CCU | 2005 VOL 4 | ISSUE 2

Colorectal Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

John L Marshall, MD

Steven A Curley, MD

Alan Venook, MD

CME Certified

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Colorectal Cancer Update
A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Colorectal cancer is among the most common cancers in the United States, and the arena of colorectal cancer treatment continues to evolve. Published results from ongoing clinical trials lead to the emergence of new therapeutic agents and regimens and changes in indications, doses and schedules for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances.

To bridge the gap between research and patient care, *Colorectal Cancer Update* utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment and incorporate these data into management strategies in the local and advanced disease settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including the use of oxaliplatin- and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Integrate emerging data on biologic therapies into the management of patients with advanced colorectal cancer.

PURPOSE OF THIS ISSUE OF *COLORECTAL CANCER UPDATE*

The purpose of Issue 2 of *Colorectal Cancer Update* is to support these global objectives by offering the perspectives of Drs Marshall, Curley, and Venook on the integration of emerging clinical research data into the management of colorectal cancer.

ACCREDITATION STATEMENT

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This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **ColorectalCancerUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**.

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UPCOMING EDUCATIONAL EVENTS

96th Annual Meeting of the American Association for Cancer Research
April 16-20, 2005
Anaheim, California
Event website: www.aacr.org/2005AM/2005AM.asp

Oncology Nursing Society: 30th Annual Congress
April 28-May 1, 2005
Orlando, Florida
Event website: www.ons.org/nursingEd/Conferences/congress.shtml

41st American Society of Clinical Oncology Annual Meeting
May 13-17, 2005
Orange County Convention Center
Orlando, Florida
Event website: www.asco.org/ac/1,1003_12-002092,00.asp

World Congress on Gastrointestinal Cancer
June 15-18, 2005
Barcelona, Spain
Event website: www.uicc.org

International Society of Gastrointestinal Oncology 2nd Annual Conference
July 14-16, 2005
Arlington, Virginia
Event website: www.isgio.org

2005 American Society for Therapeutic Radiology and Oncology Annual Meeting
October 16-20, 2005
Denver, Colorado
Event website: www.astro.org/annual_meeting

American Society of Colon and Rectal Surgeons Annual Meeting
October 16-20, 2005
San Francisco, California
Event website: www.facs.org

Editor's Note

Leaps of faith

National Cancer Institute News Release November 29, 2004

"Preliminary results from a large, randomized clinical trial for patients with advanced colorectal cancer who had previously received treatment show that those who received bevacizumab (Avastin™) in combination with an oxaliplatin (Eloxatin™) regimen known as FOLFOX4 lived longer than patients who received FOLFOX4 alone.

"The Data Monitoring Committee overseeing the trial (known as E3200) recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of demonstrating improved overall survival. Researchers found that the patients in the trial who received bevacizumab in combination with FOLFOX4 (a regimen of oxaliplatin, 5-fluorouracil and leucovorin) had a median overall survival of 12.5 months compared to patients treated with FOLFOX4 alone, who had a median overall survival of 10.7 months. This difference is statistically significant and corresponds to a 17 percent improvement in median overall survival. There was a 26 percent reduction in the risk of death (hazard ratio of 0.74) for patients in this study who received bevacizumab plus FOLFOX4 compared to those who received FOLFOX4 alone.

"The clinical trial was sponsored by the National Cancer Institute (NCI)...

"A total of 829 patients were enrolled in the study between October 2001 and April 2003. Patients previously had received a fluorouracil-based therapy and irinotecan (Camptosar®), either alone or at the same time, for advanced disease or if their disease had relapsed within six months of concluding adjuvant (postsurgical) treatment with these chemotherapy agents. Patients were randomized to one of three treatment groups. One patient group received the standard FOLFOX4 treatment plus bevacizumab. The second group received the standard FOLFOX4 treatment only, and the third group received bevacizumab alone. ...

"Treatment toxicities observed in this study were consistent with those side effects observed in other clinical trials in which bevacizumab was combined

with chemotherapy. Side effects included neuropathy (problems with nerve function) for FOLFOX4 and high blood pressure and bleeding for bevacizumab. ...

" 'These results are simply more good news for people with colorectal cancer,' said Study Chair Bruce J Giantonio, MD, of the University of Pennsylvania's Abramson Cancer Center in Philadelphia. 'We now know that bevacizumab added to second-line chemotherapy with FOLFOX4 improves survival. With these findings, we can now more confidently expect survival for people with advanced disease to be more than double what it was just a few years ago. ...'

" 'The results of this study are very important for all those living with advanced colorectal cancer,' said NCI Director Andrew C von Eschenbach, MD. 'They provide further confirmation that a biologic agent that targets a tumor's blood supply can prolong survival when combined with chemotherapy, even for patients who have previously received therapy for advanced disease.' "

When Herb Hurwitz first electrified a 2003 ASCO audience with results from a trial evaluating IFL with or without bevacizumab, my first thought was, "Now what are people going to use for first-line metastatic disease?" The obvious dilemma that had instantly been dropped on the table was that since the initial launch of the IFL-bev study, oxaliplatin-containing regimens had taken over as the preferred first-line therapy for people with metastases. Would docs make a leap of faith and assume that bevacizumab results in similar synergy with FOLFOX, and use that combination up front? What would the FDA do?

At the same time, researchers like Lee Ellis were gaining support for their postulations of novel and somewhat counterintuitive hypothetical mechanisms of action of bevacizumab. Lee and others have speculated that rather than the Folkman-like concept of cutting off tumor blood supply, bevacizumab actually *normalizes* intratumoral blood vessel architecture, allowing greater permeability for chemotherapy.

However, it was not known whether all chemo agents would be associated with a similar synergy. A key related factor was the convincing data that bevacizumab also added benefit to 5-FU/leucovorin without oxaliplatin.

The FDA took the lead by approving bevacizumab for use with any 5-FU combination, and many or most clinicians and researchers seemed to quickly conclude that FOLFOX plus bevacizumab was optimal first-line therapy. In this issue of *Colorectal Cancer Update*, John Marshall notes that this involved two leaps of faith — going from bolus 5-FU in the IFL regimen to infusional 5-FU in FOLFOX, and going from irinotecan to oxaliplatin. After more than a year of waiting, E3200 seemed to justify this practice pattern.

Other "leaps of faith" in systemic therapy for colorectal cancer are being considered more conservatively. Many of these involve the use of capecitabine instead of 5-FU. All three research leaders interviewed for this issue comment on the common clinical scenarios in which this substitution is considered: preoperative chemoradiation for rectal cancer, adjuvant therapy alone or with oxaliplatin, and first-line metastatic disease for which the potential synergy of capecitabine with bevacizumab is not clearly defined.

In our recent special edition "Think Tank" for this series, Herb Hurwitz made an interesting comment about the use of therapies without clear-cut supportive research data, specifically referring to the use of FOLFOX/bevacizumab at that time. He noted that the existence of a clinical trial containing such a therapy in a randomization arm might justify the use of that regimen in a nonprotocol setting until the definitive results of the study became available.

For more than a year, many clinicians and patients have essentially followed that path by selecting FOLFOX/bevacizumab as first-line therapy for metastatic disease. These actions have now been justified by yet another trial that has moved the field forward.

— Neil Love, MD
NLove@ResearchToPractice.net

Select publications

Fernando NH et al. **A phase II study of oxaliplatin, capecitabine and bevacizumab in the treatment of metastatic colorectal cancer.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 289**.

Fernando NH, Hurwitz HI. **Targeted therapy of colorectal cancer: Clinical experience with bevacizumab.** *Oncologist* 2004;9(Suppl 1):11-8. **Abstract**

Giantonio B et al. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169a**.

Hochster HS et al. **Bevacizumab (B) with oxaliplatin (O)-based chemotherapy in the first-line therapy of metastatic colorectal cancer (mCRC): Preliminary results of the randomized "TREE-2" trial.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 241**.

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Kabbinavar F et al. **Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Saltz LB et al. **Interim report of randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169b**.

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004;10(2):145-7. **Abstract**

John L Marshall, MD

EDITED COMMENTS

Efficacy of bevacizumab in combination with chemotherapy in first- and second-line clinical trials

The ECOG E3200 trial, which randomly assigned patients with previously treated advanced colorectal cancer to receive FOLFOX4 with or without bevacizumab, demonstrated a positive survival advantage with the addition of bevacizumab (Giantonio 2005).

These data could have an immediate impact on the clinical use of bevacizumab, particularly in patients with refractory disease or in second-line therapy.

Previously, FOLFOX had not shown an independent survival advantage in the second-line setting. In Rothenberg's study, FOLFOX showed improvement in time to progression, but not survival (Rothenberg 2003). In E3200, patients who received FOLFOX alone clearly did as well as patients who received FOLFOX in Rothenberg's study. In E3200, the addition of bevacizumab increased survival by almost a couple of months.

In the IFL plus bevacizumab front-line trial, a dramatic improvement occurred in survival and time to progression in patients who received the combination (Hurwitz 2004). Trials such as these support our argument that adding bevacizumab to chemotherapy regimens in the first- or second-line setting can result in a positive outcome for patients in terms of survival and progression-free survival.

The magnitude of benefit was greater in the front-line study, and we don't know whether that is because of some front-line phenomenon that wouldn't be seen in second-line metastatic colon cancer or if something more "additive" occurs with bevacizumab and irinotecan compared to oxaliplatin.

Synergy between bevacizumab and chemotherapy

The front-line study examining 5-FU/leucovorin with or without bevacizumab in patients with a poor performance status demonstrated an advantage from the combination (Kabbinavar 2004). Clearly, synergy exists between bevacizumab

Dr Marshall is an Associate Professor and Director of Developmental Therapeutics and GI Oncology at Lombardi Comprehensive Cancer Center at Georgetown University in Washington, DC.

and 5-FU, and it appears that when you start combining it with other chemotherapeutic agents, that benefit carries over or adds up even further (1.1).

What may be happening with bevacizumab in a number of settings is that it controls the growth of the cancer, prevents progression and, therefore, adds to progression-free survival, which is now translating into overall survival.

I believe bevacizumab works by changing the dynamics of the interstitial pressure within the tumor, which facilitates the delivery of chemotherapy. If indeed that is its mechanism of action, then the particular chemotherapy utilized shouldn't matter, and bevacizumab should improve its efficacy.

1.1 Randomized Trials of Bevacizumab plus Various Chemotherapy Regimens in Metastatic Colorectal Cancer

Author Regimen	Phase	Number of patients	Rate of response	Median time to progression	Median overall survival
Cunningham D et al[1]	II				
Cetuximab*		111	11%	1.5 months	6.9 months
Cetuximab + irinotecan		218	23%	4.1 months	8.6 months
Kabbinavar FF et al[1]	II				
Fluorouracil + leucovorin		36	17%	5.2 months	13.8 months
Fluorouracil + leucovorin + bevacizumab		68	32%	7.4 months	16.1 months† 21.5 months†
Kabbinavar FF et al[1]	III				
Fluorouracil + leucovorin		105	15%	5.5 months	12.9 months
Fluorouracil + leucovorin + bevacizumab		104	26% ($p = 0.06$)	9.2 months ($p < 0.001$)	16.6 months ($p = 0.16$)
Hurwitz H et al[1]	III				
IFL		412	35%	6.2 months	15.6 months
IFL + bevacizumab		403	45% ($p = 0.004$)	10.6 months ($p < 0.001$)	20.3 months ($p < 0.001$)
Giantonio BJ et al[2]	III				
FOLFOX4		289	NR	NR	10.7 months
FOLFOX4 + bevacizumab		290	NR	NR	12.5 months ($p = 0.0024$)

NR = not reported

* Patients in this arm were allowed to cross over to the cetuximab plus irinotecan arm on progression. Fifty-four percent of the patients on this arm crossed over with a partial response rate of 3.6 percent and a stable disease rate of 35.7 percent.

† In this trial, two groups received bevacizumab: One group received 10 mg/kg, while the other group received 5 mg/kg. The median overall survivals were 16.1 months and 21.5 months, respectively.

SOURCES: [1] Meyerhardt JA et al. **Systemic therapy for colorectal cancer.** *New Engl J Med* 2005;352(5):476-87. No abstract available

[2] Giantonio BJ et al. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** Presentation. GI ASCO 2005;**Abstract 169a**.

Continuation of bevacizumab after progression

One question the E3200 trial does not answer is whether a patient who progresses on a front-line combination of chemotherapy plus bevacizumab should be maintained on bevacizumab in the second- and third-line settings.

The suspected mechanism of action of bevacizumab suggests that patients should be maintained on this agent, but other factors — including cost and side effects — must be considered. If a patient is tolerating bevacizumab, I believe it would be difficult to justify discontinuing it when switching from a front-line to a second-line therapy. Even though E3200 doesn't answer that question directly, I believe continuing bevacizumab is a reasonable strategy in the nonprotocol setting, given the survival data in the front- and second-line settings.

Nonprotocol use of first-line FOLFOX with bevacizumab

I was surprised that after the data presented at the 2003 ASCO meeting on bevacizumab/IFL, clinicians shifted towards using FOLFOX plus bevacizumab (Hurwitz 2004). I believe this occurred because the FDA gave free reign to use bevacizumab with any intravenous 5-FU-containing regimen.

The pendulum was already swinging toward using FOLFOX as the standard front-line approach for patients with metastatic colon cancer, so oncologists went ahead and combined it with bevacizumab. That requires two leaps of faith — first, infusional 5-FU in FOLFOX rather than bolus 5-FU in the IFL regimen, and, second, oxaliplatin rather than irinotecan — without a lot of supportive data. The data from the E3200 trial support both leaps, showing bevacizumab to be safe and effective with infusion 5-FU and oxaliplatin.

Rationale for adjuvant clinical trials combining FOLFOX and bevacizumab

To date, drugs that are effective in metastatic disease are also effective in the adjuvant setting, so the obvious next step after E3200 is to test FOLFOX plus bevacizumab as adjuvant therapy. Based on the MOSAIC trial data, FOLFOX offers clear benefit in the adjuvant setting (de Gramont 2005), whereas the IFL data were negative in the adjuvant setting.

The NSABP is undertaking a study of FOLFOX plus bevacizumab versus FOLFOX alone. As it stands now, patients will receive 12 months of bevacizumab — six months concurrent with chemotherapy, followed by an additional six months of bevacizumab alone — hoping for an antiangiogenic effect on microscopic disease and the prevention of relapses.

The Intergroup is initiating a key trial for patients with Stage III disease that will have three arms. One arm will utilize FOLFOX as the standard of care, a second arm will utilize 12 cycles of fluorouracil/leucovorin with or without irinotecan (FOLFIRI), and the third arm will utilize six cycles of FOLFOX and six cycles FOLFIRI. Adding a biologic agent has also been discussed. It's an interesting study evaluating whether we can double up on chemotherapy and further

improve outcome in the adjuvant setting; however, this trial is contingent on a positive result in the PETACC-3 study, which is evaluating adjuvant FOLFIRI.

Adjuvant therapy for patients with Stage II disease

It is interesting that we tend to back away from adjuvant therapy in patients who have a lower risk, when it may be more appropriate to do exactly the opposite. Those are the patients with whom we should be the most aggressive. In the Stage II subset analysis of the MOSAIC study, the patients who received FOLFOX had a three-year disease-free survival of 87 percent. To my knowledge, that's the highest number ever reported for Stage II patients, and it's a compelling number in the clinic.

The real issue with using 12 cycles of FOLFOX in the adjuvant setting is the high rate of neurotoxicity seen at the end of that six-month treatment period. It's not life threatening, but it's a nuisance for patients.

In breast cancer we are accustomed to utilizing adjuvant chemotherapy for relatively small gains, meaning two to four percent absolute gain. I believe we should be equally aggressive when treating patients with colon cancer, and we should incorporate these adjuvant therapies as often as possible. By adopting these new therapies, we're going to cure more patients of this disease.

Safety and efficacy data from the X-ACT adjuvant trial

The X-ACT trial was conducted in Europe with approximately 2,000 patients, half of whom received full-dose capecitabine — 1,250 mg/m^2 bid, two weeks on, one week off — and the other half received the Mayo Clinic 5-FU/leucovorin regimen (Cassidy 2004b). Both of those recipes are considered "too spicy" in the United States, so we were surprised when the safety data revealed that approximately 60 percent of patients did not require a dose reduction in either arm.

Although the remaining approximately 40 percent in both arms needed dose reduction — either due to hand-foot syndrome or the more toxic side effects of the Mayo Clinic regimen, including neutropenia, sepsis and diarrhea. However, the capecitabine arm was significantly less toxic.

The trial was designed to be an equivalence study, but the analysis showed capecitabine to be superior by a couple of percentage points in both disease-free and overall survival (Cassidy 2004a). Therefore, based on the lower toxicity and slightly higher efficacy data, I believe capecitabine is a better option than the Mayo Clinic 5-FU/leucovorin regimen.

Capecitabine in the adjuvant setting for Stage II colon cancer

Often when discussing treatment with young, healthy patients with lower-risk Stage II disease, I consider using infusion 5-FU or sometimes even FOLFOX, but some patients don't want to approach it that aggressively, and some oncologists even debate whether to offer chemotherapy to those patients. I believe capecitabine, although controversial, is a good option. I recognize that we don't

have firm randomized trial data with capecitabine in Stage II disease, but in the X-ACT study, capecitabine was equivalent to bolus 5-FU, so I believe it's an option for patients with low- to moderate-risk Stage II disease.

Adjuvant chemotherapy for Stage III disease

In patients with Stage III disease, I generally use FOLFOX6 as adjuvant therapy because I believe the two-day infusion schedule is the optimal way to administer 5-FU intravenously. I discuss the MOSAIC and X-ACT data with the patients, and some patients ask about using CAPOX. I usually steer them toward one of the other options. I have treated patients with CAPOX in the adjuvant setting, and my intuition tells me that regimen is adequate so I would rather give that than nothing; however, we need the trial data to be certain.

Select publications

Cassidy J et al. **Capecitabine (X) vs bolus 5-FU/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT study): Efficacy results of a phase III trial.** *Proc ASCO* 2004a;**Abstract 3509**.

Cassidy J et al. **Improved safety of capecitabine versus bolus 5-fluorouracil/leucovorin (LV) as adjuvant therapy for colon cancer (the X-ACT phase III study).** *Proc ASCO* 2004b;**Abstract 219**.

De Gramont A et al. **Oxaliplatin/5FU/LV in the adjuvant treatment of stage II and stage III colon cancer: Efficacy results with a median follow-up of 4 years.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 167**.

Giantonio B et al. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169a**.

Hochster HS et al. **Bevacizumab (B) with oxaliplatin (O)-based chemotherapy in the first-line therapy of metastatic colorectal cancer (mCRC): Preliminary results of the randomized "TREE-2" trial.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 241**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Kabbinavar FF et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) to prolong progression-free survival in first-line colorectal cancer (CRC) in subjects who are not suitable candidates for first-line CPT-11.** *Proc ASCO* 2004;**Abstract 3516**.

Meyerhardt JA et al. **Systemic therapy for colorectal cancer.** *New Engl J Med* 2005;352(5):476-87. No abstract available

Ravdin PM, Davis GJ. **Adjuvant! a computer program for making prognostic estimates and assessing the value and risks of adjuvant therapy for individual colon cancer patients.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 291**.

Rothenberg ML et al. **Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: Interim results of a phase III trial.** *J Clin Oncol* 2003;21(11):2059-69. **Abstract**

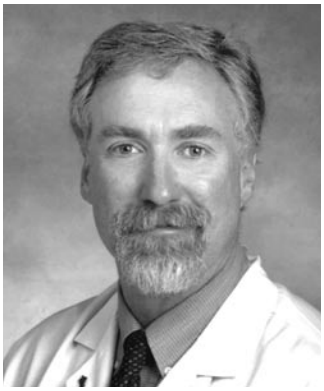
Saltz LB et al. **Interim report of randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169b**.

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004;10(2):145-7. **Abstract**

Steven A Curley, MD

EDITED COMMENTS

Radiofrequency ablation for patients with liver metastases



I began studying this modality in the laboratory in 1993 and in clinical trials in 1996. It's a technique that allows us to treat tumors that cannot be resected because they were either in a bad location or bilobar.

We've now shown that you can safely do a combination of resection of the dominant or large tumors and then ablation of the smaller tumors in the opposite lobe without an increase in the complication rate. Long-term outcomes data with that type of aggressive approach indicate good results with patients surviving for longer periods of time (Pawlik 2003).

Radiofrequency ablation has a low rate of side effects; our group has shown a less than 10 percent complication rate (Curley 2004; [2.1]). In addition to the early complications (eg, abscess in the ablated lesion or bleeding from the needle track), some patients develop late complications such as bile duct strictures or fistulae.

Others patients develop bilomas, which are large collections of bile in the liver. Fortunately, those types of side effects have a low incidence — only about 2.5 percent of patients develop long-term side effects or toxicity (Curley 2004).

Radiofrequency ablation in clinical practice

This approach is now widely used in the United States. It's a technique that is being used by surgeons and interventional radiologists. The incidence of local recurrence — what I call incomplete treatment — is much lower in the hands of surgeons, primarily because we do it intraoperatively either with laparoscopic or open ultrasound guidance.

It is important to carefully evaluate the indications for radiofrequency ablation. I use it only in patients who can be treated with curative intent alone or combined with surgical resection. I've seen patients who have undergone radiofrequency ablation for palliation of symptoms. That may be useful in select settings, but it has to be used judiciously.

Dr Curley is a Professor of Surgical Oncology and Chief of Gastrointestinal Tumor Surgery at The University of Texas MD Anderson Cancer Center in Houston, Texas.

In general, if the tumor can be surgically resected, that's what I do. In patients with colorectal cancer, with the techniques we now have available, less than five percent of patients require blood transfusions. Historically, liver resections were associated with a high risk of problems. At MD Anderson, the mortality rate is less than one percent and the complication rate is less than 30 percent.

2.1 Complication Rates Associated with Radiofrequency Ablation of Liver Tumors in Patients from a Prospective Database

	Open RFA (n=382)	Percutaneous RFA (n=226)	Overall (n=608)
Early complications	8.6%	4.4%*	7.1%
Late complications	2.6%	2.2%†	2.4%
Mortality	0.5%	0.4%	0.5%

RFA = radiofrequency ablation
* $p < 0.01$
† p = not significant for open versus percutaneous RFA

SOURCE: Curley SA et al. **Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients.** *Ann Surg* 2004;239(4):450-8. Abstract

Maximizing the benefit of radiofrequency ablation

We've seen the greatest benefit from ablation in two patient populations. The first is the patient with disease that is metastatic to the liver in a bad location (eg, nestled on the vena cava or under the hepatic veins). Surgical data demonstrate that unless you can perform a resection and obtain a tumor-free margin, you do not provide any benefit to the patient.

A tumor in that location frustrates surgeons because we know we're not going to be able to obtain a negative margin. In that patient population, we can demonstrate a benefit by performing tumor ablation with either radiofrequency or microwave.

The other patients who will benefit from ablation are the patient with hepatocellular cancer. The vast majority of them have underlying liver disease, such as cirrhosis from chronic hepatitis B or C infection, and they definitely have some element of hepatic dysfunction.

Those patients are clearly at a high risk of liver failure and death after a resection. Because we have such a high demand for liver transplants in this country, many of them aren't going to be candidates for a transplant because an organ will not be available.

We've just published our data from MD Anderson on radiofrequency ablation for early-stage hepatocellular cancer, and the results are actually better than the results after resection but not quite as good as the results after transplant. We're now using radiofrequency ablation as a bridge to transplantation in select patients.

Chemotherapy and radiofrequency ablation in patients with liver-only metastases

In patients with colorectal cancer, using radiofrequency ablation alone without any additional systemic or regional chemotherapy offers about a 15 percent to 20 percent probability of cure for unresectable disease. That's based on our own results at MD Anderson where our four-year overall survival rate is about 22 percent. Certainly, a subset of patients will be alive and without disease at four years (Abdalla 2004).

Adding chemotherapy to radiofrequency ablation — either as neoadjuvant or adjuvant therapy — nearly doubles the overall survival to 35 percent to 40 percent. In contrast, if those patients were treated only with systemic chemotherapy, that number would be less than 10 percent (Abdalla 2004). In the past, it would have been less than one percent or two percent, but the response rates are higher, with some of the FOLFOX regimens and the addition of drugs like bevacizumab.

Some patients will refuse chemotherapy or will have had previous chemotherapy and do not want more. That doesn't mean we won't offer them a resection. We know that's going to give them their highest probability of long-term survival, but we tell them they're going to need to be followed closely.

NSABP-R-04: Capecitabine versus continuous infusion 5-FU as neoadjuvant therapy for rectal cancer

A large volume of Phase II data demonstrates that capecitabine is similar to infusional 5-FU. While it's a good idea to perform the NSABP study, I'm not sure that we necessarily need it. It'll be interesting to see how that study accrues. In this country, physicians are rapidly adapting regimens based on Phase II data, but it's become a bit of a minefield because so many regimens are available. I think R-04 is going to be sort of a "thanks for confirming what we already suspected was true" type of study.

Select publications

Abdalla EK et al. **Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases.** *Ann Surg* 2004;239(6):818-25; discussion 825-7. **Abstract**

Benson AB 3rd et al. **American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer.** *J Clin Oncol* 2004;22(16):3408-19. **Abstract**

Berber E et al. **Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: A prospective study.** *J Clin Oncol* 2005;23(7):1358-64. **Abstract**

Curley SA et al. **Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients.** *Ann Surg* 2004;239(4):450-8. **Abstract**

Douglas WG et al. I**nflammatory cytokines increase hepatocellular carcinoma cells thermotolerance: Evidence of how pre-ablation inflammation may negatively impact radiofrequency ablation local control rates.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 122**.

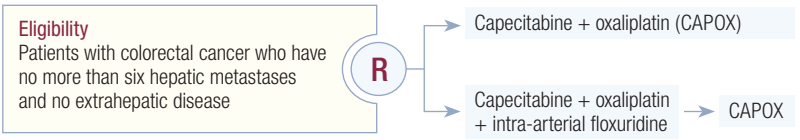
Pawlik TM et al. **Combined resection and radiofrequency ablation for advanced hepatic malignancies: Results in 172 patients.** *Ann Surg Oncol* 2003;10(9):1059-69. **Abstract**

NSABP-C-09 trial: CAPOX with or without intrahepatic FUDR

The NSABP has been bold in their research strategy, and in some cases that has had a huge positive impact. Two major studies suggest that intrahepatic FUDR following resection is beneficial; however, those studies were performed in an era before oxaliplatin and irinotecan. As a proponent of regional chemotherapy, I have no doubt that intrahepatic FUDR will be a positive addition to these combinations. Selecting the right patients for the study could make a difference, but to their credit, the NSABP is attempting to address that issue (3.1).

3.1 Phase III Trial Comparing Intravenous Oxaliplatin and Oral Capecitabine and Hepatic Arterial Infusion of Floxuridine to Intravenous Oxaliplatin and Oral Capecitabine in Patients with Resected or Ablated Metastases to the Liver from Colorectal Cancer

Protocol ID: NSABP-C-09
Accrual: 400 patients (Pending)



SOURCE: **www.nsabp.pitt.edu**, February 2005.

CAPOX (capecitabine/oxaliplatin)

At UCSF, we lean toward FOLFOX rather than CAPOX because we have data for FOLFOX, and the current data are not adequate to say that CAPOX and FOLFOX are equivalent. In practice we have seen robust responses with CAPOX, FOLFOX, FOLFIRI and CAPIRI. Although we need more data, I do not anticipate

Dr Venook is a Professor of Clinical Medicine, Associate Chief of the Division of Medical Oncology and Director of the Clinical Research Office at the UCSF Cancer Center in San Francisco, California.

that capecitabine will be a compromise for patients. The problem we have had with CAPOX has been dosing, because it can cause hand-foot syndrome. We are relatively conservative in our use of capecitabine and tend to favor it in elderly patients.

Whether research resources should be invested in investigating capecitabine in combination with either irinotecan or oxaliplatin is a good question (3.2). On one hand, with the new agents that need evaluation, it seems absurd to expend resources on proving the equivalence of combinations of capecitabine versus 5-FU. On the other hand, this has a huge impact on quality of life and patient satisfaction. In an ideal world, we would enroll more patients with colorectal cancer in clinical trials and be able to answer all of these questions.

3.2 Phase II Studies Evaluating the Combination of CAPOX as First-Line Therapy in Patients with Colorectal Cancer

Study	N	CAP/OX dose (mg/m^2)	Objective response	Median survival
Borner MM et al, 2002	43	2,500/130	49%	17.1 mo
Cassidy J et al, 2004	96	2,000/130	55%	19.5 mo
Scheithauer W et al, 2003				
Arm A	45	2,000/130*	42.2%	Not reached
Arm B	44	3,500/85†	54.5%	Not reached
Zeuli M et al, 2003	43	2,500/120	48.7%	20.0 mo

Unless otherwise indicated, capecitabine was administered on days 1-14 and oxaliplatin on day 1 every three weeks.

*Arm A: Capecitabine administered on days 1-14 and oxaliplatin on day one every three weeks
†Arm B: Capecitabine administered on days 1-7 and 14-21 and oxaliplatin on days 1 and 14 every four weeks

SOURCES: Borner MM et al. *J Clin Oncol* 2002;20(7):1759-66. **Abstract**
Cassidy J et al. *J Clin Oncol* 2004;22(11):2084-91. **Abstract**
Scheithauer W et al. *J Clin Oncol* 2003;21(7):1307-12. **Abstract**
Zeuli M et al. *Ann Oncol* 2003;14(9):1378-82. **Abstract**

Side effects of bevacizumab

Hypertension is a toxicity associated with bevacizumab, but it is almost always easily managed with oral agents. Initial concern arose over whether bevacizumab caused proteinuria, yet studies now indicate that only about 20 percent of patients develop proteinuria. A potential safety issue related to bevacizumab is the occurrence of bowel events. In patients who have had recent primary surgery, the anastomoses may be compromised by the antiangiogenic action of bevacizumab (Hurwitz 2004). That raises concern regarding the use of bevacizumab in the adjuvant setting. In these trials, we will need to "watch like a hawk" to ensure that bowel events do not become problematic.

Selection of patients with Stage II disease for adjuvant chemotherapy

The NSABP philosophically believes that the benefit from chemotherapy is accrued to patients with both Stage II and Stage III disease. The MOSAIC trial demonstrated a statistically significant benefit in three-year disease-free survival with FOLFOX versus infusional 5-FU/leucovorin in patients with Stage III disease; however, statistical significance was not yet reached in Stage II disease (de Gramont 2003).

In my opinion, the flaw in treating patients with Stage II disease in the NSABP-C-08 trial evaluating FOLFOX with and without bevacizumab is the accumulating evidence that a subset of patients with Stage II disease should not be subjected to the risk of chemotherapy.

ECOG is addressing that issue with a clever trial design that risk stratifies patients with node-negative disease. This stratification is based on the molecular features of the tumors. For example, patients who have normal 18q are observed without therapy, based on retrospective data from a number of studies suggesting that those patients do well, while patients in the study who have deletion of 18q are randomly assigned to chemotherapy.

A relative risk reduction occurs with colorectal cancer chemotherapy, so the issue lies in identifying the baseline risk. FOLFOX causes neuropathy, so in a patient with node-negative disease who may have an 82 percent likelihood of being alive and disease free five years later, you have to balance the benefit with the long-term consequence.

Nonprotocol use of adjuvant chemotherapy

Based on the results of the MOSAIC trial, we have switched from using 5-FU/leucovorin to FOLFOX as adjuvant treatment for node-positive colon cancer in the nonprotocol setting. Uncertainty lies in the important issue of how to treat patients who develop neuropathy three months into therapy. The Intergroup adjuvant study is going to sequence FOLFOX and FOLFIRI.

For patients with Stage II disease in the adjuvant setting off protocol, we present all of the options, and the decision boils down to the patient's philosophy. Statistical estimates indicate that a study would require 4,000 patients to discern a meaningful difference in chemotherapy effect in patients with node-negative disease, but I don't believe that such a study will be conducted.

Another important issue is the correlation of three-year disease-free survival with five-year overall survival in clinical trials. I am comfortable that three-year disease-free survival is a reasonable surrogate to predict benefit.

Select publications

Borner MM et al. **Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer.** *J Clin Oncol* 2002;20(7):1759-66. **Abstract**

Cassidy J et al. **XELOX (capecitabine plus oxaliplatin): Active first-line therapy for patients with metastatic colorectal cancer.** *J Clin Oncol* 2004;22(11):2084-91. **Abstract**

De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Results of the international randomized MOSAIC trial.** *Proc ASCO* 2003;**Abstract 1015**.

De Gramont A et al. **Oxaliplatin/5-FU/LV in adjuvant colon cancer: Safety results of the international randomized AI trial**. *Proc ASCO* 2002;**Abstract 525**.

Fyfe GA et al. **Bevacizumab plus irinotecan/5-FU/leocovorin for treatment of metastatic colorectal cancer results in survival benefit in all pre-specified patient subgroups.** *J Clin Oncol* 2004;22(14 Suppl):9-13;**Abstract 3617**.

Giantonio B et al. **High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169a**.

Goldberg RM et al. **N9741: FOLFOX (oxaliplatin(Oxal)/5-fluorouracil(5-FU)/leucovorin (LV) or reduced dose R-IFL (CPT-11 + 5-FU/LV) in advanced colorectal cancer (CRC): Final efficacy data from an Intergroup study.** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 3621**.

Hochster HS et al. **Bevacizumab (B) with oxaliplatin (O)-based chemotherapy in the first-line therapy of metastatic colorectal cancer (mCRC): Preliminary results of the randomized "TREE-2" trial.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 241**.

Hurwitz H. **Integrating the anti-VEGF-A humanized monoclonal antibody bevacizumab with chemotherapy in advanced colorectal cancer.** *Clin Colorectal Cancer* 2004;4(Suppl 2):62-8. **Abstract**

Hurwitz H et al. **Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC.** *Proc ASCO* 2003;**Abstract 3646**.

Hurwitz H et al. **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004;350(23):2335-42. **Abstract**

Kabbinavar F et al. **Phase II randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer.** *J Clin Oncol* 2003;21(1):60-5. **Abstract**

Saltz LB et al. **Interim report of randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer.** *Proc ASCO GI Cancer Symposium* 2005;**Abstract 169b**.

Saltz LB et al. **Irinotecan plus fluorouracil/leucovorin (IFL) versus fluorouracil/leucovorin (FL) alone in stage III colon cancer (Intergroup trial CALGB C89803).** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 3500**.

Scheithauer W et al. **Randomized multicenter Phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer.** *J Clin Oncol* 2003;21(7):1307-12. **Abstract**

Willett CG et al. **Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer.** *Nat Med* 2004;10(2):145-7. **Abstract**

Wolmark N et al. **A phase III trial comparing oral UFT to FULV in stage II and III carcinoma of the colon: Results of NSABP Protocol C-06.** *J Clin Oncol* 2004;22(14 Suppl);**Abstract 3508**.

Zeuli M et al. **Phase II study of capecitabine and oxaliplatin as first-line treatment in advanced colorectal cancer.** *Ann Oncol* 2003;14(9):1378-82. **Abstract**

Post-test:

Colorectal Cancer Update — Issue 2, 2005

QUESTIONS (PLEASE CIRCLE ANSWER):

1. E3200, which randomly assigned patients with previously treated advanced colorectal cancer to receive FOLFOX4 with or without bevacizumab, demonstrated a positive survival advantage with the addition of bevacizumab.
   a. True
   b. False

2. One theory about the mechanism of action of bevacizumab is that it works by changing the dynamics of the interstitial pressure within the tumor, which facilitates the delivery of chemotherapy.
   a. True
   b. False

3. Based on the MOSAIC trial, which of the following regimens has been shown to have a clear benefit in the adjuvant setting?
   a. FOLFOX4
   b. IFL

4. In the X-ACT adjuvant trial, which regimen demonstrated lower toxicity and superior efficacy?
   a. Capecitabine
   b. Mayo Clinic 5-FU/leucovorin regimen

5. Radiofrequency ablation is particularly well suited for patients with liver metastases in a location that would preclude obtaining negative margins upon surgical resection.
   a. True
   b. False

6. Data from MD Anderson suggest that overall survival for patients with liver-only metastases is better with surgical resection than with radiofrequency ablation.
   a. True
   b. False

7. A common toxicity associated with oxaliplatin therapy is:
   a. Hypertension
   b. Epistaxis
   c. Neuropathy
   d. Proteinuria

8. The proposed NSABP-C-09 trial is designed to evaluate intrahepatic FUDR with and without:
   a. Bevacizumab
   b. CAPOX
   c. Irinotecan
   d. Leucovorin

9. The MOSAIC adjuvant trial results reported an increase in three-year disease-free survival with FOLFOX compared to 5-FU/leucovorin.
   a. True
   b. False

10. Which of the following side effects are associated with bevacizumab therapy?
    a. Hypertension
    b. Neuropathy
    c. Hand-food syndrome
    d. None of the above

Post-test Answer Key: 1a, 2a, 3a, 4a, 5a, 6a, 7c, 8b, 9a, 10a

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *CCU* address the following learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in colorectal cancer treatment and incorporate these data into management strategies in the local and advanced disease settings..... 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials..... 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including the use of oxaliplatin- and capecitabine-containing regimens, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients..... 5 4 3 2 1 N/A
- Integrate emerging data on biologic therapies into the management of patients with advanced colorectal cancer..... 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
John L Marshall, MD	5 4 3 2 1	5 4 3 2 1
Steven A Curley, MD	5 4 3 2 1	5 4 3 2 1
Alan Venook, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity..... 5 4 3 2 1 N/A
Related to my practice needs..... 5 4 3 2 1 N/A
Will influence how I practice..... 5 4 3 2 1 N/A
Will help me improve patient care..... 5 4 3 2 1 N/A
Stimulated my intellectual curiosity..... 5 4 3 2 1 N/A
Overall quality of material..... 5 4 3 2 1 N/A
Overall, the activity met my expectations..... 5 4 3 2 1 N/A
Avoided commercial bias or influence..... 5 4 3 2 1 N/A

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Contact Information	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@ResearchToPractice.net
For CME Information	Melissa Vives, Associate CME Administrator Email: MVives@ResearchToPractice.net

This program is supported by education grants from Roche Laboratories Inc, Genentech BioOncology and Sanofi-Aventis.

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Roche Laboratories Inc, Genentech BioOncology and Sanofi-Aventis.

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Last review date: March 2005
Release date: March 2005
Expiration date: March 2006
Estimated time to complete: 3 hours