

Colorectal Oncology Research Review

Making Education Easy

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Welcome to the eleventh issue of Colorectal Oncology Research Review.

Are clinical trial cancer patients representative of those in the general population? The first two trials that we have included in this issue highlight certain differences between them, which affect treatment outcome. The following four papers review aspects of resectable disease in metastatic colorectal cancer. The last four trials that we discuss raise questions about how anti-epidermal growth factor receptor therapies should be used in metastatic colorectal cancer. According to the evidence, bevacizumab should not be combined with panitumumab or cetuximab in routine clinical practice. Much more data are needed to clarify most appropriate applications.

We hope you find this latest Review useful and look forward to hearing your comments and feedback.

Kind regards

Dr David Gibbs

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Clinical trials

Differences between clinical trial participants and patients in a population-based registry: the German Rectal Cancer Study vs. the Rostock Cancer Registry

Authors: Kalata P et al

Summary: Patient and disease characteristics of patients with stage II or III rectal cancer from the German Rectal Cancer Study (n=657; 1995–2002) were compared with those of patients from the Rostock Cancer Registry (n=371; 1997–2003). Study and Registry patients differed in age (median, 61.7 vs 65.0 years; p<0.001) and proportion of women (31.3% vs 38.4%; p<0.004). Significant age and gender differences were seen in primary resection but not in neoadjuvant subgroups. In neoadjuvant and in primary resection subgroups, Study participants were more likely than Registry patients to have tumor location in the lower third of the rectum, a higher rate of R0 resection, a greater number of lymph nodes assessed, and fewer T4 tumors. Among primary resection subgroups, Study participants were more likely to have received postoperative chemoradiotherapy. Multivariate analyses showed no effect of population type (Study vs Registry) on disease-free or overall survival in neoadjuvant subgroups, but increased risk for Registry patients in primary resection subgroups.

Comment: See Page 2.

Reference: *Dis Colon Rectum*. 2009;52(3):425-37.

<http://tinyurl.com/o6nwgw>

*Independent commentary by Dr David Gibbs,
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Clinical trials (cont.)

Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer

Authors: Sargent DJ et al

Summary: Data from 6286 patients with metastatic colorectal cancer (509 with a performance status [PS] of 2) from nine clinical trials were examined to compare treatment efficacy by PS. Compared with patients with PS of 0 or 1, PS2 patients had significantly higher rates of grade ≥ 3 nausea (8.5% vs 16.4%, respectively; $p < 0.0001$), vomiting (7.6% vs 11.9%, respectively; $p = 0.006$) and 60-day all-cause mortality (2.8% vs 12.0%, respectively; $p < 0.0001$). PS2 was prognostic for progression-free survival (PFS; HR 1.52; $p < 0.0001$; median PFS, 7.6 months for PS 0 or 1 vs 4.9 months for PS2), overall survival (OS; HR 2.18; $p < 0.0001$; median OS, 17.3 months for PS 0 or 1 vs 8.5 months for PS2), and response rate (OR 0.61; $p < 0.0001$; 43.8% for PS 0 or 1 vs 32.0% for PS2). The relative benefit and toxicity of experimental versus control treatment and monotherapy versus combination therapy were not different in PS 0 or 1 patients versus PS2 patients.

Comment: It is a truism that the results of clinical trials must be able to be generalised. However, there is some data that suggests that patients who participate in clinical trials are not representative of the general population of patients. The study from the German Rectal Cancer Study Group confirms this in rectal cancer. It showed that patients treated on a randomised study of preoperative chemoradiation were younger and had a different gender distribution than patients drawn from a cancer registry. In addition, they had differences in important prognostic variables like the likelihood of obtaining an R0 resection (resection with negative margins). This may partly reflect real differences (centres that participate in clinical trials may be more likely to utilise specialist colorectal surgeons) but it may also illustrate that patients with poorer prognosis are less likely to be entered into clinical trials.

This point is enlarged on in the report by Sargent and colleagues, who study the outcome of patients with poorer performance status in trials of chemotherapy in advanced colorectal cancer. It shows that the relative benefits of chemotherapy are the same but poor performance status patients are more likely to die on treatment, have greater toxicity, have lower response rates to treatment and survive less long.

Reference: *J Clin Oncol.* 2009;27(12):1948-55.
<http://tinyurl.com/o7p5ta>

Surgery for advanced disease

Long-term outcome of initially unresectable metastatic colorectal cancer patients treated with 5-fluorouracil/leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) followed by radical surgery of metastases

Authors: Masi G et al

Summary: This trial sought to determine the long-term outcome of 37 radically resected patients with initially unresectable metastatic colorectal cancer treated with the GONO-FOLFOXIRI regimen. Patients had a median age of 64 years, Eastern Cooperative Oncology Group Performance Status (ECOG) PS ≥ 1 in 30%, synchronous metastases in 65%, multiple sites of disease in 22%, and metastases confined to the liver in 68%. Preoperative FOLFOXIRI was administered for a median of 5.5 months. There was no perioperative mortality and all morbidities (27% of patients) resolved without sequelae. At a median 67-month follow-up, 5-year and 8-year survival rates were 42% and 33%, respectively. At 5 years, 29% of patients remained disease-free. No signs of treatment-induced liver injury were seen; no G3 vascular toxicity nor G4 steatosis occurred, and only 5% of patients developed steato-hepatitis.

Comment: See Page 3.

Reference: *Ann Surg.* 2009;249(3):420-5
<http://tinyurl.com/p4ut57>

Patients with initially unresectable colorectal liver metastases: is there a possibility of cure?

Authors: Adam R et al

Summary: Data were analysed from 184 patients with initially unresectable colorectal liver metastases (CLM) who underwent rescue surgery and were followed-up for a minimum of 5 years. The study aimed to evaluate long-term outcome after combining downsizing chemotherapy and rescue surgery and to define prognostic factors of cure. Patients had a mean number of 5.3 metastases (bilobar in 76%), associated to extrahepatic disease in 27%. Surgery was possible after one (74%) or more (26%) lines of chemotherapy. Five- and 10-year overall survival rates were 33% and 27%, respectively. Of 148 patients with a follow-up ≥ 5 years, 24 patients (16%) were considered cured (i.e. a disease-free interval ≥ 5 years from last hepatic or extrahepatic resection until last follow-up), six (25%) of whom were considered cured after repeat resection of recurrence. Twelve "cured" patients (50%) had a disease-free interval exceeding 10 years. Cured patients more often had ≤ 3 metastases of < 30 mm ($p = 0.03$) responding to first-line chemotherapy ($p = 0.05$). According to multivariate analysis, independent predictors of cure included maximum size of metastases of < 30 mm at diagnosis, number of metastases at hepatectomy as ≤ 3 , and complete pathological response.

Comment: See Page 3.

Reference: *J Clin Oncol.* 2009;27(11):1829-35.
<http://jco.ascopubs.org/cgi/content/abstract/27/11/1829>

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Surgery for advanced disease (cont.)

Effect of portal vein embolisation on the growth rate of colorectal liver metastases

Authors: Pamecha V et al

Summary: This study compared the growth characteristics of resected colorectal liver metastases in 22 patients undergoing pre-operative portal vein embolisation (PVE) with those of 20 matched controls who had not undergone PVE. The groups were comparable in demographics, stage of primary disease, volume of liver metastases at presentation and chemotherapy received. The tumour growth rate calculated from CT/MRI volumetric assessment was more rapid in the PVE group compared with that in controls (control: 0.05 mL day⁻¹, PVE: 0.36 mL day⁻¹, p=0.06). Histology showed no between-group differences in the degree of differentiation, extent of necrosis or apoptosis. However, mitotic rate was higher post-PVE, as was the proliferation index Ki67 (p=0.04).

Comment: See below.

Reference: *Br J Cancer. 2009;100(4):617-22.*

<http://tinyurl.com/pzqkbbx>

Survival after hepatic resection of colorectal cancer metastases: a national experience

Authors: Robertson DJ et al

Summary: Data were examined from 3957 Medicare beneficiaries who underwent hepatic resection of colorectal cancer metastases, to investigate operative mortality and long-term survival and determine the factors associated with those outcomes. The crude 30-day and 90-day mortality rates were 4% and 8.2%, respectively, and the 5-year survival rate was 25.5%. Factors associated with worse 90-day mortality included advancing age (HR, 1.83 for age ≥80 years vs ages 65–69 years), comorbid disease (HR, 1.40 for Charlson ≥5 vs Charlson 0), and synchronous colon/hepatic resection (HR, 2.46 for synchronous vs metachronous resection). Similarly, long-term mortality was associated with age (HR, 1.36), comorbid disease (HR, 1.51), and synchronous colon/hepatic resection (HR, 1.37 for synchronous vs metachronous resection).

Comment: These four papers examine aspects of the resection of hepatic (and other system metastasis) in patients with metastatic CRC. The first two papers look at extending the boundaries of who can be considered to have resectable disease, the second two papers sound some notes of caution.

The paper by Masi and colleagues examines the outcome of patients with initially unresectable disease who underwent chemotherapy using the FOLFOXIRI regimen. This regimen was shown in a phase III trial to confer a higher survival than FOLFOX, largely because of the increased numbers of patients who had a tumour response and who were able to undergo resection. Patients who were able to undergo surgery had good 5- and 8-year survival without an increase in perioperative mortality. The second paper by Adam and colleagues shows that some patients in this position who are able to undergo surgery will remain relapse-free at 5 years and if this occurs, later relapse is unlikely to occur. However, the paper by Pamecha and colleagues shows that one of the techniques used to allow surgery in patients with a small residual hepatic volume after surgery (preoperative portal venous embolisation) increases the growth rate of colorectal metastases (despite all patients undergoing PVE receiving chemotherapy) and worsens prognosis.

Finally, the paper by Robertson and colleagues gives a more realistic view of the outcome that can be expected from hepatic metastatectomy, with a population 5-year survival of 25.5%. While this is poorer than the 5-year survivals in excess of 50% reported from case series, it is superior to the 5-year survivals of less than 2% reported in population studies of patients treated without resection.

Reference: *Cancer. 2009;115(4):752-9.*

<http://tinyurl.com/pzy2qs>

Targeted therapy in advanced disease

Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer

Authors: Bokemeyer C et al

Summary: These researchers compared the best overall response rate (ORR) of cetuximab combined with oxaliplatin, leucovorin, and fluorouracil (FOLFOX-4) with that of FOLFOX-4 alone as first-line treatment for metastatic colorectal cancer. Patients received cetuximab (400 mg/m² initial dose followed by 250 mg/m²/wk thereafter) plus FOLFOX-4 (oxaliplatin 85 mg/m² on day 1, plus leucovorin 200 mg/m² and fluorouracil as a 400 mg/m² bolus followed by a 600 mg/m² infusion during 22 hours on days 1 and 2; n=169) or FOLFOX-4 alone (n=168). Treatment was continued until disease progression or unacceptable toxicity. KRAS mutation status was assessed in the subset of patients with assessable tumour samples (n=233). The confirmed ORR for cetuximab plus FOLFOX-4 exceeded that for FOLFOX-4 alone (46% vs 36%). A statistically significant increase in the odds for a response with the addition of cetuximab to FOLFOX-4 could not be established (OR 1.52; p=0.064). In patients with KRAS wild-type tumours, the addition of cetuximab to FOLFOX-4 was associated with a clinically significant increased chance of response (ORR 61% vs 37%; OR 2.54; p=0.011) and a lower risk of disease progression (HR 0.57; p=0.0163) compared with FOLFOX-4 alone.

Comment: See Page 4.

Reference: *J Clin Oncol. 2009;27(5):663-71.*

<http://tinyurl.com/p2sgdg>

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Targeted therapy in advanced disease (cont.)

Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer

Authors: Van Cutsem E et al

Summary: Patients with epidermal growth factor receptor-positive colorectal cancer with unresectable metastases received either FOLFIRI (irinotecan, fluorouracil, and leucovorin) alone (n=599) or in combination with cetuximab (n=599). The hazard ratio for progression-free survival in the cetuximab-FOLFIRI group compared with the FOLFIRI group was 0.85 (p=0.048). There was no significant between-group difference in overall survival (HR 0.93; p=0.31). There was a significant interaction between treatment group and *KRAS* mutation status for tumour response (p=0.03) but not for progression-free survival (p=0.07) or overall survival (p=0.44). The hazard ratio for progression-free survival among patients with wild-type-*KRAS* tumours was 0.68, in favour of the cetuximab-FOLFIRI group. Compared with FOLFIRI alone, cetuximab plus FOLFIRI was associated with higher rates of the following grade 3 or 4 adverse events: skin reactions (which were grade 3 only) (19.7% vs 0.2% of patients, p<0.001), infusion-related reactions (2.5% vs 0%, p<0.001), and diarrhoea (15.7% vs 10.5%, p=0.008).

Comment: See right.

Reference: *N Engl J Med.* 2009;360(14):1408-17.

<http://content.nejm.org/cgi/content/short/360/14/1408>

A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer

Authors: Hecht JR et al

Summary: This trial evaluated the efficacy of adding panitumumab to bevacizumab and chemotherapy (oxaliplatin- and irinotecan-based) as first-line treatment for metastatic colorectal cancer (mCRC). A total of 823 and 230 patients were randomly assigned to the oxaliplatin and irinotecan cohorts, respectively. Within each cohort, patients were randomly assigned to bevacizumab and chemotherapy with or without panitumumab 6 mg/kg every 2 weeks. Panitumumab was discontinued after a planned interim analysis of 812 oxaliplatin patients showed worse efficacy in the panitumumab arm. In the final analysis, median progression-free survival was 10.0 and 11.4 months for the panitumumab and control arms, respectively (HR 1.27); median survival was 19.4 months and 24.5 months for the panitumumab and control arms, respectively. Grade 3/4 adverse events in the oxaliplatin cohort (panitumumab vs control) included skin toxicity (36% vs 1%), diarrhoea (24% vs 13%), infections (19% vs 10%), and pulmonary embolism (6% vs 4%). The panitumumab arm of the irinotecan cohort experienced increased toxicity with no improvement in efficacy. *KRAS* analyses showed adverse outcomes for the panitumumab arm in both wild-type and mutant groups.

Comment: See right.

Reference: *J Clin Oncol.* 2009;27(5):672-80.

<http://jco.ascopubs.org/cgi/content/abstract/27/5/672>

Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer

Authors: Tol J et al

Summary: A total of 755 patients with previously untreated metastatic colorectal cancer were randomised to capecitabine, oxaliplatin, and bevacizumab (CB regimen, n=378) or the same regimen plus weekly cetuximab (CBC regimen, n=377). Median progression-free survival was 10.7 months for the CB group and 9.4 for the CBC group (p=0.01). Quality-of-life scores were lower in the CBC group. No significant between-group differences were observed for overall survival and response rates. Treated patients in the CBC group had more grade 3 or 4 adverse events, which were attributed to cetuximab-related adverse cutaneous effects. The addition of cetuximab resulted in significantly shorter progression-free survival in patients who had tumours bearing a mutated *KRAS* gene as compared with cetuximab-treated patients with wild-type-*KRAS* tumours or patients with mutated-*KRAS* tumours in the CB group.

Comment: These four trials add to our knowledge of anti-EGFR therapies in metastatic colorectal cancer, but also raise questions about how these agents should be utilised. There has been considerable excitement about such therapies since the publication of data from a reanalysis of the CO.17 trial showing that patients with non-mutated (wild-type) *KRAS* had a 5-month improvement in overall survival compared with best supportive care when treated with cetuximab. There has been enthusiasm to include anti-EGFR therapies in first-line treatment and also to combine them with other targeted agents such as bevacizumab. The reports of trials by Bokemeyer and Van Cutsem show that cetuximab added to first-line oxaliplatin-based (FOLFOX) and irinotecan-based (FOLFIRI) treatment improves response rate and progression-free survival but in neither trial was there evidence of improvement in survival. Cross-over was not reported so it is difficult to assess its effect. Nonetheless, the improvement in progression-free survival was not large, even in patients with wild-type *KRAS* (2 weeks in the oxaliplatin trial, 4.5 weeks in the irinotecan trial) and no difference in overall survival was seen (although neither trial was powered to detect a small difference). Interestingly, outcome in patients with mutant *KRAS* appeared to be made worse by the addition of cetuximab.

The latter two trials, reported by Hecht and colleagues and Tol and colleagues examined the addition of anti-EGFR (panitumumab and cetuximab) to chemotherapy and anti-angiogenic therapy with bevacizumab and shows that combination therapy *worsens* outcome compared with chemotherapy-bevacizumab alone. A number of potential reasons for this are raised including anti-EGFR therapy antagonising the effects of bevacizumab.

Whatever the reason, it can be concluded that bevacizumab should not be combined with cetuximab or panitumumab in routine clinical practice. In addition, these trials show that we still have a considerable amount to learn about how best to use these agents. At the moment, cetuximab might best be confined to third-line use in patients with relapsed CRC whose tumour does not carry *KRAS* mutations.

Reference: *N Engl J Med.* 2009;360(6):563-72.

<http://content.nejm.org/cgi/content/short/360/6/563>

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