

# Colorectal Cancer™

U P D A T E

Conversations with Oncology Investigators  
Bridging the Gap between Research and Patient Care

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***SPECIAL ISSUE***

**Proceedings from a  
Clinical Investigator  
Think Tank**



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## *Colorectal Cancer Update*

### A Continuing Medical Education Audio Series

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#### OVERVIEW OF ACTIVITY

Colorectal cancer (CRC) is among the most common types of cancer in the United States, and the treatment of this disease continues to evolve. Published results from ongoing clinical trials lead to the emergence of new therapeutic agents and regimens, changes in the indications, doses and schedules for existing treatments and the development of new genomic assays and biomarkers with prognostic and/or predictive potential. 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. 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.

#### LEARNING OBJECTIVES

- Identify the strengths and weaknesses of genomic assays, web-based models and clinicopathologic variables as tools for communicating risk of recurrence to patients with early colon cancer.
- Summarize the effect of calcium and magnesium on the prevention or amelioration of oxalipatin-associated sensory neurotoxicity or myalgias.
- Recall the results of clinical trials evaluating the addition of biologic agents to conventional adjuvant chemotherapy as treatment for Stage II and Stage III colon cancer.
- Develop up-to-date clinical management strategies for metastatic CRC, incorporating chemotherapy, anti-VEGF and anti-EGFR antibodies.
- Appraise the risk-benefit profile of continuing therapy with biologic agents beyond initial disease progression.
- Formulate a treatment plan for patients with synchronous or metachronous primary CRC and liver-only metastases.
- Evaluate the evidence supporting oxalipatin-containing chemoradiation therapy in the management of locally advanced rectal cancer.
- Counsel appropriately selected patients about participation in ongoing clinical trials.

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## ADJUVANT THERAPY OF STAGE II COLON CANCER

### RISK OF RELAPSE AND CLINICAL BENEFIT OF ADJUVANT THERAPY

#### Case description

A 44-year-old woman with a strong family history of colon cancer undergoes a right hemicolectomy for a 9- x 3.5- x 7-cm, moderately differentiated Stage IIA adenocarcinoma of the midtransverse colon with 37 nodes examined

► **DR LOVE:** Lee, what numbers can we provide this patient with in regard to her risk of recurrence and potential benefits of adjuvant chemotherapy?

► **DR ELLIS:** To be honest, it's difficult for us to keep in mind exactly what the risk is for a specific patient with a tumor of a particular molecular phenotype and a certain stage or substage of disease. With Adjuvant! Online, you can enter the patient's age, stage and other factors and determine the risk based on large databases.

► **DR LOVE:** Charlie, let me give you the Adjuvant! numbers on this patient, and tell me what you think about them. For a patient with T3N0M0 moderately differentiated colon cancer with more than 10 nodes examined, the baseline risk of recurrence at five years is stated to be 13 percent, which is reduced to 10.5 percent if the patient receives

an adjuvant fluoropyrimidine and to eight percent if the patient receives a fluoropyrimidine and oxaliplatin.

Do you agree with those numbers?

► **DR FUCHS:** I don't, for a number of reasons. First, in the subset data from the MOSAIC trial, no clear benefit is indicated with FOLFOX compared to 5-FU/leucovorin in the "low-risk" Stage II group who lacked high-risk features (Andre 2009).

► **DR LOVE:** Do you agree with the 13 percent baseline risk of recurrence?

► **DR FUCHS:** I don't have an objection to the 13 percent estimate. I'd say that the recurrence risk is probably 15 percent, but it could be 20 percent with this degree of uncertainty. These numbers are extrapolations from a selected, large database and are the best we have, but I don't know that the estimates are that precise.

### QUANTITATIVE MULTIGENE ASSAY FOR PREDICTION OF RECURRENCE IN EARLY COLON CANCER

► **DR LOVE:** Rich, can you discuss David Kerr's presentation at ASCO on the RT-PCR assay for prediction of recurrence risk for patients with Stage II colon cancer (Kerr 2009)?

► **DR GOLDBERG:** We are all anxious to have a better way of stratifying patients with Stage II colon cancer, and our current anatomic stratification is limited: Patients have either T2 or T3 disease and they either

have an adequate number of nodes examined or they don't. I believe it's noteworthy that the American Joint Committee on Cancer — a relatively conservative group — is holding its 50<sup>th</sup> anniversary meeting and the topic being addressed is “Molecular markers meet anatomic staging.”

The presentation by Dr Kerr is important because it helps us reach that milestone. Others will interpret whether we arrive at that milestone or not, but I'll frame the study for you.

This was a collaboration among QUASAR, the NSABP, the Cleveland Clinic and Genomic Health Inc. Two data sets from the NSABP and the Cleveland Clinic Foundation were used to study more than 700 genes, and researchers selected those that seemed to be predictive or prognostic in Stage II colon cancer. When they attempted to separate the wheat from the chaff, they identified 13 genes that were apparently

important in the initial set, and then they performed a validation study on patients with available tissue blocks in the QUASAR study.

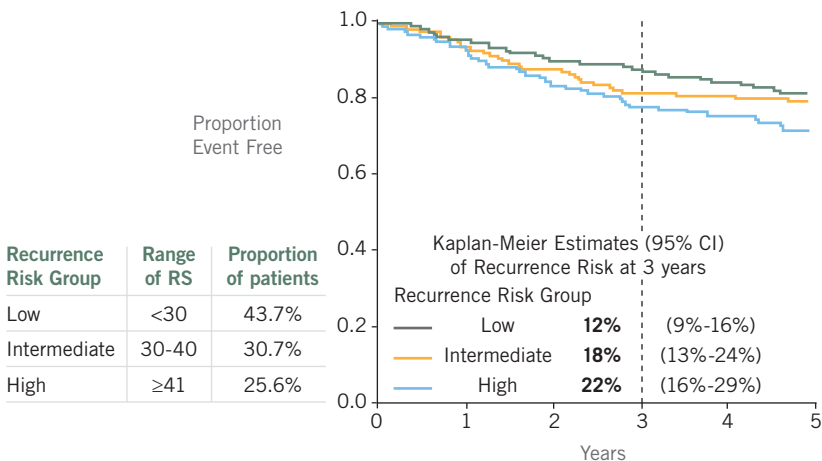
The QUASAR study enrolled more than 3,000 patients — mostly with Stage II disease — who were randomly assigned to no treatment or to 5-FU-based treatment. They were able to obtain tissue from approximately one half of the patients, and they tested this gene panel against their clinical trial outcomes.

The good news is that they were able to segregate patients, but the *delta* wasn't significant. A patient at low risk had a 12 percent likelihood of recurrence, and a patient at high risk had a 22 percent likelihood of recurrence (Kerr 2009; [1.1]).

So the magnitude of difference was not the same as that observed for the breast cancer *Oncotype DX*<sup>®</sup> assay (Paik 2004).

1.1

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



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

The investigators were shrewd in their recommendation that the colon cancer assay should not be used in isolation. It should be used with microsatellite instability, anatomic T-stage and other variables that we believe are relevant to segregating patients into high-risk and low-risk Stage II colon cancer (Kerr 2009; [1.2]).

This is a great approach, but I'd like to see the genes reexamined so that perhaps we could see a set of genes with a larger *delta*.

► **DR LOVE:** What about the issue of whether the test was predictive of benefit from chemotherapy?

► **DR GOLDBERG:** In the *Oncotype DX* assay for breast cancer, not only is the Recurrence Score<sup>®</sup> prognostic, but it's also predictive of benefit from treatment (Paik 2004). In this data set, the colon cancer Recurrence Score was prognostic but could not predict benefit from 5-FU (Kerr 2009).

► **DR HALLER:** I felt as though a slide was left out of the presentation because they stated that the same proportional benefit was observed for adjuvant chemotherapy across the risk groups. So if it's an 18 percent risk reduction, then the absolute benefit is 18 times 22 percent or 18 times 11 percent — but I want to see the published paper.

► **DR FUCHS:** The problem is that they didn't show us those data. It would have been easy for them to show us within each strata — low, intermediate and high risk — how 5-FU/leucovorin compared to surgery alone. I'm not trying to be cynical, but we've seen similar data with breast cancer, and we draw our conclusions from those data.

► **DR LOVE:** If it turns out that the proportional recurrence risk is documented, does that provide additional information that could be presented to a patient?

► **DR HALLER:** In the multivariate analysis the most significant predictors of recurrence were T-stage, MMR and Recurrence Score (Kerr 2009; [1.2]). So if a patient had a low T-stage, deficient MMR and a low Recurrence Score reflecting a five percent likelihood of recurrence, most of us would probably not administer adjuvant chemotherapy.

► **DR LOVE:** Would you offer chemotherapy to a patient with a high Recurrence Score?

► **DR HALLER:** I believe I would rely on the combination of factors. The Recurrence Score will probably not stand by itself, and we will still fall back on pathologic staging and other features, such as age and comorbidities.

► **DR HOCHSTER:** The small *delta* already reflects a selected subset of patients who do not have T4 disease, microsatellite instability or MMR deficiency. So 75 percent of all patients with Stage II colon cancer may be candidates for this gene profile test that can tell them if their risk is between 10 to 22 percent.

If you said to a patient, "You are similar to 75 percent of patients with Stage II disease for whom this test may be helpful. If you had a 10 percent risk of recurrence, would you undergo treatment? If you had a 22 percent risk, would you take adjuvant chemotherapy?"

If the answers differ, then it's probably worthwhile to request the assay.

► **DR LOVE:** In terms of practical clinical applications, do you believe it would be of use clinically?

► **DR HOCHSTER:** It would be useful to a limited extent. Again, I will assume that the proportional benefit from chemotherapy applies across the range of Recurrence Scores.

If patients have T3 colon cancer that is not MMR deficient, this test can tell them that their risk of recurrence is between 10 and 20 percent — if that’s a difference that would influence my decision as a physician, and more importantly, the patient’s decision to accept adjuvant therapy or not, I’d definitely order it.

► **DR LOVE:** You sound as if you believe that enough data have been generated to be useful in practice.

► **DR HOCHSTER:** It will be difficult to obtain anything better than this. They’ve accomplished a huge amount of work to find the genes.

I agree with Rich that it would be more useful if a greater difference was present between the high- and low-

risk profiles. However, if the test will make a difference in the patient’s clinical decision-making, I would use it.

► **DR GOLDBERG:** I would be cautious about using it yet, and I would like to see a larger difference validated.

► **DR LOVE:** Dan?

► **DR HALLER:** Based on the 10-minute presentation with missing data that we all believe to be crucial, I would not want to raise more uncertainty in a patient’s mind. I will continue to use the clinical pathologic data I have now and see how these data evolve.

► **DR LOVE:** Herb?

► **DR HURWITZ:** I believe this test will probably be useful, but not quite yet. We need to see all the data. Particularly for the bulk of patients who have T3 disease with no MMR deficiency, this test may add value. It may be the most helpful for the patients who have a recurrence risk of less than five percent. Similarly, it may be helpful in identifying patients who have a risk of recurrence that is 20 percent or greater. ■

1.2

**QUASAR Results: Clinical/Pathologic Covariates and Recurrence**

**Prespecified multivariate analysis: Patients who underwent surgery alone (n = 605)**

Variable	Categories	HR	p-value
MMR	13% deficient vs 87% proficient	0.32	<0.001
T-stage	15% T4 vs 85% T3	1.83	0.005
Tumor grade	29% high vs 71% low	0.62	0.026
No. nodes examined	62% <12 vs 38% ≥12	1.47	0.040
LVI	13% present vs 87% absent	1.40	0.175
RS per 25 units	Continuous	1.61	0.008

HR = hazard ratio; RS = Recurrence Score

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



## SELECT PUBLICATIONS

Andre 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.

Kerr D et al. **A quantitative multigene RT-PCR assay for prediction of recurrence in stage II colon cancer: Selection of the genes in four large studies and results of the independent, prospectively designed QUASAR validation study.** *Proc ASCO* 2009; **Abstract 4000.**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26.

## RECENT DEVELOPMENTS AND FUTURE DIRECTIONS IN ADJUVANT THERAPY OF COLON CANCER

### NSABP-C-08: ADJUVANT FOLFOX WITH OR WITHOUT BEVACIZUMAB

► **DR LOVE:** Lee, would you review the NSABP-C-08 data that Norm Wolmark presented at ASCO?

► **DR ELLIS:** This was a Phase III trial evaluating FOLFOX with or without 12 months of bevacizumab. The primary endpoint was a decrease in disease-free survival by approximately 25 percent at three years, and 2,700 patients were accrued.

Interestingly, while receiving bevacizumab, the patients seemed to experience a benefit. A decrease in the hazard ratio, which peaked at 0.6 at one year, coincided with the end of bevacizumab therapy (Wolmark 2009; [2.1]).

However, the primary endpoint was not met. At three years, the disease-free survival curves seemed to come together, and the hazard ratio was 0.89.

► **DR LOVE:** The AVANT trial, evaluating adjuvant FOLFOX versus FOLFOX with bevacizumab versus XELOX with bevacizumab, should be reporting soon. Do you expect the AVANT results to be essentially the same as C-08?

► **DR FUCHS:** I do. We need to be careful about how we interpret the benefits in C-08, which appear to be greater early on as opposed to later follow-up.

If you examine the Kaplan-Meier curves for all of our adjuvant trials, intervention versus control separates most in the first 18 months, and then they slowly become parallel.

► **DR ELLIS:** I expect the AVANT results will validate these data. The fact is that adding bevacizumab to FOLFOX did not increase the cure rate.

Once the bevacizumab was stopped, all the patients who had micrometastatic disease — whose disease was going to recur — experienced recurrence.

► **DR LOVE:** Is this similar to what we saw with endocrine therapy in breast cancer, in which two years of therapy is better than one year and five are better than two?

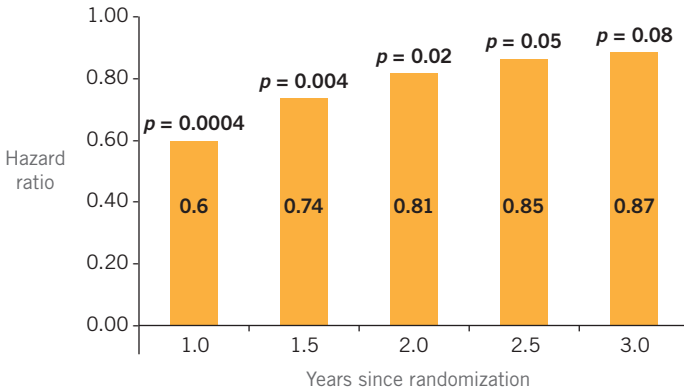
► **DR HOCHSTER:** It may not be much different biologically, but the fact is that hormones are relatively inexpensive.

sive oral drugs. I suspect the reaction to the idea of a study evaluating a longer duration of anti-angiogenic

therapy would be more positive if it involved an inexpensive pill.

2.1

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



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

PROPOSED TRIAL: CALGB-80702 — THREE VERSUS SIX MONTHS OF ADJUVANT FOLFOX WITH OR WITHOUT CELECOXIB

► **DR LOVE:** What is the next direction for adjuvant trials in colon cancer?

► **DR GOLDBERG:** The CALGB is developing a two-by-two randomization trial evaluating three versus six months of FOLFOX with or without celecoxib.

We've learned that celecoxib can be administered safely at a lower dose, which is used in this study, and the potential for celecoxib to have a strong effect in adjuvant therapy has become more compelling.

We will also collect germline, plasma and tumor DNA, and we plan to include a gene expression analysis in this trial. Gene expression studies will be conducted across the entire genome to provide an unbiased view of what panel of genes is at least prognostic.

The trial is designed to accrue 2,600 patients, so it will have statistical power, and established models exist to accomplish this. ■

SELECT PUBLICATIONS

Allegra CJ et al. **Initial safety report of NSABP C-08: A randomized phase III study of modified FOLFOX6 with or without bevacizumab for the adjuvant treatment of patients with stage II or III colon cancer.** *J Clin Oncol* 2009;27(20):3385-90.

Wolmark N et al. **A phase III trial comparing mFOLFOX6 to mFOLFOX6 plus bevacizumab in stage II or III carcinoma of the colon: Results of NSABP Protocol C-08.** *Proc ASCO 2009*;Abstract LBA4.

## SYSTEMIC THERAPY OF METASTATIC DISEASE

### TREATMENT HOLIDAYS IN THE MANAGEMENT OF METASTATIC DISEASE

► **DR LOVE:** Dan, how do you see this issue?

► **DR HALLER:** We will soon be publishing, in the *Journal of Clinical Oncology*, the updated OPTIMOX2 data, which was conducted prebiologics. The data suggest that a complete holiday from treatment may not be a good idea (3.1).

► **DR FUCHS:** Beyond the murky scientific question is the emotional component that patients struggle with. Some

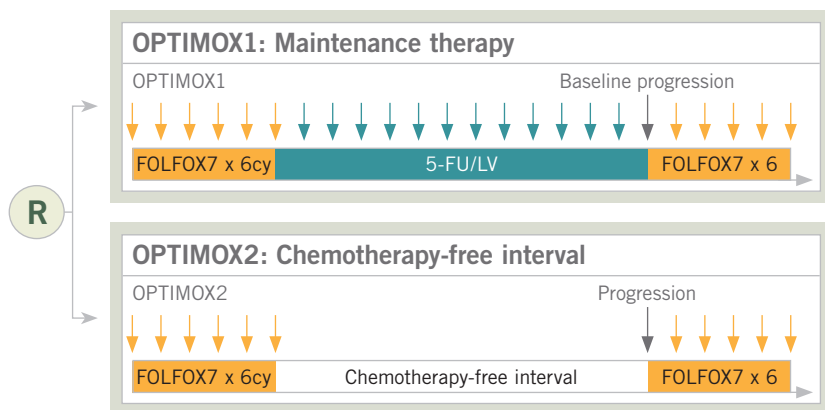
patients jump at the opportunity to discontinue treatment, and others are emotionally crippled by the idea of stopping all therapy. That's a challenge we all face in the clinic.

► **DR GOLDBERG:** For a number of patients with metastatic disease, you can start and stop chemotherapy over a period of years.

I have a notable patient who has had metastatic colon cancer for five years, and he receives treatment for about

3.1

#### OPTIMOX2: A Randomized Phase II Study of Maintenance Therapy or Chemotherapy-Free Intervals After FOLFOX for Patients with Metastatic Colorectal Cancer — A GERCOR Study



	OPTIMOX1 (n = 99)	OPTIMOX2 (n = 103)	p-value
OS	26 months	19 months	0.0549
RR	60%	59%	NR
Progression-free survival	36 weeks	29 weeks	0.08

SOURCE: Maindrault-Goebel F et al. *Proc ASCO* 2007; **Abstract 4013**.

four months a year. He has unresectable disease in the liver and lung that has responded to everything I've thrown at it. Currently he's experiencing a great response to irinotecan and panitumumab. He thrives when he's off the treatment.

On the other hand, the OPTIMOX2 data suggest that patients should not take drug holidays if time to disease progression is your endpoint.

I believe that we need to be careful about who is allowed complete treatment holidays, but in my experience responsive disease is often responsive to later lines of therapy, not only the first line.

In addition, the five-year overall survival for the patients who received FOLFOX in the NCCTG-N9741

trial was approximately 10 percent, and about half of those patients had not undergone surgery (Sanoff 2008). It raises the possibility that some patients are cured of metastatic disease with combination chemotherapy, even without biologic therapy.

Then you have the question of biologic agents and whether we should offer bevacizumab for the entire life span of these patients who are clinically free of disease.

We don't have data to suggest this is the best approach. I honestly believe that if we follow these patients carefully, we can often reel them back in when their disease starts to progress and "turn that crank" over and over again.

## VEGF TYROSINE KINASE INHIBITOR CEDIRANIB

► **DR LOVE:** Lee, looking forward, what do we know about novel agents being investigated, such as the oral tyrosine kinase inhibitor (TKI) cediranib?

► **DR ELLIS:** Cediranib targets the VEGF tyrosine kinase receptors 1, 2 and 3, and it also inhibits c-Kit and the PDGF receptor. It is potent and much more selective than the other tyrosine kinase receptor inhibitors already approved by the FDA.

The drug has been in development for some time, and a number of trials evaluating it in colon cancer are under way — such as the HORIZON III trial in the United States, evaluating FOLFOX and cediranib versus FOLFOX and bevacizumab as first-line therapy for metastatic colorectal cancer (CRC) (Robertson 2009).

The HORIZON II trial — which is not being conducted in the United States because not all of the patients receive a biologic agent — evaluates FOLFOX with or without cediranib. Both of the HORIZON trials have fully accrued, and we expect to see some results within the next 12 to 18 months.

► **DR LOVE:** What about toxicity with this agent?

► **DR HURWITZ:** I believe the most useful data on cediranib come from HORIZON I, a randomized Phase II trial evaluating low- versus high-dose cediranib in colon cancer (3.2).

The higher dose was not as well tolerated, so the lower dose was selected for the subsequent HORIZON III trial. ■

### HORIZON I: Grade III/IV Adverse Events Occurring in at Least 10 Percent of Patients

	FOLFOX + cediranib 20 mg (n = 70)	FOLFOX + cediranib 30 mg (n = 73)	FOLFOX + bevacizumab 10 mg/kg (n = 66)
Diarrhea	14%	19%	17%
Fatigue	13%	10%	14%
Hypertension	10%	22%	12%
Neutropenia	31%	34%	27%

SOURCE: Cunningham D et al. *Proc ASCO* 2008;Abstract 4028.

### SELECT PUBLICATIONS

Cunningham D et al. **A phase II, double-blind, randomized multicenter study of cediranib with FOLFOX versus bevacizumab with FOLFOX in patients with previously treated metastatic colorectal cancer (mCRC): Final PFS results.** *Proc ASCO* 2008;Abstract 4028.

Maindault-Goebel F et al. **Final results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): A GERCOR study.** *Proc ASCO* 2007;Abstract 4013.

Robertson JD et al. **Phase III trial of FOLFOX plus bevacizumab or cediranib (AZD2171) as first-line treatment of patients with metastatic colorectal cancer: HORIZON III.** *Clin Colorectal Cancer* 2009;8(1):59-60.

Sanoff HK et al. **Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741.** *J Clin Oncol* 2008;26(35):5721-7.

## TREATMENT FOR PATIENTS WITH SURGICALLY RESECTABLE LIVER AND/OR LUNG METASTASES

► **DR LOVE:** Rich, what is your approach for these patients?

► **DR GOLDBERG:** I'm an advocate for attempting to treat minimal residual disease in the potentially curative setting. If a patient presents with a primary colon tumor and synchronous liver metastases, I will resect the colon and the liver at the same time if the surgeon deems it reasonable because we're trying to eliminate disease entirely in this circumstance.

► **DR FUCHS:** We evaluate this question on an individual basis, and

for a patient with an isolated liver lesion, if the surgeon is comfortable and prefers to resect before proceeding with systemic therapy, I'm comfortable doing so. Considering the alternative scenario of a patient with a greater disease burden, we typically administer preoperative systemic therapy.

► **DR HOCHSTER:** My conceptual use of surgery is the opposite of Rich's. I prefer to administer chemotherapy first to reduce the tumor down to resistant clones alone and then have

the surgeon consolidate by taking out those resistant clones.

► **DR ELLIS:** I like to see the natural history of the disease. I treat up front with chemotherapy and restage to make sure nothing has emerged in the retroperitoneum or the lung, for example.

I'm conservative in the operating room — I wouldn't be bold enough to resect both tumors at the same time.

► **DR LOVE:** What is the status of the joint ACOSOG-NSABP trial set to evaluate preoperative versus postoperative chemotherapy for patients with resectable liver metastases?

► **DR CURLEY:** Essentially the design for both arms is a total of six months of chemotherapy and bevacizumab. The difference is that one group of patients begins with resection and then after recovery receives six

months of adjuvant therapy, as you would after resection of Stage III primary colon cancer.

The other arm of this study will evaluate three months of treatment up front, followed by surgery, followed by three months of postoperative chemotherapy, which is similar to the EORTC-40983 approach (Nordlinger 2008; [4.1]).

► **DR LOVE:** Steve, what about the issue of resection of hepatic metastases for patients with radiographic complete responses to systemic therapy?

► **DR CURLEY:** I probably receive two or three calls a month from practicing medical oncologists who've had this exact scenario develop.

The patient is faring well, and the question always is, do you still perform a resection? I tell oncologists that although some disease may

4.1

**Trial Evaluating the Benefit of Perioperative FOLFOX4 for Patients with Potentially Resectable CRC Hepatic Metastases**

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



	Perioperative FOLFOX4 + surgery	Surgery alone	HR (95.66% CI)	p-value
<b>Three-year progression-free survival</b>				
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.

be cured with chemotherapy, if the patient had resectable disease to begin with, I would still perform a resection of the area where the tumor was located. The alternative is to follow the patient until disease recurrence and then consider surgical treatment.

► **DR ELLIS:** I've seen one patient who had a complete response, and interestingly his recurrent disease turned out to be in sites other than that of his initial disease.

This goes back to the premise that these patients have micrometastatic disease at multiple sites. I was glad I didn't operate on that patient, although he had diffuse disease, because if I had operated on him blindly, I would have left disease behind.

► **DR HALLER:** Potentially heterogeneous populations of tumors are also possible in that each metastasis may be biologically distinct. So you can eliminate the ones that are exquisitely sensitive, but others either are natively resistant or become resistant.

The only case in which I've had to wait for disease to reappear was in a patient with two pulmonary nodules. I was excited because the patient had a total and complete response to chemotherapy, and when I sent him back to the surgeon, he said, "What precisely do you want me to take out?"

► **DR LOVE:** Have you seen that happen with primary tumors? You don't know where to resect?

► **DR HALLER:** Absolutely yes.

► **DR HOCHSTER:** I've had patients for whom we went back and performed colonoscopies and biopsies, and the tumors were gone.

My belief is that the primary tumor is at least as responsive as what's growing in the liver.

► **DR GOLDBERG:** Steve, do you make a distinction between miliary disease and multiple metastases? The reason I ask is that, as you know, Mike Choti is bringing forward the clinical trial evaluating chemotherapy initially or resection initially for patients with resectable disease.

The initial eligibility criteria did not include any limit to the number of liver metastases. My bias is that some upper limit probably exists above which liver surgery doesn't make sense.

► **DR CURLEY:** I agree. I believe that for a patient with miliary disease, if dozens of nodules are peppered throughout the liver, even if those vanish, you can't go back and resect them.

In such a case, you have the choice of continuing to administer bevacizumab or a fluoropyrimidine and bevacizumab or taking the patient off chemotherapy, and then if he or she experiences disease recurrence, you chart that pattern of recurrence.

I've yet to have a patient in that scenario whose disease did not recur in a miliary pattern, meaning that if the disease started out unresectable with dozens of lesions, upon disease recurrence they have dozens of lesions also.

I believe the role of surgery in that setting is minimal. It may be a consideration to administer bevacizumab alone or 5-FU and bevacizumab for a longer period as long as the patient is tolerating the therapy.

I can tell you about our own database and our experience, which we published, with resection of more than four colorectal liver metastases.

For 159 patients, the median number of metastases was eight, with a five-year disease-free survival of 22 percent and an overall survival of 51 percent (Pawlik 2006; [4.2]). So you can resect more than four hepatic metastases in a select subset of patients.

However, on further analysis by number, nobody who originally had more than 10 hepatic metastases was alive and disease free at five years.

That's a fairly arbitrary cutoff, but I believe that if a patient has more than 10 hepatic metastases, the probability of a surgical cure is extremely small.

► **DR HOCHSTER:** Do you go mainly by how much liver will be left after surgery, not the number of metastases, when deciding on the resectability?

► **DR CURLEY:** Correct. The key is to leave patients with enough volume of liver to function and regenerate so that they can lead a normal life. If I can do that, will I then go after seven or eight metastases? Certainly. ■

## 4.2

### MD Anderson Experience: Surgical Treatment of Multiple Colorectal Liver Metastases (CRLMs)

"Similar to other contemporary reports, in the current study, the overall actuarial 5-year survival rate for patients undergoing surgery for four or more CRLMs was 50.9%.

This favorable overall survival rate most likely relates to the fact that patients included in the current analysis were highly selected.

Every patient had no extrahepatic disease at the time of initial surgical treatment, most received neoadjuvant chemotherapy (89.9%), almost two thirds (72.7%) had a reduction in tumor size following preoperative chemotherapy, all patients underwent thorough intraoperative ultrasonography to avoid missing small hepatic lesions, and only 19 patients had a positive surgical resection margin."

**SOURCE:** Pawlik TM et al. *J Gastrointest Surg* 2006;10(2):240-8.

## 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.

Benoist S, Nordlinger B. **The role of preoperative chemotherapy in patients with resectable colorectal liver metastases.** *Ann Surg Oncol* 2009;16(9):2385-90.

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.

Okines A, Cunningham D. **Current perspective: Bevacizumab in colorectal cancer — A time for reappraisal?** *Eur J Cancer* 2009;45(14):2452-61.

Pawlik TM et al. **Debunking dogma: Surgery for four or more colorectal liver metastases is justified.** *J Gastrointest Surg* 2006;10(2):240-8.

Petrelli N. **Update on surgical resection of liver metastases from colorectal cancer.** *Clin Adv Hematol Oncol* 2008;6(7):514-6.



## TREATMENT OF PATIENTS PRESENTING WITH A SYNCHRONOUS PRIMARY CANCER AND UNRESECTABLE METASTASES

► **DR LOVE:** Steve, would you discuss the study recently reported in the *Journal of Clinical Oncology* on primary tumor outcomes in patients receiving systemic treatment without surgery for synchronous Stage IV CRC?

► **DR CURLEY:** This was a retrospective study of 233 patients from Memorial Sloan-Kettering Cancer Center who presented with asymptomatic — no obstruction or significant bleeding — intact primary CRC and what was believed to have been unresectable metastatic disease. So these were not patients who could potentially be treated for cure. Essentially, all of these patients received modern systemic chemotherapy regimens, the majority of which were oxaliplatin based and some were irinotecan-based therapy.

Results demonstrated that among the patients who would have been considered for surgical treatment in the past — often a diverting ileostomy/

colostomy or maybe even a palliative resection — more than 90 percent never required surgical treatment or intervention for their primary CRC. A small proportion of the patients did develop obstructions and/or perforations requiring emergency surgery, but some patients who became symptomatic still didn't require surgery, in that it was possible to either place a stent or use radiation therapy for a rectal tumor to keep their lumen patent (Poultides 2009; [5.1]). The bottom line is that a notably small proportion of patients who present with unresectable metastatic disease and asymptomatic, intact primary tumors require surgical treatment for the primary lesions (5.1).

► **DR FUCHS:** It seems as if the pendulum has swung here. Particularly when bevacizumab was approved, concern arose about perforations, and many felt that we shouldn't leave the primary tumor. However, these data

### 5.1

#### Outcome of Primary Tumors in Patients with Synchronous Stage IV Colorectal Cancer 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.

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

and other studies suggest that the addition of bevacizumab to our front-line therapy shouldn't eliminate the possibility of deferring resection of the primary tumor.

► **DR HALLER:** Most of the data on this topic come from retrospective studies

### SELECT PUBLICATION

Poultides 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.

## PREOPERATIVE CHEMORADIATION THERAPY FOR RECTAL CANCER

► **DR LOVE:** Dan, would you comment on the two data sets presented at ASCO evaluating preoperative chemoradiation therapy for rectal cancer?

► **DR HALLER:** Two studies evaluating oxaliplatin as a radiosensitizer in patients with rectal cancer were presented at ASCO 2009. A French trial evaluated two different dose levels of radiation — 45 Gray with capecitabine alone versus 50 Gray with CAPOX. This trial did not use traditional primary overall survival or local recurrence endpoints but instead attempted to show an increase in the pathologic complete response (pCR) rate from 11 percent to 20 percent.

The authors reported a pCR rate of 14 percent for capecitabine alone with 45 Gray and 19 percent for CAPOX with 50 Gray, with a *p*-value of 0.11, so the primary endpoint was not met (Gerard 2009). The second study, presented by an Italian group, was better designed. The authors evaluated infusional 5-FU at 225 mg/m<sup>2</sup> with or without weekly oxaliplatin at 60 mg/m<sup>2</sup> for six doses. Eighty-

and are exactly like the Memorial study. The reason this study was published in the *JCO* is that it was the only one reported in the era of modern chemotherapy and biologic agents. ■

three percent of patients were able to receive at least five doses of the chemotherapy, and radiation therapy was not compromised. Surgery was tolerated well, and the pCR rate was the same between the two arms. Toxicity was obviously higher in the oxaliplatin arm, including any type of treatment toxicity or diarrhea.

In an unplanned analysis at the time of surgery, 11 patients on the 5-FU and radiation therapy arm had metastatic disease versus only two patients on the 5-FU/radiation therapy/oxaliplatin arm. The implication is that oxaliplatin enhanced the efficacy of neoadjuvant systemic chemotherapy more than it was useful for downstaging (Aschele 2009; [6.1]). Both trials reported more toxicity with oxaliplatin, one clearly negative for an endpoint of pCR and one with a trend but not statistically significant. A third study that may settle this question is NSABP-R-04, which evaluates capecitabine versus continuous infusion 5-FU, both with or without weekly oxaliplatin. This trial is approximately three quarters of

the way accrued, and it's expected to close in August of 2010.

► **DR LOVE:** Dan, how has this affected your approach to therapy?

► **DR HALLER:** We are comfortable administering weekly oxaliplatin based on the ECOG-E1297 data (Rosenthal 2008), and certainly our surgeons and radiation oncologists became comfortable, believing they were seeing better responses and having easier times at surgery. Now, given these data, we have to decide whether to switch from “Why should we not use oxaliplatin?” to “Why should we be using oxaliplatin?”

► **DR LOVE:** Has anyone used neoadjuvant oxaliplatin outside of a protocol setting?

► **DR HOCHSTER:** I have, but not routinely. I have used neoadjuvant oxaliplatin for patients with bulky tumors. These data will make me rethink such an approach.

► **DR HURWITZ:** An oxaliplatin-containing regimen may be appropriate in one other setting: For a patient with symptomatic metastatic disease and a synchronous symptomatic primary tumor that requires radiation therapy. ■

6.1

**STAR-01 Trial: Preoperative 5-Fluorouracil (5-FU)-Based Chemoradiation Therapy with or without Weekly Oxaliplatin (Oxa) for Patients with Locally Advanced Rectal Cancer**

	5-FU/RT	5-FU/Oxa/RT	p-value
<b>Efficacy (n = 379, 368)</b>			
Pathologic complete response	16%	16%	Nonsignificant
<b>Adverse event (n = 379, 353)</b>			
Any Grade III/IV event	8%	24%	<0.0001
Diarrhea (Grade III/IV)	4%	15%	<0.0001
Radiation dermatitis (Grade III/IV)	2%	5%	0.038
Sensory neuropathy (Grade II)	0.5%	36%	<0.0001
<b>Metastases (M+) at surgery (n = 379, 368)</b>	11 (3%)	2 (0.5%)	0.014

SOURCE: Aschele C et al. *Proc ASCO* 2009; **Abstract CRA4008**.

**SELECT PUBLICATIONS**

Aschele C et al. **Preoperative fluorouracil (FU)-based chemoradiation with and without weekly oxaliplatin in locally advanced rectal cancer: Pathologic response analysis of the Studio Terapia Adiuvante Retto (STAR)-01 randomized phase III trial.** *Proc ASCO* 2009; **Abstract CRA4008**.

Gerard JP et al. **Randomized multicenter phase III trial comparing two neoadjuvant chemoradiotherapy (CT-RT) regimens (RT45-Cap versus RT50-Capox) in patients (pts) with locally advanced rectal cancer (LARC): Results of the ACCORD 12/0405 PRODIGE 2.** *Proc ASCO* 2009; **Abstract LBA4007**.

Rosenthal DI et al. **Phase I study of preoperative radiation therapy with concurrent infusional 5-fluorouracil and oxaliplatin followed by surgery and postoperative 5-fluorouracil plus leucovorin for T3/T4 rectal adenocarcinoma: ECOG E1297.** *Int J Radiat Oncol Biol Phys* 2008;72(1):108-13.

## QUESTIONS (PLEASE CIRCLE ANSWER):

1. In the QUASAR validation study, the Recurrence Score from the *Oncotype DX* colon cancer assay predicted the risk of recurrence in patients with Stage II colon cancer after surgery.
  - a. True
  - b. False
2. The CALGB is planning a trial evaluating six versus 12 treatments of adjuvant FOLFOX with or without celecoxib for patients with Stage III CRC.
  - a. True
  - b. False
3. In the NSABP-C-08 trial, evaluating adjuvant FOLFOX with or without 12 months of bevacizumab, the hazard ratio was 0.6 favoring treatment with bevacizumab at which point in the study?
  - a. One year after randomization
  - b. 1.5 years after randomization
  - c. Two years after randomization
  - d. 2.5 years after randomization
  - e. Three years after randomization
4. In the OPTIMOX2 trial, for patients who received FOLFOX7, maintenance therapy with 5-FU/leucovorin prolonged survival compared to \_\_\_\_\_.
  - a. Maintenance therapy with bevacizumab
  - b. Maintenance therapy with cetuximab
  - c. Maintenance therapy with capecitabine
  - d. A complete treatment-free holiday
5. The NSABP-R-04 trial is evaluating preoperative radiation therapy/ capecitabine versus radiation therapy/ 5-FU, both with or without \_\_\_\_\_ in patients with operable rectal cancer.
  - a. Bevacizumab
  - b. Oxaliplatin
  - c. Irinotecan
6. The HORIZON I trial, a randomized Phase II study, compared FOLFOX/low-dose cediranib to FOLFOX/bevacizumab to \_\_\_\_\_ as second-line therapy for metastatic CRC.
  - a. Cediranib alone
  - b. FOLFOX/high-dose cediranib
  - c. FOLFOX/cetuximab
7. 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
8. In the MD Anderson experience with surgical treatment for multiple colorectal liver metastases, the actuarial five-year survival rate for patients with four or more metastases was approximately \_\_\_\_\_.
  - a. 10 percent
  - b. 20 percent
  - c. 50 percent
9. A retrospective analysis of patients with synchronous Stage IV CRC receiving combination chemotherapy without surgery as initial treatment reported that more than 90 percent of patients never required surgical treatment or intervention for their primary CRC.
  - a. True
  - b. False
10. The STAR-01 trial, evaluating preoperative fluorouracil-based chemoradiation therapy with or without oxaliplatin for patients with locally advanced rectal cancer, reported a statistically significant benefit in pathologic complete response rate for the oxaliplatin-containing arm versus the chemoradiation therapy-only arm.
  - a. True
  - b. False

**EDUCATIONAL ASSESSMENT AND CREDIT FORM**

*Colorectal Cancer Update — Think Tank 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
QUASAR validation study of a quantitative multigene RT-PCR 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/III colon cancer	4 3 2 1	4 3 2 1
Prodige 2-ACCORD and STAR-01 study results: Oxaliplatin-containing neoadjuvant chemoradiation therapy for patients with locally advanced rectal cancer	4 3 2 1	4 3 2 1
Mechanism of action and ongoing clinical trials with the oral, small-molecule VEGF TKI cediranib	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, web-based models and clinicopathologic variables as tools for communicating risk of recurrence to patients with early colon cancer. . . . . 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
- Recall the results of clinical trials evaluating the addition of biologic agents to conventional adjuvant chemotherapy as treatment for Stage II and Stage III colon cancer . . . . . 4 3 2 1 N/M N/A
- Develop up-to-date clinical management strategies for metastatic CRC, incorporating chemotherapy, anti-VEGF and anti-EGFR antibodies. . . . . 4 3 2 1 N/M N/A
- Appraise the risk-benefit profile of continuing therapy with biologic agents beyond initial disease progression . . . . . 4 3 2 1 N/M N/A
- Formulate a treatment plan for patients with synchronous or metachronous primary CRC and liver-only metastases . . . . . 4 3 2 1 N/M N/A
- Evaluate the evidence supporting oxaliplatin-containing chemoradiation therapy in the management of locally advanced rectal cancer. . . . . 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

**EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)**

**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 moderator for this educational activity**

	4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal		4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal
<b>Faculty</b>	<b>Knowledge of subject matter</b>				<b>Effectiveness as an educator</b>				
Steven A Curley, MD	4	3	2	1	4	3	2	1	
Lee M Ellis, MD	4	3	2	1	4	3	2	1	
Charles S Fuchs, MD, MPH	4	3	2	1	4	3	2	1	
Richard M Goldberg, MD	4	3	2	1	4	3	2	1	
Daniel G Haller, MD	4	3	2	1	4	3	2	1	
Howard S Hochster, MD	4	3	2	1	4	3	2	1	
Herbert I Hurwitz, MD	4	3	2	1	4	3	2	1	
<b>Moderator</b>	<b>Knowledge of subject matter</b>				<b>Effectiveness as an educator</b>				
Neil Love, MD	4	3	2	1	4	3	2	1	

**Please recommend additional faculty for future activities:**

**Other comments about the faculty and moderator for this activity:**

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