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Colorectal Cancer™ UPDATE

An Audio Review Journal for Surgeons

Bridging the Gap between Research and Patient Care

EDITOR

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INTERVIEWS

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Colorectal Cancer Update for Surgeons

A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Colorectal cancer (CRC) is one of the most rapidly evolving fields in oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic techniques, agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — surgeons caring for patients with CRC must be well informed of these advances. To bridge the gap between research and patient care, *Colorectal Cancer Update* for Surgeons utilizes one-on-one discussions with leading colorectal cancer investigators. By providing access to the latest research developments and expert perspectives, this CME program assists gastrointestinal surgeons in the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Identify the strengths and weaknesses of genomic assays and clinicopathologic variables as tools for communicating risk of recurrence to patients with early colon cancer.
- Formulate a treatment plan for patients with synchronous or metachronous, asymptomatic or symptomatic primary CRC and liver-only metastases.
- Evaluate the pros and cons of perioperative versus postoperative systemic therapy for patients with resectable hepatic metastases.
- Counsel patients receiving bevacizumab as part of perioperative or postoperative systemic therapy about potential treatment side effects, including surgical and wound-healing complications.
- Recognize the significance of preexisting liver disease and comorbidities in the cumulative risk of steatohepatitis for patients receiving oxaliplatin or irinotecan.
- Educate patients presenting with an asymptomatic primary tumor and synchronous metastatic CRC about their risk of requiring subsequent emergent surgery if they are treated with systemic therapy alone.
- Summarize the effect of calcium and magnesium on the prevention or amelioration of oxaliplatin-associated sensory neurotoxicity or myalgias.
- Counsel appropriately selected patients about participation in ongoing clinical trials.

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INTERVIEW

Nicholas J Petrelli, MD

Dr Petrelli is Bank of America Endowed Medical Director of the Helen F Graham Cancer Center at Christiana Care in Newark, Delaware and Professor of Surgery at Thomas Jefferson University in Philadelphia, Pennsylvania.

Tracks 1-14

Track 1 **Case discussion:** A 62-year-old man who underwent a hemicolectomy two years ago for T3N0M0 colon cancer now presents with a 3-cm left hepatic lesion

Track 2 Communicating prognosis and benefits from adjuvant chemotherapy to patients with Stage II colon cancer

Track 3 Assessment of patients being considered for resection of hepatic metastases

Track 4 Pros and cons of immediate hepatic resection versus perioperative systemic therapy

Track 5 Planned NSABP trial of perioperative versus postoperative FOLFOX or FOLFIRI and bevacizumab for patients with resectable hepatic metastases

Track 6 Efficacy of chemotherapy/bevacizumab in patients with metastatic colorectal cancer (mCRC)

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Track 12 **Case discussion:** A 58-year-old man who develops metastases involving the right and middle hepatic vein four years after hemicolectomy for Stage II colon cancer

Track 13 Chemotherapy to convert unresectable hepatic metastases to resectable disease

Track 14 Patients with resectable hepatic metastases for whom perioperative chemotherapy may be contraindicated

Select Excerpts from the Interview

Tracks 3-5

DR LOVE: Would you discuss the different treatment approaches for patients being considered for resection of hepatic metastases?

DR PETRELLI: When we discuss systemic treatment options for resectable hepatic metastases, we use three terms, and it's important to have the definitions straight. The first term is *adjuvant therapy*, and that's administering systemic therapy after hepatic resection.

The second is *perioperative chemotherapy*, which is administering several cycles before surgery, performing the resection and then administering several cycles after surgery. The third is *neoadjuvant chemotherapy*, which is the administration of chemotherapy prior to surgery with the consideration of further chemotherapy afterward.

Debate on this subject has occurred at the two ends of the spectrum. I believe that the results reported by Bernard Nordlinger and the EORTC-40983 trial could convince physicians to administer chemotherapy perioperatively (Nordlinger 2008; [1.1]). However, because of the hepatic toxicity, until we have a trial of perioperative versus adjuvant chemotherapy, I will recommend that patients receive chemotherapy after surgery.

DR LOVE: What are the pros and cons of immediate hepatic resection compared to perioperative systemic therapy?

DR PETRELLI: Preoperative chemotherapy these days is likely to include either FOLFOX or FOLFIRI. We know that these regimens have certain effects on the normal liver parenchyma — irinotecan can cause steatohepatitis and oxaliplatin can cause sinusoidal dilatation and obstruction. In the EORTC trial

1.1

Trial Evaluating the Benefit of Perioperative FOLFOX4 for Patients with Potentially Resectable Colorectal Cancer Hepatic Metastases

Protocol ID: EORTC-40983; Accrual: 364 (Closed)

	Perioperative FOLFOX4 + surgery	Surgery alone	HR (95.66% CI)	*p*-value
Three-year progression-free survival				
All patients randomly assigned (n = 182, 182)	35.4%	28.1%	0.79 (0.62-1.02)	0.058
All patients who underwent resection (n = 151, 152)	42.4%	33.2%	0.73 (0.55-0.97)	0.025
Reversible postoperative complications (n = 159, 170)	25%	16%	—	0.04
Postoperative death (n = 159, 170)	1%	1%	—	—

HR = hazard ratio; CI = confidence interval

SOURCE: Nordlinger B et al. *Lancet* 2008;371(9617):1007-16.

that Dr Nordlinger reported, more serious postoperative complications were observed on the perioperative chemotherapy with surgery arm than on the surgery alone arm (Nordlinger 2008; [1.1, page 4]).

DR LOVE: What about the other side of the debate? What I've heard from that camp is, "If you don't administer too much chemotherapy, it doesn't hurt the liver much and such an approach allows the disease to declare itself." What are your thoughts about those arguments?

DR PETRELLI: They're good arguments. First let me clarify that we are talking about patients with resectable disease, so we're not discussing conversion chemotherapy. If you administer preoperative chemotherapy prior to resection and you observe a response, that's even more encouragement to administer the same chemotherapy after hepatic resection.

On the other side of the coin, that chemotherapy is affecting the liver. We know that the more cycles of chemotherapy we administer, the higher the morbidity. Therefore, I prefer to stay within six cycles of chemotherapy. If you increase that number, you're affecting the liver even more, and that morbidity will increase postoperatively.

DR LOVE: One of the questions about using preoperative and/or postoperative therapies is whether to include a biologic agent. What is known about using these agents in these situations?

DR PETRELLI: The EORTC trial evaluated FOLFOX alone, and other trials have used chemotherapy alone after hepatic resection (Bathe 2009; Nordlinger 2008), and we know the effects of some of these targeted agents in the advanced disease setting. Data from the CAIRO2 study and the PACCE study have indicated that two targeted agents are not necessarily better than one targeted agent (Hecht 2009; Tol 2009).

The next EORTC trial will be evaluating targeted agents, and I am happy to report that an NSABP trial has been approved and is set to evaluate perioperative versus postoperative FOLFOX or FOLFIRI with bevacizumab for patients with resectable hepatic metastases. The NSABP trial details are being written and should be submitted to the NCI soon. We hope to begin accrual by the end of this year or by early next year.

This trial will accrue approximately 600 patients and will not limit the number of metastases. Patients must be candidates for surgery, and ablative procedures will not be allowed as part of the potentially curative resection, so it's surgical procedures only for the main lesions.

Tracks 10-11

DR LOVE: What is the status of the NSABP-C-10 study evaluating FOLFOX with bevacizumab for patients with synchronous, asymptomatic primary and unresectable metastatic colorectal cancer (1.2, 1.3)?

1.2 **Rationale and Purpose of NSABP-C-10**

"When the primary tumor is asymptomatic and resectable but the synchronous distant metastases are unresectable, surgical resection of the primary colon tumor has never been established to have a clinical benefit.

Surgical resection of the primary tumor in this clinical scenario is more often performed to prevent anticipated complications of obstruction and perforation related to the intact primary tumor rather than for symptoms directly arising from the primary tumor at that point in time.

Recent retrospective and small prospective studies have shown that the true incidence of these tumors becoming symptomatic and then requiring surgical intervention after initial systemic chemotherapy is much lower than previously believed.

This information is derived from stage IV patient populations treated with a two-drug chemotherapy regimen (fluorouracil and leucovorin), for which response rates are much lower than response rates for currently available chemotherapy.

The purpose of this Phase II study is to establish safety and efficacy data for patients presenting with stage IV colon cancer with an asymptomatic primary tumor and distant metastases not resectable for cure who are treated with mFOLFOX6 chemotherapy and bevacizumab."

SOURCE: NSABP-C-10 Protocol, Version: November 21, 2007.

1.3 **Phase II Trial of FOLFOX with Bevacizumab for Patients with Unresectable Stage IV Colon Cancer and a Synchronous Asymptomatic Primary Tumor**

Protocol ID: NSABP-C-10
Accrual: 90 (Closed)

Eligibility	Regimen
Asymptomatic primary colon cancer Unresectable metastases	[FOLFOX + bevacizumab] every 14 days

SOURCE: NCI Physician Data Query, September 2009.

DR PETRELLI: This Phase II study will affect how we approach this patient population. The trial included a Simon design and would have been stopped if within the first 20 patients problems with obstruction or perforation were observed, but no such problems occurred.

I'm happy to report that the last patient for our 90-patient target accrual was entered onto the trial in June. We should have definitive results by the end of the year, and we'll be able to either reinforce or refute the Philip Paty data presented recently at ASCO (Poultsides 2009; [1.4]).

DR LOVE: Would you comment on the data from Dr Paty at Memorial Sloan-Kettering that were presented at ASCO?

DR PETRELLI: This was a retrospective study of 233 patients presenting with asymptomatic, unresectable primary colon or rectal cancer. Patients received modern-era chemotherapy, and 93 percent never required surgery (Poultsides 2009; [1.4]). Only seven percent underwent emergency surgery. So the overwhelming majority of these patients were spared surgery because of the agents we have today. ■

1.4

Outcome of Primary Tumors in Patients with Synchronous Stage IV Colorectal Cancer (CRC) Receiving Combination Chemotherapy with or without Bevacizumab in the Absence of Primary Surgical Resection

	Time from initiation of chemotherapy to intervention*		Survival after intervention
	N (%)	Median	Median
Operative intervention	16 (7%)	7 mo	6 mo
Nonoperative intervention	10 (4%)	12 mo	8 mo
Curative resection†	47 (20%)	8 mo	44 mo
Preemptive resection	8 (3%)	9 mo	15 mo

Median survival from initiation of chemotherapy for the 152 patients who never required an intervention was 13 months.

* Time from initiation of chemotherapy to intervention and survival after intervention for patients who underwent interventions and resections

† Elective resection of primary tumor and metastases

- Of 233 patients with confirmed intact primary CRC who received modern triple-drug combination chemotherapy (± bevacizumab) for synchronous metastatic CRC at MSKCC, 93% never required surgery to palliate primary tumor-related complications.
- Perioperative mortality for the patients undergoing subsequent surgical intervention was 0.8%.
- These findings strongly support the appropriateness of nonoperative systemic management as an initial treatment approach for intact primary CRC and synchronous metastatic CRC in the absence of overt obstruction or severe acute bleeding.

SOURCE: Poultsides GA et al. *J Clin Oncol* 2009;27(20):3379-84.

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Hecht JR et al. **A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer.** *J Clin Oncol* 2009;27(5):672-80.

Nordlinger B et al. **Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomised controlled trial.** *Lancet* 2008;371(9617):1007-16.

Poultsides GA et al. **Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment.** *J Clin Oncol* 2009;27(20):3379-84.

Tol J et al. **Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer.** *N Engl J Med* 2009;360(6):563-72.

INTERVIEW

Axel Grothey, MD

Dr Grothey is Professor of Oncology in the Department of Medical Oncology at Mayo Clinic in Rochester, Minnesota.

Tracks 1-15

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What clinical factors do you currently consider in evaluating patients with Stage II colon cancer for adjuvant therapy?

DR GROTHEY: Stage II colon cancer has long been defined as a "gray zone" for whether or not to use adjuvant therapy. How we manage these patients is a critical issue for medical oncologists and surgeons.

We know that the overall risk of disease recurrence for these patients is in the range of 20 percent at three years, but some patients might have a risk that's similar to that of patients with Stage III disease. An analysis by Mike O'Connell about three years ago indicated that patients with T4N0 disease have poorer outcomes than patients with Stage IIIA disease.

Current clinical risk factors used to identify patients at high risk of recurrence include the number of lymph nodes identified — we need 12 lymph nodes identified in the tumor specimen with good surgery and good pathology review — obstruction, perforation, T4 disease, undifferentiated tumors and lymphovascular invasion. All of these factors identify a high risk of recurrence and could sway us to recommend chemotherapy.

In principle we know that patients with Stage II disease benefit from chemotherapy. The QUASAR study showed that five-year overall survival benefit is in the range of three percent for patients with Stage II disease when we use 5-FU-based chemotherapy compared to surgery alone (Gray 2007).

Some molecular markers exist that we can at least use as prognostic markers, but they have never made it into our clinical treatment algorithms. I believe that this is changing to some extent.

Track 4

DR LOVE: Would you discuss the presentation at ASCO 2009 of the QUASAR validation study of a quantitative RT-PCR assay for prediction of recurrence in Stage II colon cancer?

DR GROTHEY: This was an interesting and highly anticipated presentation because the development of this test was supposed to elucidate which patient population should receive adjuvant chemotherapy for Stage II disease. The idea was to develop a molecular test based on RT-PCR and to find out which patient population could benefit from adjuvant 5-FU/LV chemotherapy.

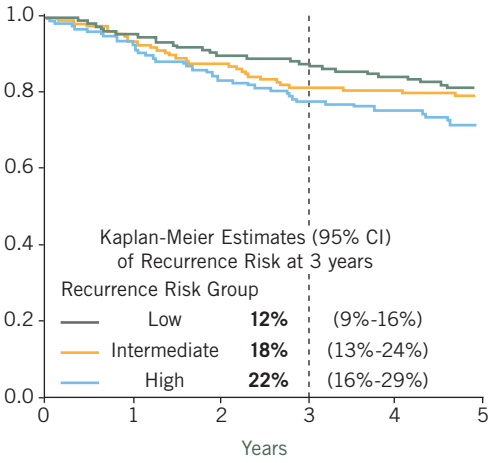
This assay underwent rigorous testing for patients with Stage II colon cancer, eventually being narrowed down to 18 genes — five reference genes, seven recurrence genes and six genes that were believed to predict benefit from chemotherapy. It was then tested on the large cohort of approximately 1,400 patients on the QUASAR study.

Unfortunately, the goal of the test was only half met because it was able to identify patients who had a better or worse prognosis, but it was not able to provide predictive value. We might identify patients who have a higher risk for recurrence but still don't know whether this group of patients would benefit from chemotherapy (Kerr 2009; [2.1]).

2.1

QUASAR Results: Recurrence Risk in Prespecified Recurrence Risk Groups (n = 711)

Recurrence Risk Group	Range of RS	Proportion of Patients
Low	<30	43.7%
Intermediate	30-40	30.7%
High	≥41	25.6%



SOURCE: With permission from Kerr D et al. *Proc ASCO* 2009;**Abstract 4000**.

Track 5

DR LOVE: What are your thoughts on the use of oxaliplatin in combination with 5-FU for patients with Stage II colon cancer?

DR GROTHEY: Thierry André recently published updated results from the MOSAIC trial and reported no difference in overall survival between the FOLFOX4 and LV5-FU2 arms for patients with low-risk Stage II disease (André 2009).

I believe that we have to be careful and rational with the use of FOLFOX. Chemotherapy for adjuvant colon cancer is more complicated than simply six months of FOLFOX. We have other tools, such as capecitabine and 5-FU/leucovorin. In this setting, my preference would probably be capecitabine because it's an oral agent and it has been shown to be at least equivalent in efficacy to intravenous 5-FU/leucovorin.

Track 6

DR LOVE: What is your clinical algorithm for adjuvant chemotherapy in patients with Stage II tumors?

DR GROTHEY: The current ASCO guidelines for treatment of Stage II disease indicate that doctors and patients should review the data and then come to a treatment decision. So I see a big question mark behind treatment for Stage II disease.

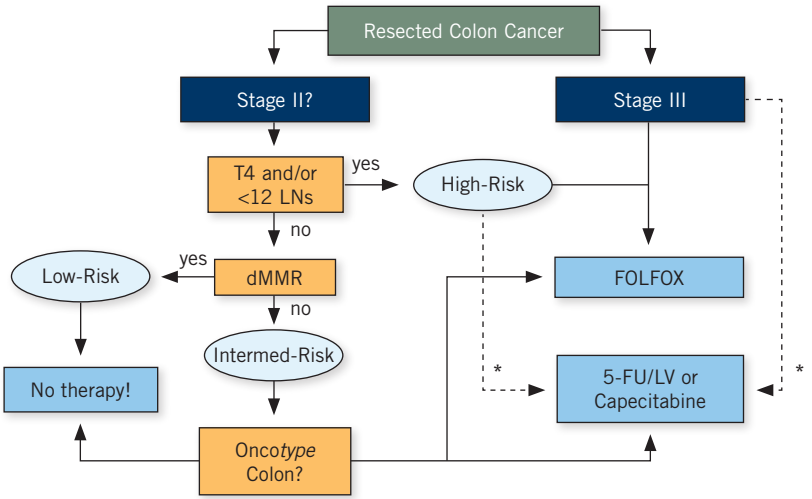
My proposed algorithm provides a little more guidance (2.2). For a number of these patients with high-risk factors, we already know the answer because we have consistent data, so let's focus on the group of patients for whom we don't have an answer.

Other factors, such as lymphovascular invasion, obstruction and perforation, are not as strong, so they're not in this algorithm. However, they are definitely relevant to the decision-making process when you discuss this question.

In the overall group of patients with Stage II disease, approximately 15 to 20 percent will have deficient mismatch repair phenotypes and should not require therapy. This leaves 60 to 70 percent of patients for whom the question still stands. For this group, I would love to have a genetic test, such as the Onco*type* DX colon cancer assay, to provide more information in guiding our approach to treatment. ■

2.2

Dr Grothey's Proposed Decision Algorithm for Adjuvant Colorectal Cancer Therapy



* Pts not considered candidates for oxaliplatin

SOURCE: Grothey A. Personal Communication. July 2009.

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André T et al. **Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial.** *J Clin Oncol* 2009;27(19):3109-16.

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INTERVIEW

Alan P Venook, MD

Dr Venook is Professor of Clinical Medicine at the University of California, San Francisco in San Francisco, California.

Tracks 1-9

Track 1 Onco*type* DX colon cancer test and assessment of risk of recurrence in Stage II colon cancer

Track 2 Informing patients with Stage II colon cancer about the risks and benefits of adjuvant chemotherapy

Track 3 Delayed cancer recurrence in patients receiving bevacizumab on NSABP-C-08

Track 4 Efficacy and tolerability of combining bevacizumab with chemotherapy for mCRC

Track 5 Time between bevacizumab and surgery: Implications for wound-healing complications

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Track 7 Chemotherapy-associated steatohepatitis

Track 8 Memorial Sloan-Kettering Cancer Center retrospective study evaluating outcomes of the primary tumor in patients with synchronous mCRC receiving chemotherapy without surgery

Track 9 K-ras testing and the use of EGFR monoclonal antibodies in mCRC

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What's your take on the Onco*type* DX colon cancer assay data that were presented at ASCO?

DR VENOOK: The data Kerr and colleagues presented were the fruits of a lot of labor in analysis of tumor specimens from patients with Stage II colon cancer (Kerr 2009). They demonstrated that a genetic risk profile can provide an estimate of recurrence risk on a continuum between about 10 and 20 percent. This information is probably important at the extreme lower and upper risks. If patients know that they have a 20 percent risk of recurrence, then that might motivate them to receive adjuvant chemotherapy. If it's 10 percent, it might not, but different patients will interpret that information differently.

What's missing from the Genomic Health Inc data set is a predictive value for the test. They can provide a prognosis of recurrence risk, but they failed to

see an ability to predict a benefit from 5-FU chemotherapy. It is true that they stated that the relative risk reduction was the same across the entire risk strata, so you can apply that information, but those data were not presented in detail.

DR LOVE: How do the discussions go with patients who have "normal-risk" Stage II colon cancer as you consider treatment?

DR VENOOK: In my experience, most patients will come to the visit with the physician already having made up their mind — they want adjuvant chemotherapy or they don't. I believe that's based on their own expectations and personal philosophy. As oncologists, we need to balance the risks associated with chemotherapy, which are small, against the potential benefits of chemotherapy in that population, which are also small but may be greater for an individual.

Track 3

DR LOVE: Would you discuss the NSABP-C-08 data presented at ASCO 2009 evaluating FOLFOX with or without bevacizumab in Stage II and Stage III colorectal cancer?

DR VENOOK: This study took the standard adjuvant therapy of FOLFOX with or without bevacizumab for six months and then continued the bevacizumab alone for an additional six months. The rationale behind using bevacizumab with chemotherapy in the metastatic setting is that it may augment the delivery of chemotherapy to tumors and also prevent tumor vascularization.

In the adjuvant setting, the belief is that if you can turn off the growth factors for an additional six months, you may allow the body's immune system to eradicate residual cancer cells.

This strategy did not change the overall outcome for patients in the adjuvant setting (Wolmark 2009). No significant difference was observed in disease-free survival at the three-year endpoint, and on the basis of other studies, we believe that this would predict that no overall survival difference would become evident.

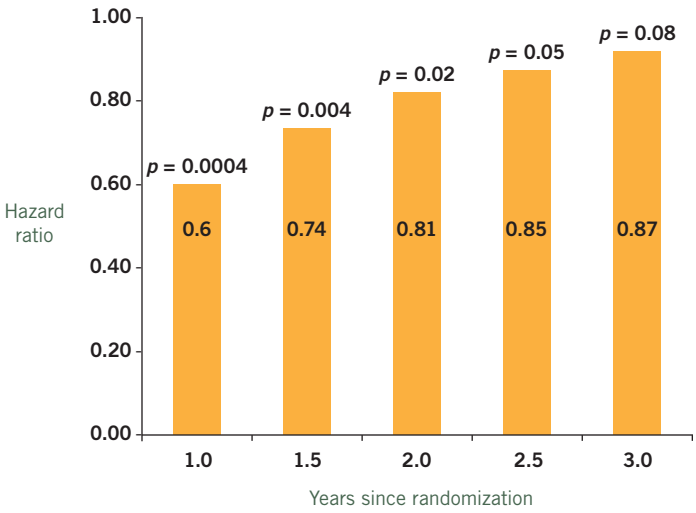
Interestingly, when they evaluated the disease-free survival intervals from six months to about a year and a half, a substantial difference appeared in disease-free survival between the two groups. The hazard ratio was 0.6 for the patients who experienced these intervals (Wolmark 2009; [3.1]). That's extremely interesting, and the fact that bevacizumab delays but doesn't prevent recurrence may speak to the mechanism of action.

Importantly, bevacizumab was well tolerated. No dramatic consequences occurred in terms of bowel perforation or major wound-healing issues (Allegra 2008). Pain and a few other global symptoms were observed.

Another study, called the AVANT trial, is also evaluating bevacizumab in the adjuvant setting. AVANT should have mature data by the end of the year, and they will be important to complement the data from NSABP-C-08. ■

3.1

NSABP-C-08: Hazard Ratio for Disease-Free Survival According to Time Since Randomization



SOURCE: Wolmark N et al. *Proc ASCO* 2009;**Abstract LBA4**.

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INTERVIEW

John N Primrose, MD

Prof Primrose is Professor of Surgery at the University of Southampton in Southampton, United Kingdom.

Tracks 1-7

Track 1 **Case discussion:** A young woman with asymptomatic type 1 diabetes who presents with synchronous symptomatic rectal cancer and bilateral hepatic metastases

Track 2 Counseling patients about the potential benefits of resection of hepatic metastases

Track 3 Use of preoperative cetuximab or bevacizumab in combination with chemotherapy for patients with resectable CRC hepatic metastases

Track 4 **Case discussion:** A 64-year-old man with obstructing rectosigmoid junction cancer and bilateral hepatic metastases

Track 5 Portal vein embolization to induce liver hypertrophy

Track 6 Oxaliplatin- and irinotecan-associated steatohepatitis

Track 7 Cytoreductive surgery for patients with hepatic CRC metastases

Select Excerpts from the Interview

Track 3

DR LOVE: Do you have any concerns about the use of preoperative cetuximab or bevacizumab in combination with chemotherapy for patients with resectable hepatic metastases from colorectal cancer?

PROF PRIMROSE: The only concern cetuximab brings is a skin rash. The toxicity in our trial thus far has been related only to the antibody, and it has not been significant.

The real issue is with bevacizumab. We don't have a trial with bevacizumab, so all I can provide to you is anecdotal and from other centers. I believe that the biggest experience probably comes from MD Anderson. They've reported that as long as you discontinue bevacizumab well in advance of surgery, problems are minimized (Kesmodel 2008).

Nick Vauthey has reported that bevacizumab might have a protective effect on the liver (Abdalla 2008; Ribero 2007; [4.1]), but these are preliminary data and we need more evidence.

DR LOVE: What is the usual interval to wait before surgery for patients receiving bevacizumab?

PROF PRIMROSE: We would not contemplate going to surgery after four weeks with a patient who's been receiving bevacizumab. I believe that even six weeks is probably too early, and I'd be more comfortable waiting eight weeks, whereas we don't have such an issue with cetuximab.

Track 7

DR LOVE: What are your thoughts on the role of cytoreductive surgery for patients with hepatic metastases of colorectal cancer?

PROF PRIMROSE: The mantra until now has been that if you offer patients resectional surgery for metastatic disease, you must be able to remove all of the disease. No residual disease should remain. I believe for a number of reasons that colorectal cancer is starting to resemble ovarian cancer, for which cytoreductive surgery is the norm. With the improved responses reported with the antibodies, perhaps we will convert colorectal cancer into more of a chronic disease.

We're currently contemplating a trial in the United Kingdom for patients with unresectable but debulkable colorectal cancer liver metastases, in which patients would be randomly assigned to appropriate chemotherapy with or without surgical debulking or ablation, even if the intention were not to cure.

4.1

Bevacizumab Improves Pathologic Response and Protects Against Hepatic Injury in Patients Receiving Oxaliplatin-Based Chemotherapy for Colorectal Cancer Liver Metastases

	5-FU/oxa	5-FU/oxa/bev	*p*-value
Pathologic response			
Complete pathologic response	11.6%	11.3%	0.59
Patients with <25% residual viable tumor cells	23.0%	45.0%	0.02
Sinusoidal dilation, n (%)			
Any grade (n = 43, 62)	53.5%	27.4%	0.006
Grade II or III (n = 43, 62)	27.9%	8.1%	0.006

Oxa = oxaliplatin; bev = bevacizumab; SOS = sinusoidal obstruction syndrome

"Although this study is limited by its retrospective nature, the increase in the magnitude of pathologic response after treatment with bevacizumab and the reduction in the incidence and severity of sinusoidal dilation strongly suggest a benefit for the use of bevacizumab-containing regimens over oxaliplatin alone.

Further studies are needed to expand on these initial findings and to provide further insight into the role of bevacizumab as a potentially protective agent against the broader spectrum of diseases associated with SOS."

SOURCE: Ribero D et al. *Cancer* 2007;110(12):2761-7.

This may be a difficult trial to recruit for, but I believe that the observations from the CLOCC trial suggest it is the direction in which we should be headed.

The CLOCC trial evaluated chemotherapy versus chemotherapy and radiofrequency ablation for patients with inoperable disease. It was closed early because of poor recruitment, but it has shown a survival benefit (Ruers 2008; [4.2]). So evidence exists that ablation in addition to chemotherapy confers a survival benefit.

Hence, why should debulking surgery not also provide a survival benefit? I believe that a paradigm shift will occur in terms of surgical therapy for metastatic colorectal cancer, and it's important that this be evaluated in a trial setting rather than simply embarked on ad hoc. ■

4.2

EORTC-40004 (CLOCC): A Phase II Study of Radiofrequency Ablation (RFA) Combined with Chemotherapy* for Unresectable Colorectal Liver Metastases (CLM)

	FOLFOX/bev*	FOLFOX/bev* + RFA	Hazard ratio
Median PFS	10.0 months	16.8 months	0.83

* FOLFOX (2002-2005) or FOLFOX/bevacizumab (2006-2007) with or without additional resection of resectable lesions

† Study was closed early at 119 patients (78.3%) due to poor accrual

"In patients with unresectable colorectal liver metastases from CRC, RFA ± resection plus chemotherapy with FOLFOX is safe and feasible and improves PFS when compared to FOLFOX alone."

SOURCE: Ruers T et al. *Proc ASCO* 2008;**Abstract 4012**.

SELECT PUBLICATIONS

Abdalla EK, Vauthey JN. **Chemotherapy prior to hepatic resection for colorectal liver metastases: Helpful until harmful?** *Dig Surg* 2008;25(6):421-9.

Kesmodel SB et al. **Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases.** *J Clin Oncol* 2008;26(32):5254-60.

Ribero D et al. **Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases.** *Cancer* 2007;110(12):2761-7.

Ruers T et al. **Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): Interim results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC).** *Proc ASCO* 2008;**Abstract 4012**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In EORTC-40983, perioperative chemotherapy was associated with _____ compared to surgical resection alone for patients with resectable liver metastases.**
   a. Improved progression-free survival
   b. More postoperative complications
   c. Higher postoperative mortality
   d. Both a and b

2. **The Phase II NSABP-C-10 trial is evaluating _____ with bevacizumab for patients with unresectable Stage IV colon cancer and a synchronous asymptomatic primary tumor.**
   a. FOLFOX
   b. FOLFIRI
   c. Both a and b

3. **A retrospective analysis of patients with synchronous Stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment reported that more than 90 percent of patients never required any surgical treatment or intervention for their primary colorectal cancer.**
   a. True
   b. False

4. **The QUASAR validation study of the quantitative RT-PCR colon cancer assay provided an estimate of _____.**
   a. Recurrence risk
   b. Benefit from adjuvant 5-FU therapy
   c. Both a and b
   d. None of the above

5. **Long-term follow-up of the MOSAIC trial reported equivalent disease-free survival and overall survival benefits for both Stage II and Stage III colorectal cancer treated with the FOLFOX regimen.**
   a. True
   b. False

6. **In a trial comparing calcium and magnesium (CaMg) to placebo for patients receiving adjuvant FOLFOX, the incidence of Grade II or higher oxaliplatin-induced sensory neurotoxicity was reduced among patients who received CaMg.**
   a. True
   b. False

7. **The NSABP-C-08 trial, comparing FOLFOX to FOLFOX with bevacizumab for patients with Stage II or Stage III colorectal cancer, reported a statistically significant advantage with the combination with regard to the trial's primary endpoint of three-year disease-free survival.**
   a. True
   b. False

8. **Data from Kesmodel and colleagues and from the BEAT registry suggest that few wound-healing complications are observed when the last dose of bevacizumab is administered _____ weeks before surgery.**
   a. Two to four weeks
   b. Six to eight weeks

9. **The addition of bevacizumab to 5-FU/oxaliplatin resulted in a significant reduction in the incidence of Grade II or III sinusoidal dilation in comparison to 5-FU/oxaliplatin alone as treatment for patients with colorectal cancer liver metastases.**
   a. True
   b. False

10. **The Phase II EORTC-40004 (CLOCC) trial reported an approximate _____ improvement in median progression-free survival with chemotherapy/bevacizumab in combination with radiofrequency ablation compared to chemotherapy alone as treatment for unresectable colorectal cancer liver metastases.**
    a. Three-month
    b. Seven-month
    c. 12-month

Post-test answer key: 1d, 2a, 3a, 4a, 5b, 6a, 7b, 8b, 9a, 10b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Colorectal Cancer Update for Surgeons — Issue 1, 2009

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Results of the QUASAR validation study of the quantitative multigene RT-PCR Onco*type* DX colon cancer assay for prediction of recurrence in Stage II colon cancer	4 3 2 1	4 3 2 1
NSABP-C-08 study results: Adjuvant FOLFOX with or without bevacizumab for patients with Stage II or III colon cancer	4 3 2 1	4 3 2 1
Findings from the Memorial Sloan-Kettering Cancer Center retrospective study evaluating outcomes of the primary tumor in patients with synchronous metastatic colorectal cancer receiving chemotherapy without surgery	4 3 2 1	4 3 2 1
Time between bevacizumab and surgery: Implications for wound-healing complications	4 3 2 1	4 3 2 1
Risk of chemotherapy-associated steatohepatitis	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Identify the strengths and weaknesses of genomic assays and clinicopathologic variables as tools for communicating risk of recurrence to patients with early colon cancer..... 4 3 2 1 N/M N/A
- Formulate a treatment plan for patients with synchronous or metachronous, asymptomatic or symptomatic primary CRC and liver-only metastases..... 4 3 2 1 N/M N/A
- Evaluate the pros and cons of perioperative versus postoperative systemic therapy for patients with resectable hepatic metastases..... 4 3 2 1 N/M N/A
- Counsel patients receiving bevacizumab as part of perioperative or postoperative systemic therapy about potential treatment side effects, including surgical and wound-healing complications..... 4 3 2 1 N/M N/A
- Recognize the significance of preexisting liver disease and comorbidities in the cumulative risk of steatohepatitis for patients receiving oxaliplatin or irinotecan..... 4 3 2 1 N/M N/A
- Educate patients presenting with an asymptomatic primary tumor and synchronous metastatic CRC about their risk of requiring subsequent emergent surgery if they are treated with systemic therapy alone..... 4 3 2 1 N/M N/A
- Summarize the effect of calcium and magnesium on the prevention or amelioration of oxaliplatin-associated sensory neurotoxicity or myalgias..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about participation in ongoing clinical trials..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ⬭ Yes, I am willing to participate in a follow-up survey.
- ⬭ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Nicholas J Petrelli, MD	4 3 2 1	4 3 2 1
Axel Grothey, MD	4 3 2 1	4 3 2 1
Alan P Venook, MD	4 3 2 1	4 3 2 1
John N Primrose, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

Name: ..... Specialty: .....

Professional Designation:

⬭ MD ⬭ DO ⬭ PharmD ⬭ NP ⬭ RN ⬭ PA ⬭ Other .....

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City, State, Zip: .....

Telephone: ..... Fax: .....

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Research To Practice designates this educational activity for a maximum of 2.75 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at CME.ResearchToPractice.com.

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Colorectal Cancer™

U P D A T E

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