to receive either preoperative radiotherapy alone (50 Gy; $n=109$) or combination chemoradiotherapy (5-FU plus LV with radiotherapy [50 Gy]) preoperatively plus 16 weeks of chemotherapy (5-FU plus LV) after surgery ($n=98$). An R₀ resection was achieved in 82 patients (84%) in the chemoradiotherapy group and in 74 patients (68%) in the radiotherapy alone group ($P=0.009$); in addition, pathologic complete response was seen in 16% and 7% of these patients, respectively. After either R₀ resection or R₁ resection (microscopic disease only at the margins), local recurrence was found in 5% and 7% and distant metastases in 26% and 39% of chemoradiotherapy patients and radiotherapy patients, respectively. Several other parameters favored the chemoradiotherapy group over the radiotherapy alone group, including local control (82% vs 67% at 5 years; log-rank $P=0.03$), cancer-specific survival (72% vs 55%; $P=0.02$), and OS (66% vs 53%; $P=0.09$). Although the number of patients in this study is relatively small, the authors concluded that the addition of chemotherapy to radiotherapy improves local control, time to treatment failure, and cancer-specific survival in patients with nonresectable rectal cancer.⁴⁹

Phase II trials have also explored novel combinations of chemotherapy and radiotherapy in the perioperative treatment of rectal cancer. In a multicenter phase II trial by Rödel and co-workers,⁵⁰ patients were treated with preoperative radiotherapy (50.4 Gy in 28 fractions) plus chemotherapy comprising CAPOX (capecitabine orally on days 1–14 and days 22–35 and oxaliplatin on days 1, 8, 22, and 29). Surgery was performed in 103 of 104 eligible patients 4–6 weeks after completion of chemoradiotherapy and was followed by four 3-week cycles of adjuvant chemotherapy with CAPOX (capecitabine on days 1–14 and oxaliplatin on day 1 of each cycle). Pathological complete response was shown in 17 patients (16%), one patient had ypT₀N₁ disease, and 53 patients (51%) showed tumor regression of more than 50% of the tumor mass

(partial response). R₀ resections were achieved in 95% of patients, and sphincter preservation was accomplished in 77%. Grade 3 or 4 diarrhea occurred in 12% of patients and sensory neuropathy in 18%. The authors suggest that this treatment strategy (preoperative chemoradiotherapy followed by surgery and then adjuvant chemotherapy) should now be tested in phase III trials comparing the efficacy of 5-FU alone and 5-FU plus oxaliplatin regimens in combination with radiotherapy.⁵⁰ Phase I trials exploring combinations of radiotherapy with dual-agent chemotherapy and therapeutic monoclonal antibodies are ongoing.

The general consensus among clinicians is that many patients with rectal cancer will require preoperative chemoradiotherapy in order to maximize local control, reduce surgical morbidity, and minimize downstream local recurrence. Postoperative chemotherapy would be advisable in cases with a perceived risk of future distant metastatic recurrence.

ROLE OF BIOMARKERS IN PATIENT SELECTION FOR THERAPY

Given the plethora of active agents available for treatment of CRC (Table 1), the relatively high cost of developing novel agents, and the moderate benefits that are gained with these agents, it would be incredibly valuable to have protein, DNA or RNA markers that might be able to identify subgroups of patients who would benefit most from a specific therapeutic agent.

Loss of heterozygosity at chromosome 17p or 18q is a common event in CRC and several studies have focused on the 17p region, which contains the p53 tumor suppressor gene. The p53 gene, and its mutation and levels of expression, has been well studied as both a prognostic factor and a predictor of response to therapy. Studies have yielded conflicting results, however, suggesting that the clinical utility of this marker is perhaps dependent on stage of disease and requires further detailed elucidation.⁵¹

Studies investigating the prognostic significance of microsatellite instability, which is caused by mutations in the mismatch repair genes, have produced more-consistent findings. The studies suggest that high levels of microsatellite instability lead to improved survival in patients with stage III CRC;⁵² however, there is much less agreement on the potential for the same high levels of microsatellite instability to predict poor response to 5-FU-based chemotherapy.

Table 1 Agents that are available for the treatment of colorectal cancer.

Class of drug	Specific drug	Common therapeutic use
Fluoropyrimidine	5-fluorouracil	First-line and second-line therapy for advanced disease; adjuvant therapy
	Capecitabine	First-line and second-line therapy for advanced disease; adjuvant therapy
Topoisomerase inhibitor	Irinotecan	First-line and second line therapy for advanced disease Can be used as a single agent or combined with a fluoropyrimidine
Platinum analog	Oxaliplatin	First-line and second-line therapy for advanced disease; adjuvant therapy Always used in combination with a fluoropyrimidine
Anti-VEGF	Bevacizumab	First-line and second-line therapy for advanced disease
Anti-EGFR	Cetuximab	Mainly second-line therapy for advanced disease after failure of irinotecan therapy
	Panitumumab	Mainly second-line therapy for advanced disease

Abbreviations: EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

Mutations in oncogenes such as *KRAS* have been positively associated with disease recurrence, poor survival, metastasis and, recently, resistance to inhibitory monoclonal antibodies against the EGFR, such as cetuximab and panitumumab.^{37,38} There are companies that run commercial tests on paraffin-embedded tumor tissue to assess the presence of the most common *KRAS* mutations. The use of such assays will probably increase in the future as clinicians try to gather potentially predictive tumor-specific information in order to guide the treatment of their individual patients.

The proangiogenic potential of an individual tumor has also been found to affect prognosis, suggesting that biomarkers such as VEGF expression and microvessel density could be useful tools for predicting whether a patient is at high risk of recurrence.⁵³ Whether these markers correlate with responsiveness to bevacizumab or other antiangiogenic drugs would be worth exploring.

Evidence is also accumulating that tumor markers important in 5-FU metabolism or treatment pathways might be useful as both prognostic and predictive factors for treatment outcome. Expression levels of the gene for 5-FU drug target TS have been widely associated with drug efficacy. A meta-analysis published in 1999 that examined TS expression and patient prognosis concluded that individuals with tumors expressing high levels of TS seem to have a poorer OS than patients with tumors expressing low levels of TS.⁵⁴ In addition, expression of the genes for dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (TP) has been shown to have a predictive role in determining treatment outcome in patients receiving adjuvant chemotherapy with

5-FU, both alone and in combination with other agents. In a multivariate study of the genes for TS, TP and DPD, patients with low expression of all three markers had significantly better survival than those with a high level of expression, but TP expression did not substantially improve the predictive power of TS and DPD expression for benefit from 5-FU-based chemotherapy.⁵⁵

By contrast, another study has called into question the importance of TS gene expression in determining response to adjuvant therapy. This study suggested that expression of the genes for other enzymes, including orotatephosphoribosyl transferase and DPD, might be more important than expression of the gene for TS.⁵⁶ We, and many others, are working to develop RNA signatures that can be used to predict response to 5-FU chemotherapy, by using Illumina (Illumina Inc., San Diego, CA) or Affymetrix (Affymetrix Inc., Santa Clara, CA) chip technology with both frozen and paraffin-embedded tissues. These RNA signatures will be pattern recognition signatures that will be used to look at the expression of many tens or hundreds of genes rather than signatures that rely on the expression of very small numbers of genes, as is usually the case in immunohistochemical analyses. Pattern recognition signatures are likely to be more informative about treatment response, which clearly involves complex gene-expression interactions because of the integrated pathways upon which cancer treatments act. We are evaluating these novel prognostic and predictive tools in a large collection of tissue samples ($n = 2,000$) assembled as part of our QUASAR adjuvant trials portfolio, highlighting the enormous translational potential of phase III clinical studies.

CONCLUSIONS

A large increase in the number of active agents available to treat CRC has occurred in the past 15 years. These active agents have pushed tumor response rates up to 50–60% among patients undergoing first-line therapy, and median survival has reached 22–24 months for patients with advanced disease.^{8–10} The use of adjuvant chemotherapy has increased absolute cure rates for stage III disease by around 10% and for stage II disease by 3–5%.⁴⁰ Current therapy strategies are complex, comprising combination chemotherapy and monoclonal antibodies, and can be very costly, particularly the addition of monoclonal antibodies to standard cytotoxic agents. There is no doubt that in the next decade a battery of tests will emerge that will enable the clinical community to select patients for treatment with specific agents. Finally, pharmacogenetic analysis raises the possibility of individually adjusting the initial dose of cytotoxic drugs to maintain efficacy while attenuating toxicity in patients who are predicted to be particularly sensitive to therapy.

KEY POINTS

- Colorectal cancer is a common disease with approximately 1 million new cases diagnosed each year
- Chemotherapy for advanced disease can palliate symptoms and extend life by 12–18 months
- Chemotherapy for early disease has increased cure rates by approximately 3–10%, depending on the stage of disease
- Novel biologic therapies have had modest effect on colorectal cancer outcomes when applied to whole populations
- In the future, patient selection for therapy on the basis of biological criteria is likely to improve response rates and decrease the toxic effects of therapeutic regimens

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Competing interests

The authors declared no competing interests.

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