# Colorectal Oncology Research Review™

Making Education Easy

Issue 6 - 2013


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### Abbreviations in this issue:

**BMI** = body mass index;
**EGFR** = epidermal growth factor receptor;
**HNSCC** = head and neck squamous-cell carcinoma;
**(m)CRC** = (metastatic) colorectal cancer;
**HR** = hazard ratio; **mt** = mutation;
**NBCSP** = National Bowel Cancer Screening Program;
**NCCN** = National Comprehensive Cancer Network;
**NSCLC** = non-small cell lung cancer;
**PDGF** = platelet-derived growth factor;
**PFS** = progression-free survival;
**VEGF(R)** = vascular endothelial growth factor (receptor);
**wt** = wild type



# Welcome to the 6th issue of Colorectal Oncology Research Review.

The first study in this issue validates the use of current NCCN guidelines for the treatment of patients with high risk stage II and stage III CRC. Another study shows the potential of the Australian NBCSP to lead to reductions in CRC mortality simply by diagnosing patients at an earlier stage. But obese or underweight patients will have poorer survival outcomes according to a review of the ACCENT database.

Studies in mCRC included in this issue show no benefit with sunitinib or axitinib and review the use of aflibercept.

We hope you enjoy our selection for this edition and your comments and feedback are welcome.

If you have colleagues or friends within Australia who would like to receive our publication, send us their contact email and we will include them for the next issue.

Kind Regards,


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## Association between adherence to National Comprehensive Cancer Network treatment guidelines and improved survival in patients with colon cancer

**Authors:** Boland GM et al


**Summary:** This study demonstrated a survival benefit for patients with stage III and high-risk stage II colon cancer who received treatment that adhered to NCCN guidelines. A higher rate of nonadherence was observed in older patients, uninsured patients or those insured with Medicaid or Medicare rather than private insurance, and in patients who received subsequent treatment at a facility other than the facility at which the cancer was first diagnosed (all $p<0.001$). The authors concluded that 'these data validate the current NCCN practice guidelines for colon cancer and support the concept of guideline-based metrics.'


**Comment:** The NCCN have created guidelines for the treatment of colon carcinoma with specific recommendations depending on tumour stage. Good evidence exists to support the use of adjuvant chemotherapy in patients with stage III disease. The same cannot be said for patients with stage II disease. Current best evidence drawn from a variety of, at times, conflicting sources supports the use of adjuvant chemotherapy only in those with 'high risk' stage II colon carcinoma (T4, grade 3, R1/R2 margins, <12 nodes assessed) and this is reflected in the NCCN guidelines.

These authors used retrospective review of outcomes for a large number of patients with colon carcinoma to determine rates of adherence to NCCN guidelines and the effect of adherence on survival. The two most important issues highlighted by this study are the apparent disparity of treatment amongst differing racial and socioeconomic groups in the US, and the clear association of survival with adherence to NCCN guidelines, in both high-risk stage II and stage III disease. One would hope that differences in the Australian health system may allow more equal access to appropriate medical care. In the absence of robust randomised data to support adjuvant chemotherapy in high-risk stage II colon carcinoma, these results add further support to the currently available pooled analyses of this issue.


***Reference: Cancer 2013;119(8):1593-1601***
http://onlinelibrary.wiley.com/doi/10.1002/cncr.27935/abstract


## Fluorouracil, leucovorin, and irinotecan plus either sunitinib or placebo in metastatic colorectal cancer

**Authors:** Carrato A et al


**Summary:** The addition of sunitinib to FOLFIRI had no effect on survival outcomes in this randomised, double-blind, placebo-controlled, phase 3 study in 768 patients with previously untreated mCRC. Patients received FOLFIRI plus sunitinib 37.5 mg/day or placebo in a 4/2 schedule (4 weeks on treatment followed by 2 weeks off) until disease progression. The study was stopped after a second prespecified interim analysis because sunitinib failed to show superiority over placebo and was associated with more grade ≥3 adverse events and laboratory abnormalities. Toxicity-related deaths, dose delays, dose reductions, and treatment discontinuations occurred more frequently with sunitinib than placebo. The combination regimen was not recommended for previously untreated mCRC.


**Comment:** see next.


***Reference: J Clin Oncol 2013;31(10):1341-1347***
http://jco.ascopubs.org/content/31/10/1341.abstract

## Axitinib and/or bevacizumab with modified FOLFOX-6 as first-line therapy for metastatic colorectal cancer

**Authors:** Infante JR et al

**Summary:** Neither the addition of continuous axitinib nor axitinib + bevacizumab improved survival outcomes in 126 patients with previously untreated mCRC in this phase 2 study. All patients received FOLFOX6 and were randomised to receive continuous axitinib 5 mg twice daily, bevacizumab 5 mg/kg every 2 weeks, or axitinib 5 mg twice daily plus bevacizumab 2 mg/kg every 2 weeks. Axitinib was numerically inferior to bevacizumab for all efficacy endpoints and patients randomised to receive axitinib had fewer treatment cycles. Hypertension and headache were more frequent with axitinib.

***Reference: Cancer 2013;Apr 19 [Epub ahead of print]***
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28112/abstract

**Comment:** The availability of oxaliplatin, irinotecan, bevacizumab and cetuximab has led to significant survival benefits for patients with mCRC. However median overall survival approaches 2 years at best and new treatment options are required.

Bevacizumab is a humanised monoclonal antibody to VEGF-A with antiangiogenic effects. Its addition to IFL, FOLFIRI and FOLFOX has led to improved outcomes in mCRC. Sunitinib is an orally available tyrosine kinase inhibitor targeting VEGF and PDGF with proven benefit in metastatic renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumour, and axitinib is a small molecule inhibitor of VEGF receptors 1, 2 and 3.

Based on preclinical and phase I data Carrato et al undertook their study to determine if the addition of sunitinib to FOLFIRI would improve PFS in previously untreated mCRC. The study was closed early after a second interim analysis on the grounds of futility. Not only was sunitinib unable to improve PFS outcomes, it was also associated with significantly increased toxicity.

Infante et al postulated that dual inhibition of both VEGF-A (bevacizumab) and VEGFR (axitinib) would provide improved response rates in mCRC, and the reported phase II study was designed to answer that question. Unfortunately axitinib was associated with increased toxicity in both axitinib-containing arms, with subsequent higher rates of treatment discontinuation and reduced dose intensity.

Whilst the use of regorafenib, a VEGFR tyrosine kinase inhibitor, has demonstrated modest activity as a single agent in previously treated mCRC, investigators are yet to identify any benefit from the addition of other small molecule VEGFR inhibitors (cediranib, vatalanib) to chemotherapy in this disease. The results of these two papers add to the list of negative studies. Whether the lack of effect seen with the addition of sunitinib and axitinib in these studies relates to reduced dose intensity of chemotherapy and sunitinib/axitinib due to adverse effects, or the inherent biology of CRC making it insensitive to the combinations is interesting to consider, but really academic, as the combinations are clearly not effective at the maximal tolerated doses. Perhaps modifications in the dosing regimen of each tyrosine kinase inhibitor may result in enhanced tolerability and improved clinical outcomes. Obviously further study is required.

## Aflibercept

**Authors:** Ciombor KK et al

**Summary:** This review of aflibercept outlined results of clinical trials which led to its recent approval by the US FDA and discussed optimal strategies for incorporating aflibercept into treatment regimens for mCRC.

**Comment:** Angiogenesis is the process of new blood vessel formation and is essential for cancer growth and survival. The process of angiogenesis has been successfully targeted by the anti-VEGFA monoclonal antibody bevacizumab as well as VEGFR tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib and regorafenib). Aflibercept is an intravenously available humanised recombinant fusion protein incorporating extracellular parts of the VEGF-1 and VEGF-2 receptors fused to the Fc portion of IgG1. It acts as a decoy VEGFR, or a 'VEGF-trap'. This paper gives a logical description and discussion of aflibercept covering its mechanism of action; clinical development; efficacy studies; and its role in mCRC as well as other malignancies.

There is some suggestion that this drug may have effect even in patients who have experienced disease progression on bevacizumab. The role of aflibercept in mCRC and other malignancies remains in question however. Studies in NSCLC, pancreatic and prostate cancers do not support a role in cancers other than mCRC at present. Even in those patients with mCRC the ideal use for aflibercept remains unclear. There are as yet no identified biomarkers predictive of response to therapy, the benefits associated with treatment are small (~1.3 – 1.5 months), the treatment is expensive and it certainly adds to patient toxicity. A lot more information is required before we can determine the ideal place in therapy of mCRC for this drug.

***Reference: Clin Cancer Res 2013;19(8):1920-1925***
http://clincancerres.aacrjournals.org/content/19/8/1920.abstract

## Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program

**Authors:** Cole SR et al

**Summary:** CRCs were diagnosed at a significantly earlier stage in people invited to the NBCSP in Australia in this cohort study. Of 3481 eligible patients, 221 had been invited to the NBSCP. These patients were more likely to have stage A lesions compared with patients who were not invited (34.8% vs 19.2%; p<0.001), and half as likely to have stage D CRC (5.4% vs 12.4%; p<0.001). A further shift towards earlier stage was seen in patients who participated in screening (stage A 38.8% vs 19.8%; stage D 3.0% vs 12.4%) and in those with positive test results (stage A 39.7% vs 19.3%; stage D 2.6% vs 12.4%). The authors concluded that 'the NBCSP should lead to reductions in CRC mortality in Australia.'

**Comment:** The aim of any screening program is to reduce disease associated mortality by allowing earlier detection and thus more effective treatment. To confirm reduced mortality due to screening requires follow-up data over a long period of time. In a disease such as colorectal carcinoma, where there is clear evidence of improved survival in earlier stage as compared to later stage disease, information regarding stage at diagnosis provides a useful surrogate for determining the effect of screening on survival/mortality. In 2003 an Australian pilot screening program of faecal immunochemical testing (FIT) was run, and later rolled out to testing of specific invited age groups. This paper describes a significant stage shift in CRC diagnosed in people participating in CRC screening as compared to those not participating. These results would be expected to translate to reduced CRC associated mortality in the future. At present CRC screening is not offered to all eligible people in Australia although it is hoped that in the future it will be. Based on the information in this study one can expect significant reduction in CRC mortality within our population due to such screening. That is of course assuming that there is reasonable uptake of screening and that the system is able to cope with the required follow-up investigations. Others have described low patient uptake of FIT and reluctance to proceed to endoscopy in the setting of positive FIT screening test. In addition, there are already excessively long waiting times for endoscopic procedures even in symptomatic patients in many public centres. As part of the ongoing roll-out of the CRC screening program these issues also need to be addressed.

***Reference: Med J Aust 2013;198(6):327-330***
http://tinyurl.com/l47need

## Effect of low-frequency *KRAS* mutations on the response to anti-EGFR therapy in metastatic colorectal cancer

**Authors:** Tourgeron D et al

**Summary:** Low frequency *KRAS* mutations <10% (*KRAS* low mt) should be considered positive for *KRAS* mutation and treated accordingly based on the results of this retrospective analysis. Tumours from 168 patients, who were treated with anti-EGFR monoclonal antibodies based on *KRAS* wt determined by direct sequencing, were retrospectively analysed by pyrosequencing. *KRAS* wt status was confirmed for 138 tumours, while 30 tumours were defined as *KRAS* low mt. Response rates were 6.7% in the *KRAS* low mt group compared with 37.0% in the *KRAS* wt group (p<0.01). Fewer *KRAS* low mt tumours were defined as stabilised (23.3% vs 32.6%; p<0.01) and significantly more had progressed (70% vs 29%; p<0.01). PFS was 2.7 months for *KRAS* low mt and 6.0 months for *KRAS* wt (p<0.01). The authors called for justification of these results in a large-scale prospective study.

**Comment:** see below.

***Reference: Ann Oncol 2013;24(5):1267-1273***
http://annonc.oxfordjournals.org/content/24/5/1267.abstract

## Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer: analysis of data from the EXTREME and CRYSTAL studies

**Authors:** Licitra L et al

**Summary:** Tumour *EGFR* expression level was found not to be predictive of cetuximab benefit in the EXTREME and CRYSTAL studies. The addition of cetuximab to chemotherapy improved survival in the first-line treatment of recurrent/metastatic HNSCC and *KRAS* wt mCRC regardless of tumour *EGFR* expression level.

**Comment:** see below.

***Reference: Eur J Cancer 2013;49(6):1161-1168***
http://www.ejcancer.com/article/S0959-8049(12)00914-8/abstract

**Comment:** Predictive biomarkers are essential to guide appropriate use of molecular therapies. Several such biomarkers have been identified and are in routine clinical use (e.g. *HER2* amplification for trastuzumab in breast cancer; *EGFR* mutation for gefitinib and erlotinib, and *ALK* gene re-arrangement for crizotinib in lung adenocarcinoma). In some cases it appears that predictive biomarkers differ for the same agent being used to treat different diseases (c-kit expression for imatinib in gastrointestinal stromal tumours vs BCR-ABL translocation for imatinib in chronic myeloid leukaemia). *Continued page 4 –>*

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Cetuximab is a monoclonal antibody to EGFR with associated survival benefits in HNSCC, mCRC (1st, 2nd and 3rd line) and NSCLC. The presence of *KRAS* mutation predicts for resistance to cetuximab and panitumumab. Pyrosequencing is a method commonly used to test for *EGFR* and *KRAS* mutation in clinical practice. The arbitrary threshold for a positive result with pyrosequencing is set at 10%. Tougeron et al made the observation that even in those patients with *KRAS* wt tumours, not all respond to EGFR monoclonal antibodies and theorised that this may be due to a relative inability of current testing methods to identify all *KRAS* mutations. They demonstrated a group of patients with 'low-frequency' *KRAS* mutation that would have been considered *KRAS* wt by standard testing. This group demonstrated inferior response rates and disease control to those with truly wt *KRAS*. These findings support larger randomised studies critically assessing testing methods and criteria for *KRAS* mutation, and associated survival outcomes.

More sensitive testing will allow improved patient selection. Care must be taken however not to exclude patients who still might gain some benefit from treatment.

The absence of *KRAS* mutation is predictive of response to cetuximab in mCRC, however this is not the case in either NSCLC or HNSCC where *KRAS* mutation is rare. In the FLEX study, high *EGFR* expression was predictive of response to cetuximab in metastatic NSCLC. However the data presented by Licitra et al suggest that the same does not apply for HNSCC or mCRC. So it seems that at present the best way to predict response to cetuximab for mCRC is by *KRAS* mutation testing (although this would preclude patients with the G13D mutation who may be expected to obtain some benefit), and for NSCLC is by assessment of *EGFR* expression. A useful biomarker for cetuximab in HNSCC is still required.

## The beneficial effect of palliative resection in metastatic colorectal cancer

**Authors:** Park JH et al

**Summary:** Palliative resection without residual disease and chemotherapy conferred a longer-term survival outcome than palliative chemotherapy alone in a subset of patients with mCRC in this retrospective study. Of 1015 patients, 168 patients had only liver and/or lung metastases and underwent curative resection. The remaining 847 patients were treated with palliative chemotherapy and/or palliative resection (n=527) combined with best supportive care. Patients who had complete resection with negative margin (n=93) had an overall survival of 51.3 months compared with 19.1 months in patients who underwent R1/2 resection (n=434) and 14.1 months in unresected patients (all p<0.001). A significant association was found between palliative resection and prolonged overall survival (HR 0.72; 95% CI 0.59 to 0.89; p=0.003).

**Comment:** Whilst a minority of patients with low volume CRC metastases to liver and/or lung can be treated with curative intent, the vast majority undergo palliative management. Previously reported studies have suggested a link between palliative resection of the primary tumour and improved survival. The findings of Park et al support earlier claims that palliative primary tumour resection in patients also treated with chemotherapy is associated with significantly improved overall survival, except in certain subgroups.

Also of interest is the data relating to the 16.5% of patients who underwent metastasectomies of curative intent. In the absence of strong supportive data many medical oncologists use 'adjuvant' chemotherapy after metastasectomy – extrapolating from early stage disease it seems the logical approach. This review reports that 94% of patients undergoing metastasectomy received adjuvant chemotherapy (mostly oxaliplatin), and that overall survival rates were improved in those that did.

The major limitation to this study is its retrospective nature. It is quite possible that selection bias existed and that those patients deemed fit enough for resection were destined to have better survival than those not chosen for resection. The only way to definitively prove benefit from palliative resection of the primary is to complete a randomised study, although patient, surgeon and physician preferences could hinder recruitment to such a study.

***Reference: Br J Cancer 2013;108:1425-1431***
http://www.nature.com/bjc/journal/v108/n7/abs/bjc201394a.html

## Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy

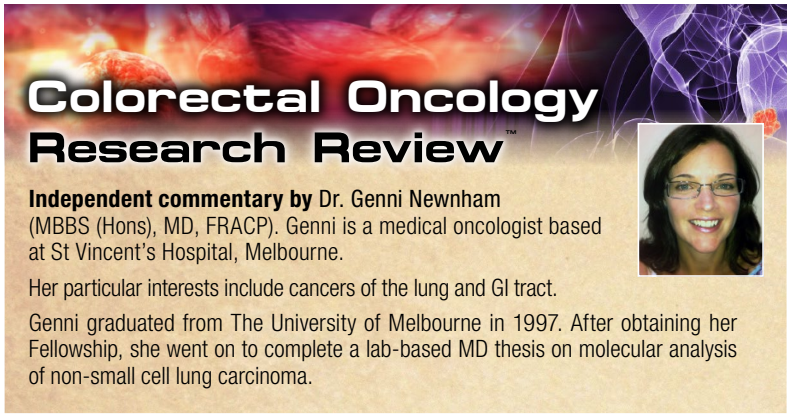
**Authors:** Sinicrope FA et al

**Summary:** Obesity and underweight status were associated with inferior outcomes in 25,291 patients with stage II and III CRC who received adjuvant chemotherapy in clinical trials and were included within the Adjuvant Colon Cancer Endpoints (ACCENT) database. Obese and underweight patients had significantly poorer survival compared with overweight and normal-weight patients during a median follow-up of 7.8 years. Men with BMI ≥35.0 kg/m$^2$ had a shorter disease-free survival than normal-weight patients (HR 1.16; 95% CI 1.01 to 1.33; p<0.05). Underweight patients had a significantly shorter time to recurrence and reduced disease-free survival (HR 1.18; 95% CI 1.09 to 1.28; p<0.0001). This effect was more significant among men than women. While BMI had a prognostic effect, BMI was not predictive of benefit from adjuvant treatment.

**Comment:** Obesity is a growing problem in the developed world and is associated with a myriad of medical complications. These authors quote alarming statistics of obesity prevalence in the US at 34%. Previous studies have identified an increased risk of CRC and mortality in obese individuals. The results presented by Sinicrope et al are in agreement with previously published studies linking both low and high BMI to poorer time to recurrence and disease-free survival. Interestingly the strength and statistical significance of these associations was much stronger in men than women, suggesting gender differences in biology. It is possible that male pattern body fat distribution with its associated metabolic complications is a factor in the witnessed gender difference in CRC outcomes and obesity. Also, the increased levels of circulating oestrogen released from fat stores in obese women may have a protective role with regards to CRC.

A better appreciation of the interaction between BMI, CRC risk and outcomes may help to inform patients and encourage beneficial lifestyle modification. I suspect the true effect of BMI on CRC development and outcomes is complex and related to duration of obesity and comorbidities rather than the presence or absence of abnormal BMI at a single point in time. Importantly benefit from adjuvant chemotherapy appears unaltered by BMI.

***Reference: Cancer 2013;119(8):1528-1536***
http://onlinelibrary.wiley.com/doi/10.1002/cncr.27938/abstract




## Phase 2 study of preoperative radiation with concurrent capecitabine, oxaliplatin, and bevacizumab followed by surgery and postoperative 5-fluorouracil, leucovorin, oxaliplatin (FOLFOX), and bevacizumab in patients with locally advanced rectal cancer: ECOG 3204

**Authors:** Landry JC et al

**Summary:** The efficacy of neoadjuvant treatment with radiation therapy and concurrent capecitabine, oxaliplatin and bevacizumab was investigated in 54 patients with resectable T3/T4 rectal adenocarincomas. All patients were scheduled to undergo surgery 6 weeks after radiation and neoadjuvant therapy and to commence postoperative FOLFOX plus bevacizumab therapy 8 to 12 weeks after surgery. Neoadjuvant therapy was completed in 49 patients who then underwent surgery. A complete pathologic response was achieved in 9 (17%) patients so the primary endpoint of a 30% pathologic response was not reached. However 32 (59%) patients experienced pathologic tumour downstaging. Grade 3 acute toxicity was reported by 53% of patients and 15% reported worst grade 4 acute toxicity. Surgical complications, such as increased wound healing, occurred in 47% of patients and were thought by the authors to possibly be related to the addition of bevacizumab, oxaliplatin, or both. They concluded that 'continued observation of these patients will establish the long-term morbidity and efficacy of this combined modality approach'.

**Comment:** Standard therapy for locally advanced rectal carcinoma includes neoadjuvant chemoradiation with infusional 5FU prior to definitive resection. Studies have demonstrated equivalent efficacy when 5FU infusion is replaced with capecitabine. The use of oxaliplatin and bevacizumab in the treatment of advanced CRC leads to improved outcomes when compared to 5FU-based treatment alone and for these reasons this study was designed to determine if the same applies for the neoadjuvant treatment of locally advanced rectal carcinoma. Unfortunately since this trial was designed it has become apparent that the addition of oxaliplatin to neoadjuvant chemoradiation for rectal carcinoma results in increased toxicity without improved response rates, consistent with the results reported here.

The rationale behind adding bevacizumab to the adjuvant component of therapy in this study is less clear, as all evidence to date in CRC suggests no benefit from doing so.

Whether the high surgical complication rate seen in this study relates to the addition of oxaliplatin or bevacizumab or both is unclear, although it is likely that both agents are implicated, bevacizumab most strongly.

As the authors point out, disease-free survival and overall survival data are not yet mature and will be reported at a later date. However, based on the results presented it is unlikely that this combination will be recommended for the treatment of locally advanced rectal carcinoma.

***Reference: Cancer 2013;119(8):1521-1527***
http://onlinelibrary.wiley.com/doi/10.1002/cncr.27890/abstract