2005 · Vol 2 · Issue 2

Patterns of Care in Medical Oncology

Management of Early and Advanced Cancer of the Colon and Rectum

Adjuvant Systemic Therapy for Colon Cancer

Treatment of Metastatic Colon Cancer

Treatment of Rectal Cancer

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FROM THE PUBLISHERS OF:

Breast Cancer® UPDATE | Colorectal Cancer™ UPDATE | Lung Cancer™ UPDATE | Non-Hodgkin's Lymphoma™ UPDATE | Prostate Cancer™ UPDATE

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Continuing Medical Education (CME) Information

STATEMENT OF NEED/TARGET AUDIENCE

It is important for practicing oncologists to be aware of similarities and differences between his or her practice patterns and those of others in community practice. It is also important for oncologists to recognize that heterogeneity exists in the oncology community, especially in clinical situations for which there is suboptimal research evidence.

This program focuses on the self-described practice patterns of randomly selected medical oncologists on a variety of key clinical issues in cancer. This CME program will provide medical oncologists with information on national cancer patterns of care to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

Upon completion of this activity, participants should be able to:

- Compare and contrast management strategies of his or her clinical practice with those of other community oncologists for the treatment of cancer.
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE

The purpose of this issue of *Patterns of Care* is to support these objectives by comparing the perspectives of 103 randomly selected community medical oncologists interviewed in depth in August 2005 and to offer in-depth commentary from faculty regarding their practice patterns in the management of colorectal cancer.

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Faculty affiliations and disclosures continued on page 39.

Editor's Note: Consensus and controversy

After many years of conducting patterns of care surveys in breast cancer, we are very pleased to present our first initiative outside of that tumor type. This monograph delivers the results of a national telephone survey of 100 randomly selected US-based medical oncologists, who detailed their likely nonprotocol treatment recommendations for a variety of colorectal cancer case scenarios. Colorectal cancer represents one in six office visits for these physicians, who have been in practice an average of about 14 years (Figure 1). As in prior similar surveys, about two thirds of these clinicians actively participate in clinical trials, with both industry and the government (Figure 2).

One of the most striking features of the survey data is the mixture of consensus and heterogeneity in the responses of these docs.

It is interesting to consider that in some of the survey scenarios, if a patient were to seek a second, third, fourth and even fifth opinion, it is possible or even likely that multiple, very different treatment plans would be suggested, with great variation in the personal and financial costs and perhaps in the antitumor efficacy.

How about 99 second opinions? Figures 3 and 4 provide two examples of what we found in our current colorectal cancer survey. Of note are a number of situations in which a current consensus is apparent, but in other situations, there is considerable heterogeneity of responses.

Figure 3 is an example of a situation in which a consensus exists, specifically with regard to adjuvant systemic therapy for younger patients with Stage III disease. Clearly the FOLFOX message has been transmitted and received, yet one could wonder why the FOLFOX answer to this question is not 100 percent. However, in more than 20 years of conducting these surveys in breast cancer, we have consistently observed that even in situations where the clinical research community is unified in their treatment approach, there is always a small fraction of oncologists — usually at least 10 percent — taking another path. Part of this variability could be a function of inaccuracies in such informal surveys, but in my opinion these outliers are for real.

It would be interesting to evaluate whether this small group is familiar with current clinical research data and disagrees with the perspectives of colleagues or whether they have been suboptimally informed about emerging data sets and

FIGURE 1 n = 101

Demographics

What percentage of your total patient office visits are for the following primary cancers (including diagnosis, treatment and post-treatment follow-up)?

Cancer	Percent of visits
Breast cancer	25%
Lung cancer	19%
Colorectal cancer	17%
Non-Hodgkin's lymphoma	15%
Prostate cancer	11%
Other cancers	13%

How many years have you been in practice?

Mean	13.9

FIGURE 2 n = 103

Participation in Colorectal Cancer Research

On which types of clinical trials do you enroll colorectal cancer patients?

None, I am not involved in clinical trials	35%
Industry sponsored	36%
Cooperative groups/CTSU	52%
Investigator initiated	7%
Institutional	11%
NCI	6%

Have you enrolled colorectal cancer patients on clinical trials through the Cancer Trials Support Unit (CTSU)?

Yes	27%
No	73%

How many patients per month do you enroll in clinical trials?

Mean	1.5

could benefit by more effective continuing education. I believe the answer is a combination of these two factors.

Figure 3 also demonstrates another consistent finding in our surveys: The diversity of treatment recommendations tends to increase with age and is particularly divergent in octogenarians. Note that in Figure 4, which focuses on metastatic disease, in the scenario of the 85-year-old patient with metastatic disease, more than a dozen treatment approaches are utilized, ranging from no systemic therapy to combination chemotherapy and biologic treatment.

In our breast cancer Patterns of Care series, we recently conducted two simultaneous studies involving both oncologists in practice and clinical investigators specializing in breast cancer. As one might expect, there was a greater degree of consensus among the investigators than among the community practitioners. It would be interesting to launch a parallel effort in colorectal cancer, and I suspect there would be similar findings.

What does this all mean and how, if at all, is it relevant to efforts in continuing oncology education and patient counseling?

From a CME perspective, we think that the data reinforce the need for case-based education, such as our *Meet The Professors* audio series. The roundtable format that juxtaposes clinical investigators and community-based oncologists is ideal for discussing the application of clinical research information to daily treatment decisions. In preparing for these recordings, I conduct one-on-one teleconferences with each community doc, in which we review cases they wish to present. This also provides me with an opportunity to discover the current most pressing dilemmas in clinical practice, which become the focal points for the recording.

For this reason, we are about to launch our first *Meet The Professors* program* in colorectal cancer. This format will allow us to explore the complex biopsychosocial determinants of critical treatment decision-making in colorectal oncology, and hopefully we will learn more about why in similar patient populations, we see both consensus and controversy in treatment recommendations.

— Neil Love, MD
NLove@ResearchToPractice.net

* **www.MeetTheProfessors.com**

This survey was developed with Dr Axel Grothey, who also reviewed the findings and discussed these in an interview, which is excerpted throughout this monograph, along with select comments from other clinical investigators on our *Colorectal Cancer Update* audio series. The data in this monograph reflect a series of telephone surveys conducted in August 2005 with fax/email support of randomly selected US-based medical oncologists who spend more than 50 percent of their time in patient care. Sample sizes of 50 to 103 respondents (as noted) are presented.

FIGURE 3

n = 50

Adjuvant Therapy in Patients with Stage III Colon Cancer

- *Woman in average health*
- ***T3** tumor in the left descending colon*
- ***15/25** lymph nodes positive*

Which adjuvant systemic therapy regimen, if any, would you most likely recommend?

	Age 38	Age 65	Age 75	Age 85
5-FU/LV (bolus-Roswell Park)	—	—	10%	16%
5-FU/LV (bolus-Mayo Clinic)	—	—	2%	8%
5-FU/LV (infusion)	—	—	2%	2%
5-FU/LV + bevacizumab	—	—	2%	—
FOLFOX	92%	92%	60%	14%
FOLFOX + bevacizumab	8%	6%	2%	—
FOLFIRI	—	—	2%	—
Capecitabine	—	2%	16%	46%
CAPOX	—	—	2%	2%
FLOX	—	—	2%	2%
Observation	—	—	—	10%

FIGURE 4

n = 53

Treatment of Metastatic Colon Cancer: No Prior Systemic Therapy

- *Patient in otherwise average health*
- *Treated for Stage II sigmoid cancer 3 years ago (no adjuvant chemotherapy)*
- *CT scan reveals 6 metastases in both lobes of liver (5/8 liver segments affected)*
- *No evidence of extrahepatic metastases*

Which systemic therapy, if any, are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
5-FU/LV (bolus-Roswell Park)	—	—	2%	2%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	—	4%	15%
5-FU/LV (bolus-Mayo Clinic)	—	—	2%	2%
5-FU/LV (bolus-Mayo Clinic) plus bevacizumab	—	—	—	4%
5-FU/LV (bolus-Mayo Clinic) plus cetuximab	—	2%	—	—
5-FU/LV (infusion) plus bevacizumab	2%	2%	5%	4%
FOLFOX	2%	—	6%	4%
FOLFOX plus bevacizumab	83%	71%	49%	17%
FOLFOX plus cetuximab	2%	—	—	—
FOLFIRI plus bevacizumab	2%	6%	4%	—
FOLFIRI plus bevacizumab and cetuximab	2%	2%	2%	2%
IFL plus bevacizumab	—	2%	2%	—
Capecitabine	—	—	6%	24%
Capecitabine plus bevacizumab	—	—	2%	4%
CAPOX	—	2%	11%	9%
CAPOX plus bevacizumab	4%	7%	2%	4%
Other systemic therapy	—	—	—	—
No systemic therapy recommended	3%	6%	3%	9%

SELECT PUBLICATIONS

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/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* 2005;**Abstract 3501**.

Giantonio BJ et al. **High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200.** *Proc ASCO* 2005;**Abstract 2**.

Gill S et al. **Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: Who benefits and by how much?** *J Clin Oncol* 2004;22(10):1797-806. **Abstract**

Grothey A, Sargent DJ. **FOLFOX for stage II colon cancer? A commentary on the recent FDA approval of oxaliplatin for adjuvant therapy of stage III colon cancer.** *J Clin Oncol* 2005;23(15):3311-3. No abstract available

Hurwitz HI et al. **Bevacizumab in combination with fluorouracil and leucovorin: An active regimen for first-line metastatic colorectal cancer.** *J Clin Oncol* 2005;23(15):3502-8. **Abstract**

Kabbinavar FF et al. **Combined analysis of efficacy: The addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer.** *J Clin Oncol* 2005;23(16):3706-12. **Abstract**

Kelly H, Goldberg RM. **Systemic therapy for metastatic colorectal cancer: Current options, current evidence.** *J Clin Oncol* 2005;23(20):4553-60. **Abstract**

Wolmark N et al. **A Phase III trial comparing FULV to FULV + oxaliplatin in stage II or III carcinoma of the colon: Results of NSABP Protocol C-07.** *Proc ASCO* 2005;**Abstract 3500**.

Adjuvant Systemic Therapy for Colon Cancer

FIGURE 5

n = 50

Risk of Relapse and Mortality in Patients with Stage II Colon Cancer

- *65-year-old man in average health*
- ***T4 tumor***
- *0/19 lymph nodes positive*

How would you estimate this patient's 5-year risk of relapse and mortality?

	5-year risk of relapse		5-year risk of mortality	
Therapy	Estimated	Actual*	Estimated	Actual*
No chemotherapy	40%	23%	28%	18%
5-FU/LV	31%	19%	22%	15%
FOLFOX	26%	17%	18%	13%

Which adjuvant systemic therapy regimen, if any, would you most likely recommend for this patient?

5-FU/LV (bolus-Roswell Park)	10%
FOLFOX	66%
FOLFOX + bevacizumab	4%
Capecitabine	6%
FLOX	2%
Observation/would not recommend systemic therapy	12%

* = Adjuvant! Online

FIGURE 6

n = 50

Adjuvant Chemotherapy for Stage II Colon Cancer

What percentage of your patients with Stage II colon cancer receive adjuvant chemotherapy?

Mean	39%

*Which of the following best describes how you approach discussion of the possibility of **adjuvant** chemotherapy with patients with Stage II disease, even if you are not going to recommend it?*

Discuss with almost all patients as a possibility (more than 80 percent)	82%
Discuss with 51 to 80 percent	8%
Discuss with 26 to 50 percent	8%
Discuss with 11 to 25 percent	—
Discuss with five to 10 percent	—
Rarely or never bring this up (less than five percent)	2%

Colorectal Cancer Update 2005 (2)

DR JOHN MARSHALL: 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. I think that 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.

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.

Interview, August 2005

DR LOVE: What are your thoughts on these patterns of data related to the risk of recurrence and the use of adjuvant chemotherapy in breast and colon cancer (Figure 7)?

DR AXEL GROTHEY: This is very interesting and reflects what we see in practice, particularly in terms of the 10 percent risk of recurrence. When the categories of *very likely* and *more likely than unlikely* are combined, more than 65 percent of the breast cancer patients would receive chemotherapy, while approximately 40 percent of the colon cancer patients would receive chemotherapy. That is a significant difference, and this is relevant.

DR LOVE: In a recent colorectal cancer think tank, Peter Ravdin mentioned that the number of people utilizing the colon cancer Adjuvant! model is about one tenth the number who utilize the breast cancer Adjuvant! model.

FIGURE 7

n = 50

Risk of Recurrence and Use of Adjuvant Chemotherapy

How likely are you to recommend adjuvant chemotherapy to a 55-year-old woman with colon cancer (Stage II) or breast cancer with each of the following risks of recurrence?

	10% risk of recurrence		20% risk of recurrence		30% risk of recurrence	
	Colon	Breast	Colon	Breast	Colon	Breast
Very likely	12%	23%	33%	75%	61%	94%
More likely than unlikely	31%	44%	39%	19%	31%	2%
More unlikely than likely	26%	23%	20%	2%	6%	2%
Very unlikely	31%	10%	8%	4%	2%	2%

FIGURE 8

n = 50

Use of Computer Models in Clinical Practice

How often do you use computer models/programs in your practice to evaluate individual cancer patients in the adjuvant setting?

	Colon cancer	Breast cancer
Always	29%	57%
Sometimes	53%	43%
Rarely	18%	—
Never	—	—

FIGURE 9

n = 50

Use of Computer Models in Clinical Practice

Which of the following models do you use to estimate your cancer patients' risk of relapse and/or mortality?

	Colon cancer	Breast cancer
Peter Ravdin's Adjuvant! model	32%	36%
Mayo Clinic model	—	8%
Both models	2%	12%
Neither model	66%	44%

What was your take in this survey on the number of oncologists utilizing the Adjuvant! model for both breast and colon cancer risk estimates?

DR GROTHEY: I thought that it was very interesting that the oncologists appear to be using the models so much more in breast cancer. I believe that the oncologists' predictions for recurrence and mortality in the adjuvant setting for Stage II and Stage III patients are also quite accurate (Figures 10-12).

DR LOVE: According to the survey data, adverse risk factors such as angiolymphatic invasion, obstruction and microsatellite instability have significant impacts on whether or not doctors choose to recommend chemotherapy (Figures 10-12); do you support this observation?

DR GROTHEY: Yes, if an adverse risk factor can be identified, it clearly shifts toward the recommendation of chemotherapy. That is exactly what has happened with this data — risk factors were identified and chemotherapy was recommended.

I was surprised that the molecular risk factor — the microsatellite-stable patient with 18q deletion — actually shifted practice as much as some of the clinical factors.

Furthermore, I was a little bit concerned about the magnitude of difference in the shift toward treating for an obstructing tumor compared to treatment for a tumor that had an inadequate sample size of lymph nodes — zero of eight lymph nodes.

The awareness of the importance of lymph-node dissection, which is a very, very strong prognostic factor, is not as large as it should be. That factor is as important as obstruction or other clinical risk factors.

FIGURE 10

n = 50

Adjuvant Therapy in Patients with Stage II Colon Cancer

- *Man in average health*
- *Nonobstructing, nonperforating lesion in the right colon*
- *T3 tumor*
- *Moderately differentiated, no angiolymphatic invasion*

Which adjuvant systemic therapy regimen, if any, would you most likely recommend for each scenario?

	0/19 lymph nodes positive		0/8 lymph nodes positive	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park)	20%	4%	16%	8%
5-FU/LV (bolus-Mayo Clinic)	—	—	4%	—
5-FU/LV (infusion)	2%	2%	—	2%
FOLFOX	22%	—	30%	2%
FOLFOX + bevacizumab	2%	—	—	—
Capecitabine	8%	6%	8%	8%
CAPOX	—	—	—	—
Observation/would not recommend systemic therapy	46%	88%	42%	80%

FIGURE 11

n = 50

Adjuvant Therapy in Patients with Stage II Colon Cancer

- *Man in average health*
- *Nonperforating lesion in the right colon*
- *T3 tumor*
- *Moderately differentiated*
- *0/19 lymph nodes positive*

Which adjuvant systemic therapy regimen, if any, would you most likely recommend?

	Obstructing		Angiolymphatic invasion	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park)	10%	12%	14%	10%
5-FU/LV (bolus-Mayo Clinic)	4%	—	6%	—
5-FU/LV (infusion)	—	2%	2%	2%
FOLFOX	64%	4%	54%	4%
FOLFOX + bevacizumab	2%	2%	2%	—
Capecitabine	8%	14%	8%	16%
CAPOX	—	—	2%	—
FLOX	—	2%	—	—
Observation	12%	64%	12%	68%

FIGURE 12

n = 50

Adjuvant Therapy in Patients with Stage II Colon Cancer

- *Man in average health*
- *Nonobstructing, nonperforating lesion in the right colon*
- *T3 tumor*
- *Moderately differentiated, no angiolymphatic invasion*
- *0/19 lymph nodes positive*
- ***Tumor tested for microsatellite instability and found to be of the MSS type (microsatellite stable); in addition, an 18q deletion is detected***

Which adjuvant systemic therapy regimen, if any, would you most likely recommend?

	Age 38	Age 65	Age 75	Age 85
5-FU/LV (bolus-Roswell Park)	10%	18%	16%	10%
5-FU/LV (bolus-Mayo Clinic)	4%	8%	2%	—
5-FU/LV (infusion)	—	2%	2%	—
FOLFOX	64%	34%	8%	—
FOLFOX + bevacizumab	4%	2%	—	—
Capecitabine	2%	8%	16%	12%
CAPOX	4%	4%	4%	—
Observation	12%	24%	52%	78%

Colorectal Cancer MTP September 2005

DR LOVE: In general, for Stage II disease, which regimen do you generally utilize when you treat a patient in their sixties?

DR GEORGE FISHER: For patients in good health, I would have no real concerns about the safety of administering chemotherapy. It is a question of how much discomfort that person would be willing to tolerate for six months. In a patient with high-risk disease who wanted to receive a regimen that offered the highest absolute benefit, then that would be a FOLFOX regimen. And if that person was shy of doctors' visits, IVs, needles, 48-hour infusions, or had catheter contraindications, I believe that CAPOX is certainly a suitable alternative.

Colorectal Cancer Update 2005 (4)

DR LOVE: What are your thoughts about adjuvant chemotherapy for patients with Stage II colon cancer?

DR ROBERT DIASIO: Typically, patients with no evidence of lymph node involvement, no matter how deeply the tumor appears to extend, do not receive chemotherapy for Stage II disease. However, increasing data suggest that some patients with penetration of the intestinal wall, who would not have been treated in the past, may benefit from chemotherapy.

The ASCO committee published an aggressive position paper stating that perhaps Stage II patients should be offered adjuvant therapy. While we don't have any convincing objective data to validate the use of adjuvant therapy in Stage II disease, subsets within that population may benefit. The ultimate proof of the benefit in such patients will come from ongoing adjuvant studies.

One reason it may be difficult to demonstrate a benefit from adjuvant therapy in Stage II disease is that fewer events occur. However, the MOSAIC trial and some of the earlier Intergroup studies have suggested certain patients can benefit from chemotherapy.

Colorectal Cancer Update 2005 (3)

DR LOVE: In general, what is your approach to adjuvant therapy in patients with high-risk Stage II colon cancer?

DR AIMERY de GRAMONT: I would certainly offer adjuvant FOLFOX to patients with Stage III or high-risk Stage II disease.

In patients with a very good prognosis, the potential risks and benefits of an adjuvant regimen must be weighed in a discussion that should occur between the patient and physician.

We presented data from the patients with Stage II disease in the MOSAIC adjuvant trial. In an analysis of the patients with high-risk Stage II disease (eg, T4, bowel obstruction, tumor perforation, venous invasion or fewer than 10 lymph nodes analyzed), the difference in disease-free survival in favor of FOLFOX was over five percent.

In patients with high-risk Stage II disease, adjuvant FOLFOX should be considered.

FIGURE 13

n = 50

Adjuvant Therapy in Patients with Stage III Colon Cancer

- *Woman in average health*
- *Tumor in the left descending colon*

Which adjuvant systemic therapy regimen, if any, would you most likely recommend for each scenario?

	T2 tumor, 1/25 lymph nodes positive		T3 tumor, 15/25 lymph nodes positive	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park)	—	22%	—	16%
5-FU/LV (bolus-Mayo Clinic)	—	4%	—	8%
5-FU/LV (infusion)	4%	4%	—	2%
5-FU/LV + bevacizumab	—	—	—	—
FOLFOX	82%	2%	92%	14%
FOLFOX + bevacizumab	6%	2%	6%	—
FOLFIRI	—	—	—	—
Capecitabine	2%	22%	2%	46%
CAPOX	2%	2%	—	2%
FLOX	4%	2%	—	2%
Observation	—	40%	—	10%

- *Same case except patient has a **history of myocardial infarction in the past year***

Which adjuvant systemic therapy regimen, if any, would you most likely recommend?

	T2 tumor, 1/25 lymph nodes positive		T3 tumor, 15/25 lymph nodes positive	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park)	—	12%	4%	16%
5-FU/LV (bolus-Mayo Clinic)	2%	4%	2%	6%
5-FU/LV (infusion)	4%	4%	2%	2%
FOLFOX	72%	2%	82%	—
FOLFOX + bevacizumab	2%	2%	—	—
5-FU/LV + bevacizumab	—	—	—	—
FOLFIRI	—	—	—	8%
Capecitabine	12%	26%	4%	39%
CAPIRI	—	—	—	—
CAPOX	4%	2%	4%	—
FLOX	4%	2%	2%	2%
Observation	—	46%	—	27%

Colorectal Cancer Update 2005 (3)

DR PAULO HOFF: For those patients who present with Stage II disease, the decision about the use of adjuvant chemotherapy is complicated. Obviously, we have to discuss the potential benefits and toxicities of chemotherapy. I tend to suggest adjuvant chemotherapy more strongly if their disease has a high-risk feature (eg, obstruction, perforation or lymphovascular invasion).

Once I explain all the options, even some patients in whom I would prefer to use FOLFOX surprisingly ask to receive capecitabine. They feel attracted to the oral agent. Also, for patients with severe comorbid conditions or the very frail elderly patients, I tend to use adjuvant capecitabine instead of FOLFOX.

Colorectal Cancer Update 2005 (4)

DR LOVE: Do you think that capecitabine can be utilized in the adjuvant setting as a substitute for 5-FU?

DR PHILIP PHILIP: In situations in which a single-agent fluoropyrimidine is being used or contemplated, capecitabine should be used. I don't believe at this time that, if given the option, a patient will opt for intravenous treatment unless an issue arises regarding who will pay for the capecitabine. Capecitabine should be the drug of choice for patients who will receive a single-agent fluoropyrimidine because it's easier to administer and doesn't interfere much with the patient's daily routine. It has side effects, and we have to pay attention to them. But overall, it's a treatment that patients will prefer.

In which patients should we use single-agent therapy? In patients with Stage III disease, the data on adjuvant FOLFOX have completely transformed my practice. I use FOLFOX in patients with Stage III disease, except in those who refuse the combination, cannot take a neurotoxic drug or are too old for such a combination. Those patients who don't receive adjuvant FOLFOX receive single-agent capecitabine. The next question becomes, Can we combine capecitabine with oxaliplatin? Adjuvant CAPOX is still experimental, and it should be used as part of a clinical trial. We still have to wait for the head-to-head comparison with FOLFOX.

Interview, August 2005

DR LOVE: In general, what adjuvant chemotherapy would you be most likely to recommend to a patient with Stage III colon cancer who had a T2 tumor and one of 25 positive lymph nodes?

DR GROTHEY: I would recommend FOLFOX for a 38-, 65- or 75-year-old patient. In an 85-year-old patient I would more than likely utilize capecitabine.

DR LOVE: The survey shows that in the adjuvant setting for the 85-year-old patient with lower-risk disease, the frequency of using 5-FU monotherapy is approximately the same as the amount of capecitabine being given.

DR GROTHEY: Yes, and this is happening based on extensive experience with 5-FU regimens and the fact that the dosing of capecitabine has not been completely established in the United States. There is concern about the toxicity associated with capecitabine. However, there is clear advantage with capecitabine in terms of convenience. There's no doubt about that. I would prefer to see more patients on capecitabine than on bolus 5-FU.

DR LOVE: What therapy should be recommended to a Stage III patient who is concerned about oxaliplatin-associated neuropathy and would prefer not to take an oxaliplatin-containing regimen?

DR GROTHEY: In that situation capecitabine should be recommended. However, most patients can tolerate some oxaliplatin. Cumulative toxicity does not occur within the first three or four months. Whatever regimen you choose to combine with oxaliplatin — whether you utilize FLOX or FOLFOX — there is evidence that a little bit of oxaliplatin is better that none. We assume that the same holds true for combining oxaliplatin with capecitabine-based regimens.

Colorectal Cancer Update 2005 (5)

DR LOVE: What is your opinion of the NSABP-C-07 trial comparing Roswell Park 5-FU versus FLOX?

DR GROTHEY: The results from NSABP-C-07 were more positive than most experts expected. NSABP-C-07 randomly assigned patients with Stage II or III colon cancer to receive the Roswell Park regimen of 5-FU/leucovorin (three cycles of an eight-week regimen) with or without oxaliplatin 85 mg/m^2 administered at weeks one, three and five (FLOX).

Compared to the FOLFOX4 regimen used in the MOSAIC adjuvant trial, the FLOX regimen in NSABP-C-07 had the same duration of therapy but a lower cumulative dose of oxaliplatin (765 mg/m^2 versus 1,020 mg/m^2). Although the dose intensity of oxaliplatin was lower and a bolus 5-FU regimen was used as the backbone for the FLOX regimen, they found an increase in the three-year disease-free survival that was almost identical to that in the MOSAIC trial: about a five percent absolute increase.

This suggests that the addition of oxaliplatin to any 5-FU-based regimen is of benefit in the adjuvant setting. Secondly, it shows we probably have two alternatives to choose from: FOLFOX or FLOX.

Colorectal Cancer Update 2005 (3)

DR LOVE: How has the X-ACT trial impacted your utilization of capecitabine in the adjuvant setting?

DR MICHAEL O'CONNELL: The X-ACT trial established the principle that oral chemotherapy could be effective in the adjuvant setting, compared to intravenous chemotherapy. Capecitabine offers the patient the advantage of not requiring IV injections. The dosage level that was used is a bit higher than most oncologists in the United States have been able to administer to their patients, and it raises some interesting questions about possible pharmacogenetic differences between the populations in Europe and the United States.

FIGURE 14

n = 50

Risk of Relapse and Mortality in Patients with Stage III Colon Cancer

- *65-year-old woman in average health*
- ***T4** tumor in the left descending colon*
- ***2/25** lymph nodes positive*

How would you estimate this patient's 5-year risk of relapse and mortality?

	5-year risk of relapse		5-year risk of mortality	
Therapy	Estimated	Actual	Estimated	Actual
No chemotherapy	60%	49%	44%	42%
5-FU/LV	44%	32%	33%	28%
FOLFOX	36%	27%	27%	24%

Which adjuvant systemic therapy regimen, if any, would you most likely recommend for this patient?

5-FU/LV (infusion)	2%
FOLFOX	86%
FOLFOX + bevacizumab	6%
Capecitabine	2%
FLOX	4%

I believe the data are very compelling and suggest that there might be an advantage for capecitabine over the Mayo Clinic method of administering 5-FU and leucovorin in the primary endpoint of disease-free survival, which practically reached statistical significance in favor of the capecitabine. The primary goal of the study was to demonstrate noninferiority. They certainly accomplished that. I now believe that in clinical practice, for a patient in whom fluoropyrimidine therapy is considered appropriate, capecitabine is a viable option.

Colorectal Cancer Update 2004 (5)

DR HOCHSTER: The X-ACT trial was a comparison of adjuvant capecitabine to the Mayo Clinic 5-FU regimen. We now know adjuvant capecitabine is equal to or perhaps slightly better than the Mayo Clinic regimen. I think that's a very important observation, and adjuvant capecitabine is a reasonable option for a well-educated patient who can be relied upon to take pills on a regular basis.

This requires a highly motivated patient who will call you or come in when they start to develop diarrhea, hand-foot syndrome or any of the toxicities. I don't have a hesitation to use adjuvant capecitabine, based on the clinical data at this point in the adjuvant setting.

Colorectal Cancer Update 2005 (3)

DR LOVE: In general, what is your treatment approach in the adjuvant setting for a patient with Stage III colon cancer?

DR LEONARD SALTZ: I'm pretty comfortable with the MOSAIC data, so I generally use FOLFOX in the adjuvant setting for patients with Stage III disease. When I have a patient who is particularly dependent on their fine-motor skills, I discuss with them whether we want to include oxaliplatin in their treatment because the neurotoxicity might compromise their quality of life. If I'm concerned about a patient's ability to tolerate combination chemotherapy, I might consider using one of several schedules of 5-FU/leucovorin or capecitabine.

Colorectal Cancer Update 2005 (1)

DR CHRIS TWELVES: In the MOSAIC trial, the addition of oxaliplatin resulted in a significant reduction in the risk of recurrence in the adjuvant setting.

I believe the MOSAIC data are the new gold standard. Only time will tell what that means for individual patients. A gold standard doesn't necessarily mean the therapy applies to all patients. There are toxicities related to oxaliplatin, such as myelosuppression and neurotoxicity, and I don't believe oxaliplatin-based adjuvant therapy will replace single-agent treatment across the board.

I anticipate a rapid move towards oxaliplatin-based treatments, especially in the younger, fitter and higher-risk patients. However, I believe a single-agent fluoropyrimidine will still be an appropriate option for a substantial proportion of older, more frail patients or patients at lower risk of disease recurrence.

Colorectal Cancer Update 2005 (1)

DR LOVE: Can you discuss the ongoing NSABP trial investigating the addition of bevacizumab to FOLFOX in the adjuvant setting?

DR NORMAN WOLMARK: The NSABP-C-08 trial opened in October 2004. The trial design is simple and straightforward — modified FOLFOX-6 with or without one year of bevacizumab. The eligibility criteria include patients with Dukes' B or C colon cancer.

Originally, we wanted to make this trial as broad-based as possible and include FLOX (bolus 5-FU/leucovorin/oxaliplatin). The FDA didn't particularly embrace that idea; their response was justified because we didn't have data from NSABP-C-07. In view of the MOSAIC adjuvant trial data with a FOLFOX regimen, I think a FOLFOX-inspired regimen is reasonable. So we eliminated the possibility of having FLOX as a control arm. Also, we were thinking of including a capecitabine/oxaliplatin (CAPOX)

FIGURE 15

n = 50

Oxaliplatin-Related Neuropathy

*What percentage of your patients on oxaliplatin or oxaliplatin-containing regimens develop **acute** neuropathy?*

Mean	34%

*What percentage of your patients on oxaliplatin or oxaliplatin-containing regimens develop **chronic** neuropathy?*

Mean	36%

In what percentage of patients do you find the peripheral neuropathy associated with oxaliplatin to be reversible?

Mean	65%

On average, how many cycles of FOLFOX in the adjuvant setting are your patients able to tolerate?

Mean	8.2

FIGURE 16

n = 50

Oxaliplatin-Related Neuropathy

You have a patient on an adjuvant oxaliplatin-containing regimen who develops Grade III neurotoxicity after 8/12 planned cycles.

Which of the following would be your likely treatment plan?

Stop oxaliplatin, continue other agent(s)	70%
Stop oxaliplatin and change other agent(s)	10%
Replace oxaliplatin with another agent and continue other agents	10%
Stop all treatment for a period of time and restart when toxicity regresses	6%
Stop all treatment	2%
Continue treatment/no change	2%

arm, but the sample size would have been much greater.

We really wanted to address a pivotal question — whether the benefits associated with bevacizumab as first-line therapy for metastatic colorectal cancer can be translated to the adjuvant setting. Once we came to grips with that as our unequivocal principal aim, the trial was structured to address it.

The sample size is manageable at about 2,600 patients. Theoretically, we hope bevacizumab will be more effective in the adjuvant setting. We hope the prolongation in time to progression seen in patients with advanced disease, if translated to the adjuvant setting, will result in lives saved.

Colorectal Cancer Update 2005 (2)

DR ALAN VENOOK: 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.

Colorectal Cancer Update 2005 (4)

DR PHILIP: The specific question that is being asked by NSABP-C-08 relates to whether there is a benefit to adding bevaci-zumab to FOLFOX. The duration of therapy with bevacizumab is also of interest in this study because it continues after adjuvant chemotherapy for another six months.

We also have to evaluate the toxicity associated with this regimen because of what we've seen with bevacizumab. NSABP-C-08 is a good trial because the best use of bevacizumab might be early in the natural history of the disease.

This may be the way to go, but one of the concerns with the regimen is, obviously, toxicity. We'll need to see what happens.

Colorectal Cancer MTP September 2005

DR LOVE: Is there a role for irinotecan in the adjuvant setting, for example, in a patient with neuropathy or who cannot tolerate oxaliplatin?

DR PETER ENZINGER: The PETACC trial investigated infusional 5-FU/leucovorin with or without irinotecan. In that trial the primary endpoint was

FIGURE 17

n = 50

Use of Adjuvant CAPOX Off Protocol

Have you used CAPOX (capecitabine and oxaliplatin) off protocol in the adjuvant setting?

Yes	32%
No	68%

For those answering "yes," in how many patients?

Median	5

Have you used CAPOX (capecitabine and oxaliplatin) plus bevacizumab off protocol in the adjuvant setting?

Yes	12%
No	88%

For those answering "yes," in how many patients?

Median	2

FIGURE 18

n = 50

Use of Magnesium and Calcium for Oxaliplatin-Related Neuropathy

Do you use magnesium and/or calcium to prevent or treat neuropathy associated with oxaliplatin or oxaliplatin-containing regimens?

	Current use
Yes, for prevention	46%
Yes, for treatment	14%
Yes, for both prevention and treatment	12%
No	28%

For those who have used magnesium and calcium for oxaliplatin-related neuropathy, how effective you have found it?

Extremely effective	8%
Somewhat effective	70%
Not effective	11%
Don't know	11%

not statistically significant.

However, I believe that there is some borderline benefit for using irinotecan in the adjuvant setting. You could argue that in a patient who has high-risk Stage III disease but for some reason upon receiving the first dose of FOLFOX has an allergic reaction to oxaliplatin, that may be a patient in whom you could use the FOLFIRI regimen.

The ACCORD study specifically looked at high-risk colon cancer patients and did not identify a difference between the patients who received irinotecan and those who did not. That being said, it was clear that investigators removed their patients — or the patients removed themselves — from the study, if they were randomized to receive only 5-FU and leucovorin. The bottom line, in my mind, is that FOLFIRI may be an option in a patient who wishes to receive aggressive therapy and who cannot, for some reason or another, tolerate oxaliplatin.

Interview, August 2005

DR LOVE: In your experience, what percent of patients on oxaliplatin-containing regimens develop acute neuropathy?

DR GROTHEY: Approximately 90 percent of patients develop cold-induced symptoms. The mean response to the question regarding oxaliplatin-related neuropathy (Figure 15) is considerably less than I would have expected. Perhaps the physicians are not aware of this — so this may define an educational need.

When you ask a patient a subjective question, such as whether they have experienced side effects, it is a very dynamic process. If you do not ask, the patients may not forward the information. However, when you ask a patient directly, "So, did you have any side effects from the treatment?" I would expect that more than 70 percent of patients would respond, "Yes, I experienced some nerve problems." This is completely underrepresented, and it may be due to confusion identifying acute and chronic neuropathy — which is important for clinical management.

DR LOVE: In terms of chronic neuropathy, do you agree with the mean response of 36 percent?

DR GROTHEY: This question is left open in terms of severity. In the end, it's a matter of how you define chronic neuropathy. I would say this is more like-

ly what the physicians perceive. Almost every patient experiences some form of neuropathy, although it might not affect activities of daily living. So perhaps a better question would be, What percentage of your patients develops chronic neuropathy that affects the activities of daily living?

DR LOVE: Do you agree with the survey response that patients are able to tolerate an average of eight cycles of an oxaliplatin-containing regimen?

DR GROTHEY: Yes.

Colorectal Cancer Update 2004 (4)

DR LOVE: Do you find that most patients are able to tolerate oxaliplatin-related neuropathy?

DR FISHER: Certainly the toxicity seems tolerable. In the MOSAIC trial, about 18 percent of the participants had Grade III neuropathy during or shortly after the study. At one-year follow-up, that decreased to one percent. Grade III neuropathy is no fun, but patients have been living with cisplatin neurotoxicity for years. I think adjuvant FOLFOX is finding believers, not only in academic circles but also in the community. In particular, it's being used for young patients with high-risk Stage III disease.

Interview, August 2005

DR LOVE: Do you use calcium and magnesium to prevent oxaliplatin-related neuropathy?

DR GROTHEY: We utilize these agents within a clinical trial. We currently have a placebo-controlled trial — calcium/magnesium versus placebo in the adjuvant setting — that we proposed to run through the NCCTG. However, one of the comments that we have received was that physicians were reluctant to enroll patients in the placebo arm because they are using calcium/magnesium in their clinical practice.

Seventy-eight percent of the physicians surveyed who use magnesium and calcium believe it is effective. This is higher than I would have expected, but on the other hand, physicians wouldn't use it if they didn't see any effectiveness.

Colorectal Cancer Update 2005 (1)

DR LOVE: What are your thoughts on the role of CAPOX in the adjuvant and metastatic settings?

DR TWELVES: As one who participates in clinical trials, I prefer to wait for evidence from randomized studies before using new combinations off protocol in the adjuvant and metastatic settings. However, with CAPOX I'm torn because everything we've seen to date from the clinical trials suggests that 5-FU can be substituted with capecitabine in these clinical settings. In addition, I would be very surprised if CAPOX doesn't emerge as being equivalent to the FOLFOX regimen, alone or in combination with bevacizumab. I do believe CAPOX, off protocol, is a reasonable option at this time.

Colorectal Cancer Update 2005 (3)

DR HOFF: There is great interest, especially in the community, in having an oral chemotherapy-based regimen, and the CAPOX regimen is very attractive in that regard. Given the opportunity, patients tend to choose oral agents. We have the X-ACT adjuvant study showing that capecitabine was equivalent and had a hint of being better than bolus 5-FU/leucovorin. I think the data from the Phase II CAPOX trials in the advanced setting are intriguing enough to say that it's at least equivalent to FOLFOX.

I wouldn't recommend CAPOX as my first option in the adjuvant setting, because obviously we prefer to use evidence-based medicine. However, I would not necessarily find it incorrect to use CAPOX in the adjuvant setting. Scientifically, it makes sense.

Colorectal Cancer MTP September 2005

DR LOVE: Can you outline the design of the international AVANT trial?

DR WOLFF: The AVANT trial investigates adjuvant therapy for patients with Stage III colon cancer. There are three arms to that trial, and there are two questions being asked. The first question being addressed is, Are CAPOX and FOLFOX equivalent? The second question is, Does bevacizumab add to adjuvant therapy?

Patients on the first arm will receive FOLFOX alone. Patients on the second arm will receive FOLFOX plus bevacizumab. And patients in the third arm will receive CAPOX plus bevacizumab. However, there is not an arm directly comparing CAPOX versus FOLFOX. My belief is that bevacizumab will work with both the CAPOX and FOLFOX. What we will learn from this study is whether or not bevacizumab adds to standard adjuvant chemotherapy and whether CAPOX and FOLFOX are equivalent in terms of efficacy as adjuvant chemotherapy.

This study is very nicely done. I do not believe that the toxicity is going to be unmanageable based on our experience with these regimens in the past.

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FIGURE 19

n = 53

Treatment of Metastatic Colon Cancer: No Prior Systemic Therapy

- *Patient in otherwise average health*
- *Treated for Stage II sigmoid cancer 3 years ago (no adjuvant chemotherapy)*
- ***2 metastases in right lobe of liver (maximum diameter 3 centimeters)***
- *No evidence of extrahepatic metastases*

Which of the following treatment strategies, if any, are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
Immediate resection of liver metastases alone, no postoperative systemic therapy	4%	6%	8%	15%
Systemic therapy alone	—	6%	30%	50%
Resection of liver metastases followed by systemic therapy	70%	68%	43%	17%
Resection of liver metastases followed by hepatic artery infusion	2%	—	2%	—
Resection of liver metastases followed by hepatic artery infusion and systemic therapy	9%	5%	4%	2%
Hepatic artery infusion and systemic therapy, no surgery	—	—	4%	2%
Hepatic artery infusion alone, no surgery, no systemic therapy	—	2%	—	—
Neoadjuvant systemic therapy followed by resection of liver metastases	15%	13%	9%	6%
Observation	—	—	—	8%

Which systemic therapy, if any, are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
FOLFOX plus bevacizumab	69%	61%	32%	9%
FOLFOX	13%	9%	11%	6%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	—	4%	13%
Capecitabine	—	2%	9%	17%
CAPOX	2%	8%	7%	11%
FOLFIRI plus bevacizumab	4%	8%	4%	—
Other systemic therapy	8%	4%	26%	26%
No systemic therapy recommended	4%	8%	7%	18%

Utilization of select specific agents

	Age 38	Age 65	Age 75	Age 85
Oxaliplatin	91%	81%	56%	32%
Capecitabine	4%	10%	24%	38%
Bevacizumab	79%	72%	55%	40%
Irinotecan	6%	8%	6%	—

FIGURE 20

n = 53

Treatment of Metastatic Colon Cancer: No Prior Systemic Therapy

- *Patient in otherwise average health*
- *Treated for Stage II sigmoid cancer 3 years ago (no adjuvant chemotherapy)*
- ***CT scan reveals 6 metastases in both lobes of liver (5/8 liver segments affected)***
- *No evidence of extrahepatic metastases*

Which of the following treatment strategies are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
Immediate resection of liver metastases alone, no postoperative systemic therapy	—	—	—	—
Systemic therapy alone	69%	79%	88%	85%
Resection of liver metastases followed by systemic therapy	4%	2%	2%	2%
Resection of liver metastases followed by hepatic artery infusion	—	—	—	—
Resection of liver metastases followed by hepatic artery infusion and systemic therapy	2%	2%	—	—
Hepatic artery infusion and systemic therapy, no surgery	4%	2%	—	—
Hepatic artery infusion alone, no surgery, no systemic therapy	2%	4%	2%	—
Neoadjuvant systemic therapy followed by resection of liver metastases	15%	9%	6%	4%
Neoadjuvant systemic therapy and hepatic artery infusion followed by resection of liver metastases	2%	—	—	—
Observation	2%	2%	2%	9%

Which systemic therapy, if any, are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
FOLFOX plus bevacizumab	83%	71%	49%	17%
FOLFOX	2%	—	6%	4%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	—	4%	15%
5-FU/LV (infusion) plus bevacizumab	2%	2%	5%	4%
Capecitabine	—	—	6%	24%
CAPOX	—	2%	11%	9%
CAPOX plus bevacizumab	4%	7%	2%	4%
FOLFIRI plus bevacizumab	2%	6%	4%	—
Other systemic therapy	4%	6%	10%	14%
No systemic therapy recommended	3%	6%	3%	9%

Utilization of select specific agents

	Age 38	Age 65	Age 75	Age 85
Oxaliplatin	91%	82%	68%	34%
Capecitabine	4%	10%	21%	41%
Bevacizumab	93%	91%	70%	49%
Irinotecan	4%	10%	8%	2%

FIGURE 21

n = 53

Treatment of Metastatic Colon Cancer: No Prior Systemic Therapy

Synchronous liver and lung metastases

- *Patient in otherwise average health*
- *Presents with T3 sigmoid tumor and 5/12 positive lymph nodes*
- *2 metastases in right lobe of liver (maximum diameter 3 centimeters)*
- *3.5-centimeter peripheral lesion in lung*
- *All histologically confirmed metastases*

Which of the following treatment strategies are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
Immediate resection of liver metastases alone, no postoperative systemic therapy	—	—	—	2%
Systemic therapy alone	76%	82%	90%	86%
Resection of liver metastases followed by systemic therapy	10%	8%	4%	2%
Resection of liver metastases followed by hepatic artery infusion	—	—	—	—
Resection of liver metastases followed by hepatic artery infusion and systemic therapy	—	—	—	—
Hepatic artery infusion and systemic therapy, no surgery	—	—	—	—
Hepatic artery infusion alone, no surgery, no systemic therapy	—	—	—	—
Neoadjuvant systemic therapy followed by resection of liver metastases	12%	8%	4%	2%
Resection of both liver and lung metastases followed by systemic therapy	2%	2%	2%	2%
Observation	—	—	—	6%

Which systemic therapy, if any, are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
FOLFOX plus bevacizumab	88%	80%	54%	19%
FOLFOX	2%	4%	8%	4%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	—	2%	12%
Capecitabine	—	—	6%	25%
Capecitabine plus bevacizumab	—	—	2%	8%
CAPOX	—	—	6%	12%
CAPOX plus bevacizumab	4%	8%	6%	4%
Other systemic therapy	6%	8%	16%	10%
No systemic therapy recommended	—	—	—	6%

Utilization of select specific agents

	Age 38	Age 65	Age 75	Age 85
Oxaliplatin	96%	92%	74%	41%
Capecitabine	4%	8%	20%	51%
Bevacizumab	92%	91%	74%	47%

DR LOVE: How would you approach a patient who presents with synchronous hepatic and lung metastases (Figure 21)?

DR GROTHEY: This presentation has a very poor prognosis. What is not an appropriate choice here is resection of liver metastases followed by systemic chemotherapy. This is probably one area where clinical investigators and community oncologists differ in opinion. I would approach this patient with neoadjuvant therapy followed by resection of the metastases.

DR LOVE: When you encounter a patient who has bilateral liver metastases, presenting with a nonobstructing lesion, would you resect the primary tumor (Figure 22)?

DR GROTHEY: I would not resect the primary tumor, particularly in young patients. I was a bit surprised in the shifting with age, because if I had an 85-year-old patient with a nonobstructing tumor and metastases, I would prefer to take care of the primary tumor and prevent any obstruction problem. For a 38-year-old patient, I would have clearly said, "No resection of the primary tumor." In an 85-year-old, I would probably resect the primary tumor.

Colorectal Cancer Update 2005 (3)

DR LOVE: What treatment strategy would you recommend for a patient who presents with metastatic disease and asymptomatic primary colon cancer?

DR O'CONNELL: We have a study that has been approved by the National Cancer Institute, which will evaluate the need for resection of an asymptomatic primary colon cancer in patients who present with metastatic disease. There's been a lot of controversy about this in the literature. Approximately 25 percent of patients with metastatic colorectal cancer who have an unresected primary will develop a complication — primarily obstruction — if that tumor isn't resected.

Now that we have more effective systemic chemotherapy, our goal is to determine whether we can avoid the need for resection in patients who don't have any symptoms related to the primary tumor but who have distant, unresectable metastatic disease. We'll treat them all with the modified FOLFOX6 regimen plus bevacizumab. Our endpoint of this Phase II trial is to determine the local complication rates.

Colorectal Cancer Update 2005 (1)

DR LOVE: Can you talk about the NSABP trial investigating CAPOX with or without intra-arterial infusion in patients with hepatic metastases?

DR WOLMARK: NSABP-C-09 is for patients with liver-only metastases that have been removed or ablated. Patients will receive CAPOX with or without intra-arterial FUDR. The European data with CAPOX for patients with liver-only disease certainly influenced the decision of the hepatic surgeons to use CAPOX as the baseline therapy. The question being tested is the role of intra-arterial FUDR. I think the real challenge is to see if hepatic surgeons from different institutions with different concepts can work together to develop a clinical trial.

Colorectal Cancer Update 2005 (2)

DR LOVE: What systemic therapy regimen do you generally recommend for a patient with metastatic colon cancer?

DR VENOOK: 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 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. 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.

Colorectal Cancer Update 2005 (4)

DR PHILIP: At our institution, we evaluated the combination of capecitabine and oxaliplatin (CAPOX). At this time, our front-line nonprotocol treatment approach includes bevacizumab and CAPOX. Granted, no Phase III trial data are available comparing CAPOX to FOLFOX.

However, in the metastatic disease setting, taking into account the convenience for patients of receiving an oral agent instead of continuous infusion 5-FU, we feel that CAPOX would be better than FOLFOX. I probably would not make the same comment for adjuvant therapy. But in the metastatic disease setting, my approach would be bevacizumab plus CAPOX.

Interview, August 2005

DR LOVE: What are your thoughts in general, as you evaluate the data in the survey, in terms of the amount of CAPOX being recommended?

DR GROTHEY: It is what I would have expected, although not necessarily what I would like. I think that the difference between FOLFOX and CAPOX — in the absence of Phase III data — is not so great that FOLFOX should dominate all of these answers. This is an interesting phenomenon, particularly when you look at what is happening across the Atlantic, where FOLFIRI is relatively more dominating compared to what we see here. The split in Europe is 60-40 or 55-45 in favor of FOLFOX, but FOLFIRI has substantial market share. Here, FOLFIRI has a minor share.

I believe that CAPOX is a rational choice in the metastatic setting. For

FIGURE 22

n = 53

Treatment of Widely Metastatic Disease: No Prior Systemic Therapy

- *Patient in otherwise average health*
- *T3, N1 sigmoid tumor (non-obstructing)*
- ***12 liver metastases in both liver lobes***

*Would you recommend resection of the **primary** tumor?*

	Age 38	Age 65	Age 75	Age 85
Percent answering "yes"	38%	30%	21%	11%

Which of the following treatment strategies are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
Immediate resection of liver metastases alone, no postoperative systemic therapy	—	2%	—	—
Systemic therapy alone	92%	94%	96%	92%
Resection of liver metastases followed by hepatic artery infusion and systemic therapy	4%	4%	4%	4%
Hepatic artery infusion and systemic therapy, no surgery	2%	—	—	—
Neoadjuvant systemic therapy followed by resection of liver metastases	2%	—	—	—
Observation	—	—	—	4%

Which systemic therapy, if any, are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
FOLFOX plus bevacizumab	81%	71%	53%	18%
FOLFOX	2%	4%	7%	6%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	—	2%	13%
Capecitabine	—	—	6%	22%
Capecitabine plus bevacizumab	—	—	—	6%
CAPOX	—	2%	4%	11%
CAPOX plus bevacizumab	7%	9%	9%	4%
FOLFIRI plus bevacizumab	2%	4%	5%	—
Other systemic therapy	8%	8%	14%	16%
No systemic therapy recommended	—	2%	—	4%

Utilization of select specific agents

	Age 38	Age 65	Age 75	Age 85
Oxaliplatin	93%	87%	73%	39%
Capecitabine	7%	11%	19%	48%
Bevacizumab	96%	91%	79%	47%
Irinotecan	2%	6%	7%	4%

FIGURE 23

n = 53

Treatment of Widely Metastatic Disease: No Prior Adjuvant Chemotherapy

- *Patient in otherwise average health*
- *T3, N1 sigmoid tumor (non-obstructing)*
- ***12 liver metastases and diffuse peritoneal metastases***

*Would you recommend resection of the **primary** tumor?*

	Age 38	Age 65	Age 75	Age 85
Percent answering "yes"	11%	11%	2%	2%

Which of the following treatment strategies are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
Immediate resection of liver metastases alone, no postoperative systemic therapy	—	—	—	—
Systemic therapy alone	96%	96%	98%	90%
Resection of liver metastases followed by hepatic artery infusion	—	2%	—	—
Resection of liver metastases followed by hepatic artery infusion and systemic therapy	2%	2%	2%	2%
Neoadjuvant systemic therapy followed by resection of liver metastases	2%	—	—	—
Observation	—	—	—	8%

Which systemic therapy, if any, are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
FOLFOX plus bevacizumab	83%	69%	53%	15%
FOLFOX	2%	4%	5%	4%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	—	2%	13%
Capecitabine	—	2%	5%	23%
Capecitabine plus bevacizumab	—	—	2%	7%
CAPOX	—	2%	4%	7%
CAPOX plus bevacizumab	7%	9%	9%	7%
Other systemic therapy	8%	14%	20%	16%
No systemic therapy recommended	—	—	—	8%

Utilization of select specific agents

	Age 38	Age 65	Age 75	Age 85
Oxaliplatin	95%	84%	74%	36%
Capecitabine	7%	13%	24%	49%
Bevacizumab	95%	89%	81%	49%

FIGURE 24

n = 53

Treatment of Metastatic Colon Cancer: Prior Adjuvant Chemotherapy

- *Patient in otherwise average health*
- *Completed treatment **1 year ago** for a Stage III lesion with resection and adjuvant chemotherapy for 6 months*
- *Patient now presents with 12 liver metastases*

Which systemic therapy, if any, would you most likely recommend for each scenario?

	Patient received 5-FU/LV		Patient received capecitabine	
	Age 65	Age 85	Age 65	Age 85
FOLFOX plus bevacizumab	73%	15%	77%	20%
FOLFOX	—	7%	—	7%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	11%	—	15%
5-FU/LV (bolus-Roswell Park)	—	4%	—	7%
Capecitabine	—	13%	—	6%
Capecitabine plus bevacizumab	2%	11%	—	2%
CAPOX	—	7%	—	6%
CAPOX plus bevacizumab	9%	8%	4%	6%
FOLFIRI plus bevacizumab	8%	—	5%	—
Other systemic therapy	8%	20%	14%	22%
No systemic therapy recommended	—	4%	—	9%

Utilization of select specific agents

	Patient received 5-FU/LV		Patient received capecitabine	
	Age 65	Age 85	Age 65	Age 85
Oxaliplatin	84%	37%	85%	39%
Capecitabine	11%	41%	4%	20%
Bevacizumab	98%	51%	92%	53%
Irinotecan	14%	12%	13%	8%

oxaliplatin in general, I think the standard of care is clearly a combination regimen. You would have to make a case for why you would not be able to use a combination regimen, particularly since we know that FOLFOX and CAPOX regimens are very well tolerated. In fact, rather than using the Mayo Clinic regimen, I would rather use FOLFOX, because it's better tolerated.

DR LOVE: What about the tolerability of CAPOX versus FOLFOX?

DR GROTHEY: I think there is no difference in tolerability once you have determined the right dose of capecitabine. My personal preference is for FOLFOX over CAPOX. This is more or less what is reflected in this survey. You would have to make a case as to why you would utilize CAPOX rather than FOLFOX.

The primary case to be made for selecting CAPOX over FOLFOX is convenience. There are patients that I have put on CAPOX because they want to travel. They want to be more independent.

I personally use a lot of capecitabine in combination with bevacizumab after a patient can no longer tolerate FOLFOX because of the oxaliplatin neurotoxicity. When you look at the patient who was treated one year ago for a Stage III lesion with FOLFOX, no one recommended FOLFOX re-treatment. I would have like to have seen at least one or two patients receiving FOLFOX. Interestingly, in the patient with a Stage III lesion who received six months of FOLFOX six months ago with no change in Grade II neurotoxicity, the same pattern emerges.

Colorectal Cancer Update 2004 (6)

DR LOVE: How do you generally approach

FIGURE 25

n = 53

Treatment of Metastatic Colon Cancer: Prior Adjuvant Chemotherapy

- *Patient in otherwise average health*
- *Completed treatment **1 year ago** for a Stage III lesion with resection and adjuvant **FOLFOX** for 6 months*
- *Patient now presents with 12 liver metastases*

Which systemic therapy, if any, would you most likely recommend for each scenario?

	No lingering neurotoxicity		Lingering Grade II neurotoxicity	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	13%	2%	13%
Capecitabine	—	13%	—	15%
Capecitabine plus bevacizumab	—	11%	—	9%
CAPIRI plus bevacizumab	4%	2%	2%	2%
FOLFIRI plus bevacizumab	71%	16%	64%	17%
FOLFIRI plus cetuximab	5%	2%	5%	2%
IFL plus bevacizumab	4%	—	13%	—
Irinotecan	—	4%	—	5%
Other systemic therapy	16%	32%	14%	30%
No systemic therapy recommended	—	7%	—	7%

Utilization of select specific agents

	No lingering neurotoxicity		Lingering Grade II neurotoxicity	
	Age 65	Age 85	Age 65	Age 85
Oxaliplatin	8%	4%	4%	8%
Capecitabine	6%	32%	6%	32%
Bevacizumab	91%	55%	91%	53%
Irinotecan	92%	39%	92%	34%

the patient who has relapsed after adjuvant oxaliplatin-based therapy?

DR DANIEL HALLER: My approach to patients with a colorectal cancer recurrence after adjuvant therapy depends on when the relapse occurs. Obviously, this is now an issue because of the results from the MOSAIC adjuvant trial. In a patient who relapses less than six months after adjuvant FOLFOX and still has neuropathy, I would use FOLFIRI plus bevacizumab as first-line therapy. That type of patient would need all the help available, not sequential therapy.

A patient who relapses after adjuvant FOLFOX and doesn't have neuropathy could be treated as a "virgin patient," and whichever chemotherapy regimen is best for that patient should be selected, independent of their adjuvant therapy. In those situations, I base my chemotherapy decision on the Tournigand data. Then I select the most tolerable and efficacious biologic agent and marry it to the chemotherapeutic regimen that is best for the patient.

The best regimen is dependent upon both its efficacy and toxicity. For example, the first violinist in the Philadelphia Orchestra might be treated with FOLFIRI plus bevacizumab. In my clinic, patients will not be treated with IFL plus bevacizumab; they also won't be treated with capecitabine plus bevacizumab outside of a trial. For the nonviolinist, most often FOLFOX plus bevacizumab would be selected.

In certain patients, bolus 5-FU/leucovorin — the Roswell Park regimen — plus bevacizumab, as used in the trial by Kabbinavar and one of the arms of the trial by Hurwitz, would be a reasonable option. Based on the data from the trial by Hurwitz, the efficacy of the

FIGURE 26

n = 53

Treatment of Metastatic Colon Cancer: Prior Adjuvant Chemotherapy

- *65-year-old patient in otherwise average health*
- *Completed treatment **6 months ago** for a Stage III lesion with resection and adjuvant chemotherapy for 6 months*
- *Patient now presents with 12 liver metastases*

Which systemic therapy, if any, would you most likely recommend for a patient who received the following agents as adjuvant therapy?

	5-FU/LV	FOLFOX	Capecitabine
FOLFOX plus bevacizumab	75%	4%	74%
5-FU/LV (bolus-Roswell Park) plus bevacizumab	—	—	2%
5-FU/LV (bolus-Mayo Clinic) plus cetuximab	—	—	2%
CAPOX	—	2%	—
CAPOX plus bevacizumab	7%	—	6%
CAPIRI plus bevacizumab	4%	4%	—
CAPIRI plus cetuximab	—	4%	—
FOLFIRI plus bevacizumab	6%	59%	6%
FOLFIRI plus cetuximab	—	4%	2%
IFL plus bevacizumab	2%	13%	2%
Irinotecan plus bevacizumab	2%	4%	4%
Irinotecan plus bevacizumab and cetuximab	2%	2%	2%
Oxaliplatin plus cetuximab	2%	2%	—
Cetuximab	—	2%	—
No systemic therapy recommended	—	—	—

Utilization of select specific agents

	5-FU/LV	FOLFOX	Capecitabine
Oxaliplatin	85%	8%	81%
Capecitabine	11%	10%	6%
Bevacizumab	98%	87%	96%
Irinotecan	16%	91%	16%

Roswell Park regimen plus bevacizumab is somewhere in between the efficacy for IFL alone and IFL plus bevacizumab. I believe the Roswell Park regimen plus bevacizumab is probably less efficacious than FOLFOX plus bevacizumab.

Interview, August 2005

DR LOVE: What is your take on the treatment choices in the survey for the patient with colon cancer who progresses on FOLFOX/bevacizumab?

DR GROTHEY: I would not have expected 50 percent of the physicians to select cetuximab — whether or not it is with FOLFIRI. I would have anticipated something in the range of approximately 20 percent. This is not an approved regimen in this situation and it is clearly off label. It is interesting to see that 25 percent of the patients continue to receive bevacizumab.

The idea is that with bevacizumab, you enhance the activity of chemotherapy, regardless of the type of chemotherapy. You target genetically stable

FIGURE 27

n = 53

Second-Line Therapy for Metastatic Colon Cancer

- *Patient in otherwise average health*
- *Receives **FOLFOX/bevacizumab** first line for 6 months*
- *Patient has partial response then **develops subsequent pulmonary and hepatic metastases***

Which systemic therapy, if any, would you most likely recommend second line?

	Age 38	Age 65	Age 75	Age 85
Capecitabine	2%	2%	2%	18%
CAPIRI plus cetuximab	4%	6%	9%	4%
FOLFIRI plus bevacizumab	19%	19%	15%	6%
FOLFIRI plus cetuximab	22%	19%	13%	6%
FOLFIRI	9%	9%	7%	7%
IFL plus cetuximab	6%	7%	6%	—
Irinotecan plus cetuximab	15%	15%	17%	15%
Irinotecan	9%	9%	11%	13%
Other systemic therapy	14%	14%	20%	26%
No systemic therapy recommended	—	—	—	5%

Utilization of select specific agents

	Age 38	Age 65	Age 75	Age 85
Capecitabine	8%	10%	17%	34%
Bevacizumab	25%	25%	25%	15%
Cetuximab	51%	51%	51%	34%
Irinotecan	94%	95%	93%	62%

endothelial cells and increase the delivery of chemotherapy into the tumor, where you have the anti-angiogenic effect.

Cetuximab has the same overall effect, but it is expensive and it is a last-line indication. So you can use it as a later option, particularly after second-line bevacizumab, which works in patients who have not previously received bevacizumab.

The continuation of bevacizumab in second line is really interesting. I believe that a continuation of bevacizumab is logical. However, FOLFOX/bevacizumab followed by FOLFIRI followed by irinotecan/cetuximab is perhaps the best-established sequence at present.

I personally continue bevacizumab because of the idea that it works on normal, genetically stable cells. My hypothesis is that the resistance we observe with FOLFOX/bevacizumab as first-line therapy is to FOLFOX, not to bevacizumab. Bevacizumab enhances the activity of chemotherapy; in colorectal cancer, it has been shown for 5-FU, irinotecan, cetuximab and oxaliplatin.

As we're targeting genetically stable endothelial cells that provide neovascularization to the tumor, I think it definitely makes sense to use it this way. The role of bevacizumab following disease progression, however, is unclear. This is the main reason SWOG and NCCTG will be conducting a trial, the Intergroup Bevacizumab Continuation trial, in which patients who have progressed on FOLFOX/bevacizumab or FOLFOX followed by 5-FU/leucovorin/bevacizumab will be randomly assigned to additional therapy with or without bevacizumab.

Colorectal Cancer Update 2005 (1)

DR LOVE: What is your general treatment algorithm for a patient with metastatic colon cancer?

DR HOWARD HOCHSTER: In a clinical setting, I've been comfortable using an oxaliplatin-based regimen in combination with bevacizumab as first-line therapy for patients with metastatic disease, based on the TREE study and our own

FIGURE 28

n = 53

Second-Line Therapy for Metastatic Colon Cancer

- *Patient in otherwise average health*
- *T3, N1 sigmoid tumor (non-obstructing)*
- *12 liver metastases*
- *Receives **FOLFOX/bevacizumab** first line*
- *Patient has partial response, **and after 4 months of treatment, no further reduction can be achieved***

Which of the following treatment strategies are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
Continue FOLFOX/bevacizumab	21%	21%	19%	13%
Stop oxaliplatin, continue 5-FU/bevacizumab	13%	13%	15%	15%
Stop oxaliplatin and 5-FU, continue bevacizumab	6%	6%	8%	9%
Stop oxaliplatin and bevacizumab, continue 5-FU	—	—	—	4%
Stop all therapy and observe	13%	15%	19%	29%
Stop all and switch to another regimen	47%	45%	39%	30%

If you switch to another regimen, which of the following are you most likely to recommend?

	Age 38	Age 65	Age 75	Age 85
Capecitabine	—	—	5%	25%
Capecitabine plus bevacizumab	4%	4%	9%	19%
CAPIRI plus cetuximab	—	—	5%	—
FOLFIRI plus bevacizumab	20%	21%	10%	—
FOLFIRI plus cetuximab	16%	17%	14%	6%
FOLFIRI	4%	4%	5%	6%
IFL plus bevacizumab	4%	4%	9%	—
IFL plus cetuximab	4%	4%	5%	—
Irinotecan	8%	8%	9%	13%
Irinotecan plus cetuximab	32%	30%	19%	19%
Cetuximab	—	—	5%	6%
Panitumumab	4%	4%	5%	6%
Other systemic therapy	4%	4%	—	—

Utilization of select specific agents

	Age 38	Age 65	Age 75	Age 85
Capecitabine	4%	4%	19%	44%
Bevacizumab	32%	33%	29%	19%
Cetuximab	52%	50%	48%	31%
Irinotecan	92%	91%	76%	44%

FIGURE 29

n = 53

Treatment of Metastatic Colon Cancer: No Prior Chemotherapy

*What is your typical first-, second- and third-line choice of systemic therapy for a **65-year-old chemotherapy-naïve patient with metastatic colon cancer in otherwise average health**?*

	1st-line	2nd-line	3rd-line
FOLFOX plus bevacizumab	76%	2%	—
Capecitabine	—	—	33%
CAPOX plus bevacizumab	2%	—	6%
FOLFIRI plus bevacizumab	4%	20%	—
FOLFIRI plus cetuximab	2%	20%	2%
FOLFIRI	—	9%	—
Irinotecan plus cetuximab	—	15%	26%
Cetuximab	—	—	6%
Other systemic therapy	16%	34%	22%
No systemic therapy recommended	—	—	5%

Utilization of select specific agents

	1st-line	2nd-line	3rd-line
Oxaliplatin	86%	12%	12%
Capecitabine	8%	12%	51%
Bevacizumab	89%	38%	11%
Cetuximab	4%	43%	53%
Irinotecan	10%	84%	36%

personal experience. The best data for improved time to progression, response rate and survival are with bevacizumab as first-line therapy, and I am most comfortable using oxaliplatin in the first-line setting. Therefore, I tend to use FOLFOX with bevacizumab in patients not enrolled on a protocol. We have seen nice responses and patients staying on those regimens for a long time.

Irinotecan and cetuximab would be very reasonable second-line options, whether it's with single-agent irinotecan and adding in cetuximab at the time of progression or, taking out the reimbursement issues, starting with both cetuximab and irinotecan together, which would make sense.

The third-line setting is wide open, and clinical trials would definitely have a value in identifying new agents.

Colorectal Cancer Update 2005 (4)

DR PHILIP: For patients with disease that has progressed on an oxaliplatin-based treatment, we move to an irinotecan-based therapy. The question becomes, Do we use irinotecan as a single agent or in combination with a fluoropyrimidine (eg, capecitabine or 5-FU/leucovorin)? The third- or fourth-line options would be any of these agents with or without cetuximab.

Interview, August 2005

DR LOVE: According to the physicians' responses, a substantial number of doctors continue to order EGFR testing (Figure 30). Why do you think this is occurring?

DR GROTHEY: I believe that a number of physicians request EGFR testing to avoid the hassle of communicating with the insurance company. If the test results are positive, there is no need to worry about reimbursement issues. However, if the results are negative, the doctor has to struggle to make a case to utilize cetuximab. We need to translate to the community oncologists that this test is not really necessary.

Another interesting question is, Do you test in the primary tumor for EGFR in colon cancer? In breast cancer patients, we automatically determine the hormone receptor status of the primary tumor. For the colon cancer patient, testing the primary tumor for EGFR positivity is not needed. If you utilize cetuximab, it's better to use it with irinotecan

FIGURE 30

n = 53

Clinical Use of EGFR Testing

Do you generally order EGFR staining/testing on tumor specimens in each of the following settings?

	Primary tumors	Metastatic disease
Yes	42%	62%
No	58%	38%

Which of the following best describes how frequently you base decisions on the positivity or negativity of EGFR staining/testing results?

Always	35%
Sometimes	50%
Rarely	12%
Never	3%

If you wanted to use cetuximab in a patient whose tumor tested negative for EGFR, would you still treat the patient with cetuximab?

Yes	58%
No	42%

FIGURE 31

n = 53

Clinical Use of Irinotecan and Cetuximab

In your patients with metatstatic disease who experience disease progression on an oxaliplatin-containing regimen, how do you generally proceed when you want to begin treatment with irinotecan and cetuximab?

Start irinotecan and add cetuximab if no response	32%
Start irinotecan and add cetuximab upon disease progression	25%
Start both irinotecan and cetuximab simultaneously	43%

(Figure 31). Although it is logical to say, "If you have first-line oxaliplatin, you don't necessarily need cetuximab" because it is not approved and it is expensive. Additionally, it is not as beneficial in a salvage therapy setting.

Colorectal Cancer Update 2005 (3)

DR LOVE: Should the decision whether or not to administer cetuximab be based on EGFR testing/staining results?

DR SALTZ: We published an article in the *Journal of Clinical Oncology* that reports activity with cetuximab in colorectal cancer in tumors that do not express the EGFR by immunohistochemistry (IHC).

These are very compelling data. We all wanted to believe that EGFR would be an important prognostic indicator, but our technology for assessing EGFR expression is flawed.

We generally use the primary tumor as the basis for the EGFR status of the metastasis, but that appears to be inaccurate. Data show that EGFR degrades over time.

At this time, no clinical decision should be made on the basis of EGFR staining. Specifically, no patient should be excluded from a therapy — cetuximab or otherwise — simply because their IHC staining for EGFR is negative and, just as importantly, no patient should be treated with these agents simply because the tumor is strongly EGFR positive.

Interview, August 2005

DR LOVE: The number of physicians who believe that capecitabine can be regarded as equivalent to 5-FU in the neoadjuvant, adjuvant and metastatic settings is pretty intriguing. It appears as though they are influenced by the results of the X-ACT trial. What is your interpretation of this?

DR GROTHEY: They may believe that capecitabine is a substitute for 5-FU in these settings; however, the dosing of capecitabine has not yet been well defined in the United States. A large trial in patients with colon cancer is being conducted, which utilizes a dose of 1,000 mg/m^2 twice a day in a one week on, one week off schedule.

Personally, in the adjuvant setting, I start with a dose of 2,500 mg/m^2 in two divided doses and then decrease as needed. In the metastatic setting, I prefer to start with 2,000 mg/m^2 in two divided doses. When dosing capecitabine with oxaliplatin, I utilize 850 mg/m^2 twice a day, based on the American experience.

Colorectal Cancer MTP September 2005

DR ROBERT WOLFF: The maximum dose of capecitabine that I use as a single agent is 2,000 mg/m^2 in two divided doses. If I combine capecitabine with another agent, including irinotecan, oxaliplatin, or radiation, the dose is decreased to the 1,500 to 1,800 mg/m^2 range. If a patient experiences toxicity, the dose is reduced accordingly.

Colorectal Cancer Update 2004 (5)

DR LOVE: What action do you instruct your patients to take if they experience capecitabine-related toxicity?

FIGURE 32

n = 103

Capecitabine as a Substitute for 5-FU

Do you believe capecitabine can be regarded as a substitute for 5-FU in combination regimens with irinotecan and/or oxaliplatin?

	Neoadjuvant or adjuvant setting	Metastatic setting
Yes	65%	81%
No	15%	9%
Not sure	20%	10%

Do you use capecitabine in your practice?

Yes	97%
No	3%

n = 99

How do you generally dose capecitabine monotherapy when using capecitabine in a 2 weeks on/1 week off schedule?

2,500 mg/m^2 in 2 divided doses (1,250 mg/ m^2 BID)	20%
2,000 mg/m^2 in 2 divided doses (1,000 mg/m^2 BID)	67%
1,700 mg/m^2 in 2 divided doses (850 mg/m^2 BID)	7%
1,650 mg/m^2 in 2 divided doses (825 mg/m^2 BID)	2%
Other	4%
None (I don't use capecitabine monotherapy)	—

n = 96

How do you generally dose capecitabine when using in combination with oxaliplatin?

2,500 mg/m^2 in 2 divided doses (1,250 mg/ m^2 BID)	3%
2,000 mg/m^2 in 2 divided doses (1,000 mg/m^2 BID)	39%
1,700 mg/m^2 in 2 divided doses (850 mg/m^2 BID)	25%
1,650 mg/m^2 in 2 divided doses (825 mg/m^2 BID)	15%
Other	6%
None (I don't use capecitabine in this combination)	12%

n = 99

How do you generally schedule capecitabine?

2 weeks on, 1 week off	95%
1 week on, 1 week off	—
3 weeks on, 1 week off	1%
Monday through Friday on, weekends off	2%
Other	2%
None (I don't use capecitabine)	—

DR CASSIDY: We make an effort to ed- ucate patients about the potential for diarrhea because if patients develop diarrhea, they may become dehydrated and require hospitalization. Sometimes diarrhea is associated with neutropenia. Diarrhea and neutropenia together are dreaded side effects of the fluoro pyrimidines.

I tell my patients they should stop treatment and inform us if they are having diarrhea more than five times in a 24-hour period.

Hand-foot syndrome is a bit more subtle. Patients often develop a minor degree of hand-foot syndrome with the first cycle of capecitabine, and it may be worse with the second cycle. At that point, we reduce the capecitabine dose.

Because of that strategy, I don't see many patients with severe hand-foot syndrome. We also tell patients to stop treatment if they develop redness of their hands or feet with pain that interrupts their level of functioning.

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FIGURE 33

n = 99

Tolerability of Capecitabine Therapy

What percentage of your patients on capecitabine or capecitabine-containing regimens develop hand-foot syndrome that requires dose reduction or delay?

Mean	33%

FIGURE 34

n = 99

Discontinuation of Multivitamins for Patients Taking Capecitabine

How often, if ever, do you instruct patients to discontinue taking multivitamins when you prescribe capecitabine?

Always	20%
Sometimes	20%
Rarely	29%
Never	31%

FIGURE 35

n = 99

Instructions to Patients Who Experience Capecitabine-Related Hand-Foot Symptoms

Which of the following best describes how you instruct your patients taking capecitabine to contact your office if they experience the following hand-foot related symptoms?

	Redness	Pain	Redness and pain	Blisters
Contact office	68%	62%	40%	25%
Discontinue and contact office	15%	38%	60%	75%
No action	17%	—	—	—

FIGURE 36

n = 99

Instructions to Patients Who Experience Capecitabine-Related Gastrointestinal Symptoms

Which of the following best describes how you instruct your patients taking capecitabine to contact your office if they experience the following gastrointestinal symptoms?

	Loose stools	Abdominal cramping	Diarrhea
Contact office	65%	50%	44%
Discontinue and contact office	19%	46%	56%
No action	16%	4%	—

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FIGURE 37

n = 50

Treatment of Node-Negative Rectal Cancer

- *Man in average health*
- *T3, N0 rectal cancer by endoscopic ultrasound*

Which treatment strategy would you most likely recommend for a lesion located at each of the following distances?

	8 cm from anal verge		12 cm from anal verge	
	Age 65	Age 85	Age 65	Age 85
Immediate resection	4%	44%	8%	46%
Resection followed by adjuvant radiochemotherapy	16%	6%	30%	12%
Resection followed by adjuvant chemotherapy	2%	4%	2%	6%
Resection followed by radiotherapy	2%	12%	2%	14%
Neoadjuvant radiotherapy followed by resection and chemotherapy	2%	6%	4%	2%
Neoadjuvant radiochemotherapy followed by resection and chemotherapy	54%	12%	42%	10%
Neoadjuvant radiochemotherapy followed by resection alone	16%	16%	10%	10%
Neoadjuvant chemotherapy followed by resection	—	—	—	—
Neoadjuvant chemotherapy followed by resection and radiochemotherapy	4%	—	2%	—

Colorectal Cancer Update 2004 (6)

DR HALLER: Since the 1991 consensus conference, the American model for the management of rectal cancer had generally consisted of surgery followed by postoperative chemoradiation therapy for patients with Stage II or Stage III disease, but I now believe that preoperative chemoradiation therapy is the gold standard for patients with rectal cancer.

Currently, both adjuvant and neoadjuvant chemoradiation therapy are acceptable options, but based on the German Rectal Cancer trial comparing preoperative and postoperative chemoradiation therapy, more people will be switching to the preoperative model. In the United States, preoperative or postoperative radiation therapy alone would be an unacceptable option.

We are mostly using neoadjuvant chemoradiation therapy, so I believe a standard regimen would consist of infusional 5-FU and radiation therapy. According to Joel Tepper's presentation of the Intergroup-0114 trial results, the bolus 5-FU regimens have more toxicity and equal efficacy compared to the infusional regimen; however, patients who are confounded by infusional therapy might choose one of the bolus regimens.

In patients who do not want infusional therapy, the cumulative data for capecitabine suggest that it could be substituted. I'm not willing to simply say capecitabine can be substituted in every patient, but I believe it's an option.

Colorectal Cancer Update 2005 (5)

DR LOVE: What is your general approach for neoadjuvant chemotherapy for patients with rectal cancer?

DR GROTHEY: The Mayo Clinic is a conservative institution, and we are using continuous-infusion 5-FU in this situation, but I think the data are compelling that capecitabine can be used as a substitute. Outside of clinical trials, we shouldn't be afraid to use capecitabine. Having said that, this is currently being investigated in NSABP-R-04, which compares radiation therapy with either capecitabine or infusional 5-FU.

A second randomization will evaluate the addition of oxaliplatin. The future involves increasing the efficacy of neoadjuvant chemotherapy because in the end, patients eventually succumb to distant metastases.

Adding more effective chemotherapy up front in combination with radiation therapy will allow us to maintain systemically active chemotherapy, which might attack micrometastases as early as possible.

I'm sure it will enhance the pathologic complete response rate following chemoradiation therapy, which is a predictor for overall survival. Hence, we'll have local control improvement, and with the use of combination chemotherapy early on, we might have an impact on distant metastases.

Inteview, August 2005

DR LOVE: Can you describe a rectal cancer case where you would not recommend neoadjuvant therapy?

DR GROTHEY: In a situation where the lesion is high — 12 centimeters from the anal verge — I would recommend resection followed by chemotherapy. How-

FIGURE 38

n = 50

Treatment of Node-Positive Rectal Cancer

- *Man in average health*
- *T3, N1 rectal cancer (2 enlarged lymph nodes on endoscopic ultrasound)*

Which treatment strategy would you most likely recommend for a lesion located at each of the following distances?

	8 cm from anal verge		12 cm from anal verge	
	Age 65	Age 85	Age 65	Age 85
Immediate resection	2%	26%	—	28%
Resection followed by adjuvant radiochemotherapy	14%	10%	24%	8%
Resection followed by adjuvant chemotherapy	2%	4%	6%	22%
Resection followed by radiotherapy	—	22%	—	12%
Neoadjuvant radiotherapy followed by resection and chemotherapy	6%	8%	6%	8%
Neoadjuvant radiochemotherapy followed by resection and chemotherapy	68%	18%	58%	14%
Neoadjuvant radiochemotherapy followed by resection alone	6%	8%	4%	8%
Neoadjuvant chemotherapy followed by resection	—	4%	—	—
Neoadjuvant chemotherapy followed by resection and radiochemotherapy	2%	—	2%	—

ever, the majority of respondents selected neoadjuvant radiochemotherapy. The decision not to utilize neoadjuvant therapy is determined by the location of the lesion. The higher the tumor is located, the less important radiation becomes.

In discussing neoadjuvant strategies, the key issue is the radiation component, and if we want to extrapolate, we have some data from the Dutch trial looking at the location of the tumor relative to the risk of recurrence. For a patient who has a tumor located 12 centimeters from the anal verge, recurrence rates — even without radiation — are less than five percent.

DR LOVE: In terms of the general recommendation for neoadjuvant therapy in patients with rectal cancer, most physicians use intravenous 5-FU as opposed to capecitabine. What is your opinion on that?

DR GROTHEY: This is clearly because we don't have any Phase III neoadjuvant data with capecitabine in rectal cancer available yet. I was actually surprised that for older-age patients, the recommendation for capecitabine increased to almost one fourth of patients. This is interesting, and it shows potential for this drug because apparently it's perceived as more tolerable for elderly patients. If we are able to document that capecitabine is equally effective — which is a matter of ongoing trials — then it could be a nice replacement for intravenous 5-FU. I think in the future we will see more usage of CAPOX.

The primary reason we use capecitabine is patient convenience. I believe that 5-FU and capecitabine are interchangeable in terms of efficacy. In dosing capecitabine, I tend to use capecitabine twice a day Monday through Friday during radiation as a radiosensitizer. We tell patients not to use multivitamins while they are taking capecitabine.

DR LOVE: How about CAPOX in the neoadjuvant setting?

DR GROTHEY: To be honest, I thought it would have been used more. We do have published data on that, including results published in the *Journal of Clinical Oncology* over two years ago. So, you could use it with the idea that oxaliplatin adds significant efficacy in terms of the systemic recurrence. However, based on this survey, it does not appear that CAPOX is utilized in the neoadjuvant setting for rectal cancer.

Colorectal Cancer Update 2005 (4)

DR LOVE: What do you think about NSABP-R-04, evaluating preoperative radiotherapy with capecitabine versus 5-FU and the second randomization to add oxaliplatin?

DR PHILIP: I have mixed thoughts with respect to the first randomization in NSABP-R-04 of infusional 5-FU or capecitabine because I already use capecitabine with radiation therapy. We started using this at our institution several years ago when there weren't any protocols available. We reviewed and published our experience confirming the safety of this approach; therefore, we have been using capecitabine routinely in these patients in the clinical setting.

I am interested in the second randomization in the trial using oxaliplatin. I have started using that in combination with radiation therapy in some, but not all, patients. For example, I have used oxaliplatin in healthier patients

FIGURE 39

n = 50

Neoadjuvant and Adjuvant Therapy for Rectal Cancer

- *Patient in average health*
- *T3 rectal cancer*
- *Lesion is 8 cm from the anal verge*

*Which **neoadjuvant** systemic therapy, if any, would you most likely recommend?*

	Node-negative (N0)		Node-positive (N1)	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park)	8%	6%	10%	4%
5-FU/LV (bolus-Mayo Clinic)	2%	4%	2%	6%
5-FU/LV (infusion)	26%	14%	22%	10%
5-FU/LV (infusion) + bevacizumab	4%	2%	2%	2%
Infusional 5-FU (no LV)	32%	18%	28%	20%
Infusional 5-FU (no LV) + bevacizumab	—	2%	—	2%
Infusional 5-FU + oxaliplatin (no LV)	2%	—	—	—
FOLFOX	6%	—	10%	2%
FOLFOX + bevacizumab	4%	—	8%	—
FOLFIRI	—	—	—	—
Capecitabine	8%	22%	8%	18%
CAPOX	4%	—	4%	—
No systemic therapy recommended	4%	32%	6%	36%

*Which **adjuvant** systemic therapy, if any, would you most likely recommend?*

	Node-negative (N0)		Node-positive (N1)	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park)	14%	8%	8%	6%
5-FU/LV (bolus-Mayo Clinic)	2%	6%	2%	6%
5-FU/LV (infusion)	34%	18%	24%	20%
5-FU/LV (infusion) + bevacizumab	2%	2%	2%	2%
FOLFOX	26%	—	42%	—
FOLFOX + bevacizumab	4%	4%	6%	4%
IFL + bevacizumab	2%	—	2%	—
Infusional 5-FU (no LV)	2%	—	2%	—
Capecitabine	6%	24%	6%	30%
CAPIRI	—	2%	—	2%
CAPOX	4%	—	2%	—
FLOX	2%	2%	4%	4%
No systemic therapy recommended	2%	34%	—	26%

FIGURE 40

n = 50

Treatment of Rectal Cancer After Neoadjuvant Therapy

- *Man in average health*
- *T3 rectal cancer by endoscopic ultrasound*
- *Lesion is 8 cm from the anal verge*
- ***Undergoes neoadjuvant chemoradiation therapy with CAPOX***
- *Upon resection, there is complete pathologic response*

Which postoperative systemic therapy, if any, would you most likely recommend?

	Node-negative (N0)		Node-positive (N1)	
	Age 65	Age 85	Age 65	Age 85
5-FU/LV (bolus-Roswell Park)	6%	10%	8%	10%
5-FU/LV (bolus-Mayo Clinic)	2%	4%	4%	4%
5-FU/LV (infusion)	4%	4%	8%	8%
FOLFOX	26%	—	34%	—
FOLFOX + bevacizumab	—	—	2%	4%
FOLFIRI + bevacizumab	2%	2%	2%	2%
IFL + bevacizumab	—	—	2%	—
Capecitabine	4%	12%	6%	18%
CAPIRI	—	2%	—	—
CAPOX	22%	2%	22%	4%
FLOX	2%	—	—	—
Bevacizumab	2%	2%	—	—
No systemic therapy recommended	30%	62%	12%	50%

with a better performance status and in patients with whom I have special concerns about not being able to preserve the sphincter, where I want to obtain a maximum pathologic response.

Colorectal Cancer Update 2005 (5)

DR CHRISTOPHER CRANE: The NSABP designed R-04 to compare capecitabine with venous infusional fluorouracil in patients receiving preoperative radiotherapy for locally advanced rectal cancer, but I don't believe such a trial is necessary. The study design has now been changed to incorporate oxaliplatin, which I believe is our only opportunity to understand whether that drug will benefit such patients. The final design is a two-by-two randomization of infusional 5-FU versus capecitabine with a second randomization to oxaliplatin or not.

I believe everyone will agree that the amended design is better. If I had to guess what this trial would show, my guess would be that capecitabine will be equally effective but less toxic than infusional 5-FU and that oxaliplatin will improve response but not long-term outcome.

DR LOVE: What about the role of neoadjuvant bevacizumab in the treatment of rectal cancer?

DR CRANE: Bevacizumab has been proven in many disease sites to improve the effects of chemotherapy. Approximately three years ago, before it was approved with radiation therapy, we had the opportunity to investigate this agent. We conducted a Phase I trial of 50 patients with pancreatic cancer (ID02-146) who received capecitabine, radiation therapy and bevacizumab, and the results were very exciting. In the patients who received five mg/kg of bevacizumab every two weeks, which was the final recommended dose, we saw a 50 percent partial response rate. Six of the 12 patients had their tumors shrink by 50 percent, which is a "high bar" endpoint for pancreatic cancer.

The regimen was well tolerated, and the RTOG is now conducting a Phase II study with bevacizumab, capecitabine and radiation therapy in patients with locally advanced pancreatic cancer that cannot be surgically excised (RTOG-0411).

At MD Anderson, we currently

FIGURE 41

n = 50

Duration of Adjuvant Chemotherapy for Rectal Cancer

What is the typical duration of the adjuvant or postoperative chemotherapy regimen you generally recommend at each of the following ages?

	Age 38	Age 65	Age 75	Age 85
Four months	24%	30%	38%	32%
Six months	74%	68%	60%	40%
Other	2%	2%	2%	—
None/do not recommend adjuvant chemotherapy	—	—	—	28%

FIGURE 42

n = 50

Locoregional Therapy for Rectal Cancer

	Median
Percent of patients referred to you after primary resection of their rectal cancer who underwent total mesorectal excision	46%
Percentage of patients with node-positive rectal cancer who receive preoperative radiation with chemotherapy	65%
Percentage of patients with rectal cancer who undergo APR for their cancer	39%

have a neoadjuvant Phase II study with the same regimen in patients presenting with locally advanced rectal cancer. Investigators at Mass General published a Phase I trial in *Nature Medicine* and presented it at ASCO in 2004. In this trial, patients with primary rectal cancer received neoadjuvant bevacizumab, 5-FU and radiotherapy.

It was initially reported that five out of six patients had either microscopic residual or complete pathologic responses to the preoperative regimen, and I know from personal communication that these results are holding up, and now 11 out of 12 patients have had this response. In addition, no surgical catastrophes have been encountered following this regimen as long as six weeks elapse before the patient undergoes surgery.

These data open a lot of doors for the future of these patients and chemoradiation in general. In clinical trials, we will be evaluating bevacizumab's ability to enhance the effect of radiation therapy.

One of our focuses at MD Anderson is organ preservation, and with bevacizumab, instead of removing radiation therapy from the neoadjuvant treatment equation, this agent, when used with radiation therapy, may lessen how radical a surgery needs to be. I want to stress that this is investigational, but the responses are better, and I believe they will also translate into better local control.

Colorectal Cancer Update 2005 (6)

DR VENOOK: Bevacizumab obviously has great potential in the rectal cancer setting. Chris Willett's paper in *Nature Medicine* was a very clever and interesting development. These were patients with primary or locally advanced rectal cancer who received a single dose of bevacizumab and, in 12 days, were re-evaluated with imaging and biopsy and then received 5-FU/radiotherapy. Blood flow, blood volume and tumor vasculature all were impacted by a single dose of bevacizumab to these tumors that were in situ. So certainly, there's biological activity of bevacizumab alone, and I think this really needs to be looked at in neoadjuvant studies.

DR HOFF: We try to put these patients on protocol as much as possible. Right now, we have a preoperative Phase II protocol with capecitabine, bevacizumab and radiation therapy. If patients cannot participate in this study, we usually use preoperative capecitabine with radiation therapy.

Colorectal Cancer Update 2004 (4)

DR LOVE: What are your thoughts regarding bolus 5-FU, infusional 5-FU and capecitabine for the adjuvant treatment of rectal cancer?

DR WOLFF: In the adjuvant setting, when infusional 5-FU rather than bolus 5-FU is combined with radiation therapy, disease-free and overall survival are improved. Infusional 5-FU is a better radiosensitizing agent. The advantage of infusional 5-FU with radiation therapy is probably more of a systemic than a local control benefit.

An Intergroup trial published in *The New England Journal of Medicine* demonstrated a trend toward better local control using infusional 5-FU compared to bolus 5-FU. That study is proof of the

principle that infusional 5-FU is a superior treatment modality when combined with radiation therapy.

Capecitabine is an interesting alternative to infusional 5-FU for several reasons. With infusional 5-FU, catheter-related problems can develop, such as thrombosis and infection. Additionally, patients are required to carry an ambulatory pump. When the pump is on for a couple of weeks it's no big deal, but generally by the fifth week of radiation therapy, patients are tired of it. Capecitabine is a nicer route of administration.

Additionally, capecitabine is a prodrug, and it has to be converted to 5-FU at the intracellular level. One of the enzymes responsible for that conversion is thymidine phosphorylase (TP), which is expressed in higher concentrations in the rectal mucosa.

At the biological level, that may mean that the rectum, the rectal mucosa and the tumor cells have a higher intracellular concentration of 5-FU, leading to both an active cytotoxic benefit and more radiosensitization. We have therefore been interested in evaluating capecitabine as a radiosensitizer compared to infusional 5-FU.

In the future, we will combine capecitabine with bevacizumab. That trial is not yet open, but we will pursue not only conventional cytotoxic agents with radiation but also utilize biologic agents such as bevacizumab for this group of patients.

Interview, August 2005

DR LOVE: What is your opinion of the survey findings related to locoregional therapy for rectal cancer?

DR GROTHEY: The number of patients who have undergone total mesorectal resection — 50 percent — seems to be quite low. Interestingly, the number of patients who have undergone APR seems a little bit high — it should be under 20 percent.

Of course, this could be due in part to the definition of what qualifies as rectal cancer. Is the 12-centimeter tumor still rectal cancer, or is it sigmoid cancer? This should be factored into the equation; when the oncologists answered the question, were they only thinking of low rectal cancers? We define rectal cancer as a lesion located between the anal verge and up to 12 centimeters from the anal verge. Our goal is to reduce the need for APR to less than 20 percent.

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This program is supported by an education grant from Roche Laboratories Inc.

This program is supported by an education grant
from Roche Laboratories Inc.

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Last review date: November 2005
Release date: November 2005
Expiration date: November 2006
Estimated time to complete: 2.00 hours