Management of Cancer of the Colon and Rectum in the Adjuvant and Metastatic Settings

Adjuvant Systemic Therapy for Colon Cancer
Treatment of Metastatic Colon Cancer
Neoadjuvant and Adjuvant Treatment of Rectal Cancer

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A Survey Comparing Practice Patterns of GI Clinical Investigators and Practicing Oncologists

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PowerPoint files of the graphics contained in this document can be downloaded at www.ResearchToPractice.com/POC/Colorectal.
OVERVIEW OF ACTIVITY
It is important for the practicing oncologist to be aware of similarities and differences between his or her practice patterns, those of others in community practice and those of colorectal cancer clinical investigators. 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. Also included are clinical investigator commentary and references addressing these issues. This CME program will provide medical oncologists with information on national cancer patterns of care to assist with the development of clinical management strategies.

LEARNING OBJECTIVES
• Compare management strategies of community oncologists and cancer clinical investigators in the neoadjuvant, adjuvant and metastatic settings, and use this information to develop practical colorectal cancer treatment algorithms.
• Identify clinical scenarios for which relative agreement and heterogeneity exist in patterns of care for colorectal cancer, and apply these findings to individualized treatment plans for patients.
• Counsel patients with colorectal cancer about the benefits and risks of multiple acceptable treatment options when they exist.
• Recognize the rate at which practice-changing clinical research affects oncologists’ decision-making, and explain how this affects patient access to standard and novel therapeutics.
• Recall the design and eligibility criteria for ongoing colorectal cancer clinical trials, and consider appropriate patients for study participation.

ACCREDITATION STATEMENT
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Research To Practice designates this educational activity for a maximum of 2 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY
To receive credit for this activity, the participant should read the monograph and complete the Educational Assessment and Credit Form located in the back of this book or on our website at www.ResearchToPractice.com/POC/Colorectal. PowerPoint files of the graphics contained in this document can be downloaded at www.ResearchToPractice.com/POC/Colorectal.

COMMENTS IN THIS MONOGRAPH
To highlight the practice issues presented in this survey, a number of excerpts are included from CME publications. For the related audio programs from Research To Practice, please visit www.ResearchToPractice.com.

ABOUT THIS SURVEY
This survey was completed in October 2008 by 100 community-based medical oncologists and 25 oncologists who specialize in gastrointestinal cancer management (see list on page 4) in the United States. The community-based oncologists were randomly selected from a proprietary mailing list used by Research To Practice for distribution of its CME programs, and the specialists included physicians who have participated in education programs with Research To Practice and others referred for this project.
FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:


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Editor’s Note: Lots of questions but not a lot of really good answers

The enclosed survey of 25 US-based clinical investigators specializing in GI cancers, and 100 randomly selected medical oncologists in general practice is the fourth Patterns of Care study we have conducted on the management of colorectal cancer. For this particular report, in addition to our tried-and-true case-based questions, we’ve added a new and interesting feature. Based on input obtained during dozens of conversations and roundtables with clinical investigators and docs in practice, we identified eight clinical decisions that meet the following criteria:

1. The scenario is relatively common in clinical practice.
2. The scenario is the focus of current clinical research efforts.
3. Investigators and docs in practice often consider the scenario challenging or problematic.

As we did in a similar breast cancer survey that introduced this new quantitative approach to CME needs assessment, we asked the respondents to tell us how often they encounter these scenarios and relate, on a 1-10 scale, to what extent they would value CME platforms (such as this one) that attempt to provide input from their peers on these issues. What these different scenarios are and how they stack up against one another in the minds and practices of medical oncologists can be seen in the unique depiction that we like to call a table graph (Figures 2-3). What is not readily apparent from this graphic but particularly striking is that while many docs are making choices in these common and important clinical situations that must be categorized as state of the art, the available treatment options for patients facing them are suboptimal and cry out for new interventions with better outcomes. Below find a summary of each.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com

1. Scenarios at initial diagnosis

Primary locally advanced rectal cancer

*Approximate number of times a year oncs in practice encounter this scenario:* 12

*Fraction of oncs in practice who rate their interest in CME for this decision a 9 or 10:* 25%

*Comment:* Oncologists are often involved in deciding whether to use preop chemoradiation therapy and, later on, postop systemic treatment, and with both there is considerable debate about issues such as selection of patients and choice of agents. From the patient’s perspective, the result may determine not only whether a recurrence is later diagnosed but also if sphincter-sparing surgery can be performed.

Adjuvant systemic therapy

*Approximate number of times a year oncs in practice encounter this scenario:* 16

*Fraction of oncs in practice who rate their interest in CME for this decision a 9 or 10:* 38%

*Comment:* As in lung and breast cancer, these decisions are particularly challenging because even in Stage III disease, most patients do not benefit from treatment. We know from a recent survey of 85 patients going through the adjuvant colon cancer experience that when first meeting with their oncologist, most are receiving Adjuvant!-like numbers on the risk of recurrence with and without treatment.

This is a major departure from just a few years ago, when even people with breast cancer were generally not receiving this information. The initial findings from this fascinating project also suggest that the perception of benefit from treatment is much greater than clinical trials actually document.

Primary colon or rectal cancer and simultaneous metastases

*Approximate number of times a year oncs in practice encounter this scenario:* 10

*Fraction of oncs in practice who rate their interest in CME for this decision a 9 or 10:* 39%

*Comment:* The thinking about these relatively common scenarios has changed dramatically in the last few years with an increasing emphasis on starting systemic therapy first rather than reflexively recommending surgery. Most of these patients are not curable, and the goal — as currently being studied in NSABP trial C-10 — is to palliate by avoiding the discomfort of major surgery during what is often a limited period of survival.

2. Scenarios that occur primarily with patients treated previously

During a recent Meet The Professors audio recording session in Washington, DC, Dr Ken Hoffman, a community-based practitioner in Teaneck, New
Editor’s Note (Continued)

Jersey, commented in his always eloquent and thoughtful manner about the deep emotional wound experienced by both physician and patient when cancer recurrence is diagnosed after adjuvant therapy.

In particular, patients who have struggled through adjuvant cytotoxics are particularly crestfallen when only two to three years later, the failure of this treatment becomes evident.

First-line systemic therapy for metastatic disease

Approximate number of times a year oncs in practice encounter this scenario: 20

Fraction of oncs in practice who rate their interest in CME for this decision a 9 or 10: 42%

Comment: Many clinical investigators believe the benefits of FOLFOX/bev and FOLFIRI/bev in patients with K-ras wild-type tumors are similar, and the decisions might be made based on relative toxicities, and patient preferences and concerns about hair loss and diarrhea (FOLFIRI) versus FOLFOX (neuropathy). This is a painful choice when the goal is palliation, and bevacizumab adds the risk of bowel perforation and hypertension.

Second-line systemic therapy for metastatic disease

Approximate number of times a year oncs in practice encounter this scenario: 16

Fraction of oncs in practice who rate their interest in CME for this decision a 9 or 10: 37%

Comment: The options here are even more diminished, and at this point the management of tumor-related symptoms may become more much more challenging, with hospice care not too far in the future. Physicians and patients must sift through potential options based on evolving research reports in this setting, where realistic benefits are minimal but often overstated, as commented on by Dr Leonard Saltz in the November 1 issue of the JCO (Figure 1).

One of the important roles of CME here is to separate what Len correctly calls the “hype” of cancer research from the reality of it, as in his example of a recent trial report where the “statistically significant” improvement in overall survival was six weeks. Again, these modest benefits occur in the setting of treatments that often carry significant toxicity.

Potentially resectable metastases

Approximate number of times a year oncs in practice encounter this scenario: 7

Fraction of oncs in practice who rate their interest in CME for this decision a 9 or 10: 46%

Comment: The consideration here is primarily hepatic resection, a procedure resulting in far greater risk and morbidity than surgery on the primary tumor. Although most investigators believe that a substantial number of these patients in community practice may not be fully evaluated for this potentially curative intervention, the sad fact is that with current available predictive and prognostic tools, most of these patients will die of progressive disease despite this very major surgery.

Commentary by Dr Len Saltz “Progress in Cancer Care: The Hope, the Hype and the Gap between Reality and Perception”

“Many of the recent advances that have been made in cancer care have been, although arguably important, relatively modest. Sometimes, however, these modest, incremental advances have been presented, discussed, or at least perceived by medical and lay audiences alike, as major advances or so-called breakthroughs. …

A recent press release about a clinical trial result quoted a knowledgeable individual as saying how gratified he was that patients could now be offered a treatment with a ‘significant’ survival advantage. Few doctors, fewer laymen, and even fewer patients reading that statement would have assumed that in fact this advantage was an extension of median survival by a total of 6 weeks. The more precise term to use would have been a ‘statistically significant’ survival advantage. …

We have made many important advances in cancer treatment over the past decades, and we can be proud of these accomplishments, but many of the steps forward have been small ones, and there is still much more work to be done. It is counterproductive to foster the perception of greater success than has actually been achieved, as this would risk jeopardizing our credibility, setting our patients up for disappointment, and fostering a complacent acceptance of modest, incremental advances in cancer drug development.”

DR ALAN P VENOOK: We are enrolling patients on ECOG-E5202, which I believe is an incredibly important study. Patients with Stage II disease are risk-stratified based on the molecular features of their cancer. Patients at low risk, who are expected to comprise approximately 60 percent of the patients, are observed. Patients at high risk — deletion on 18q, microsatellite stability — receive FOLFOX or FOLFOX/bevacizumab.

I believe that’s such an absolutely important study to distinguish who doesn’t need chemotherapy and to see whether the data hold up. It would be wonderful to save so many patients from exposure to chemotherapy.

DR JOHN L MARSHALL: For patients with Stage II disease, it’s clear that we’re dramatically overtreating. We’re administering chemotherapy to 100 patients to help what may be three to six people in the long run. I’m not fundamentally against that, but I would like to figure out who may benefit and administer chemotherapy to them. We are trying to recruit to a clinical trial (ECOG-E5202) that groups patients according to the tumor’s genetic markers, and we’ve had some luck.

For the most part, patients are interested in pursuing chemotherapy. Patients with education — whether it’s fair education or not — will opt to receive chemotherapy. My feeling is that community physicians are treating more of these people than they were before. They’re also using a lot more capecitabine in this patient population.
the potential benefit of adjuvant therapy for the population as a whole is marginal. If you were to treat all patients who have Stage II colon cancer with adjuvant therapy, the absolute benefit would probably be in the range of five percent or less for the most active chemotherapy regimen.

The challenges are in defining which patients are at the greatest risk of relapse from the group of patients with Stage II disease and in selecting those patients for adjuvant therapy because their potential for benefit is greater. Patients have different values with regard to the tradeoffs of the potential benefits and side effects. This requires a discussion about the option of adjuvant therapy — the potential hazards, which are well defined, and the potential benefits, which are less well defined for any individual.

The doctor and patient have to come to an agreement and understanding about what is best for that individual patient. With regard to the issue about whether all patients with Stage II colon cancer should be referred to a medical oncologist, my answer is that all of those patients should engage in a discussion about adjuvant therapy and whether it’s right for them.

Colorectal Cancer Update Issue 4, 2007

**DR DANIEL J SARGENT:** When the FDA was presented with a trial of FOLFOX versus 5-FU/leucovorin that showed a nonsignificant benefit in the subgroup of patients with Stage II disease, the FDA also considered that no other data exist showing that treatment benefits patients with Stage II disease. Based on this, the FDA did not consider an interpolation justified.

That was the FDA’s perspective, but Dr Grothey and I wrote an editorial in the *Journal of Clinical Oncology* criticizing that decision. Our feelings were based on a fundamental paradigm with clinical trials, which is that, in the absence of compelling data, the best result is the overall result. The overall results should be based on all patients in the trial — that result is consistent with the prospectively designed, planned analysis of the clinical trial.

Based on that paradigm and the fact that in MOSAIC the relative risks of relapse for patients with Stage III (HR = 0.76) and Stage II disease (HR = 0.80) were similar and the formal test result for interaction was highly nonsignificant — suggesting that the benefit of treatment was the same for Stage III disease as it was for Stage II — we did not see any compelling reason to go against the fundamental principle of clinical trials, which is to use the data from the entire trial.

Colorectal Cancer Update Issue 5, 2007

**DR RICHARD M GOLDBERG:** The most important data regarding adjuvant therapy for colon cancer are from the update of the MOSAIC trial. It hasn’t changed what we expected, but it has confirmed what we hoped. Prior to this update, we
had only disease-free survival data. Now we have an advantage for overall survival at six years.

The good news from MOSAIC was that the patients with Stage III disease definitely gained approximately a five percent survival advantage. The bad news was that the patients with Stage II disease did not appear to gain a significant survival advantage with FOLFOX compared to 5-FU/leucovorin.

What does that mean? For all comers with Stage II disease, the ASCO guidelines still apply. You need to have an individualized discussion with those patients, tell them what they can expect and ask them whether that’s enough for them to receive adjuvant treatment. I’m always on the fence about whether to offer FOLFOX or only a fluoropyrimidine to patients with Stage II disease who want treatment.

**DR STEVEN R ALBERTS:** The CONcePT trial was meant to address two issues. One was the stop-and-go approach of using multidrug chemotherapy and then 5-FU or capecitabine to try to maintain the response. The other aim was to evaluate the use of calcium and magnesium to decrease oxaliplatin-induced peripheral neuropathies. Although this trial enrolled patients with mCRC, the results can be translated into the adjuvant setting.

CONcePT was halted partway through the trial by the Data Safety Monitoring Committee based on an early analysis, which suggested that calcium and magnesium were causing a detrimental effect in terms of the response rate and potentially progression-free survival.

In further follow-up, after the data were reviewed by an independent review group to evaluate the outcomes in terms of scans, it appears that patients receiving calcium and magnesium were not harmed and, indeed, some benefit may have occurred, in that patients seemed to demonstrate a better response rate and a longer duration of disease control. As the trial was stopped early, some concern
still exists. Can we rely on that information, and can we still safely administer calcium and magnesium to our patients? While CONCePT was ongoing, a separate trial through the North Central Cancer Treatment Group investigated calcium and magnesium in a symptom-control trial. The analysis from that trial again suggested no potential harm in administering calcium and magnesium, in terms of response rates.

So with some caution, the message that came out at ASCO was it appears that calcium and magnesium are probably not harmful and may be of some benefit in controlling the peripheral neuropathy, which seemed to be true in both the symptom-control trial and the CONCePT trial. A benefit to patients in terms of response rates was also apparent.

**Colorectal Cancer Update Issue 3, 2008**

**DR ALBERTS:** In the adjuvant setting, we are awaiting the results of NSABP-C-08, evaluating FOLFOX with or without bevacizumab. Data from this trial may be available in 2009 or 2010. If bevacizumab shows a benefit, then FOLFOX with bevacizumab will likely become the new standard treatment in the adjuvant setting.

The question then would be how to build on this trial. The other approach under investigation is FOLFOX with or without cetuximab in the NCCTG-N0147 trial. That trial is still accruing patients, and we may not have data for another three years.

In terms of the initial safety data that were presented, patients on the FOLFOX with bevacizumab arm received bevacizumab for a full year, so concern was raised about toxicities, such as bleeding and bowel perforation. However, the safety data revealed no significant increase in these side effects with bevacizumab.

In terms of bowel perforations, one thought is that perhaps in the advanced setting, metastatic disease is attached to the bowel wall and with a rapid regression, that somehow leads to a perfora-
Obviously, everybody is pleased about these data, and if NSABP-C-08 turns out to be a positive trial, we know it is safe to use this approach.

You could make the argument that CAPOX is a reasonable clinical option right now in the adjuvant setting. My impression is that CAPOX is as effective as FOLFOX in the advanced disease setting. That was proved by the NO16966 trial in the metastatic setting that’s been presented on several occasions.

The toxicity profiles are acceptable, and the efficacy in advanced disease is the same. I believe that this would be a reasonable option in clinical practice now.

**DR JEFFREY A MEYERHARDT:** Patients on CALGB-C89803 completed two questionnaires: the first one at approximately three months into chemotherapy and the second around six months after completing therapy.

We created a metric called metabolic equivalent task (MET), which is basically a measure of energy expenditure for nine different activities, such as walking, jogging or biking. For each, patients were asked whether they engaged in the activity and, if so, how often and for how many minutes.

Then we created categories of multiples of three MET hours per week. For example, sitting still for one hour is equivalent to one MET hour, or walking for one hour at two to three miles per hour each week is equivalent to three MET hours per week. The reference range was less than three MET hours per week.

We found that colon cancer survivors who engaged in at least 18 MET hours of exercise per week had approximately a 50 percent reduction in the risk of disease recurrence or mortality, or a 50 percent improvement in the disease-free survival rate, compared to those in the reference range.
Walking at a pace of two to three miles per hour for one hour six times a week equals 18 MET hours. Of course there are ways to do it more efficiently or in less time. Jogging or running for an hour equals seven or 10 MET hours, respectively.

Most of the patients on the study did some combination of exercise rather than one single aerobic activity.

Obviously our study was observational, and patients were not randomly assigned to one level of physical activity or another. Also, one could argue that the healthier patients are the patients who are able to exercise more.

To minimize the bias from patients who were becoming more ill, we didn’t count events, recurrences or deaths within six months of the activity assessment.

One explanation for our findings is that factors such as obesity and lack of physical activity increase one’s insulin levels and insulin-like growth factor, both of which have been shown to be mitogens for tumor development, metastasis and angiogenesis.

Therefore, if patients avoid obesity or increase their level of physical activity, they may be decreasing those levels. If cancer recurrences result from micro-metastatic disease that grows, metastasizes and develops a blood supply, then inhibiting those factors may prevent those events from occurring.

SELECT PUBLICATIONS

Allegra CJ et al. Initial safety report of NSABP C-08, a randomized phase III study of modified 5-fluorouracil (5-FU)/leucovorin (LCV) and oxaliplatin (OX) (mFOLFOX6) with or without bevacizumab (bev) in the adjuvant treatment of patients with stage II/III colon cancer. Proc ASCO 2008; Abstract 4006.


De Gramont A et al. Oxaliplatin/SFU/LV in adjuvant colon cancer: Updated efficacy results of the MOSAIC trial, including survival, with a median follow-up of six years. Proc ASCO 2007; Abstract 4007.


Hochster HS et al. Effect of intravenous (IV) calcium and magnesium (Ca/Mg) versus placebo on response to FOLFOX + bevacizumab (BEV) in the CONCePT trial. Gastrointestinal Cancers Symposium 2008; Abstract 280.


Nikouli DA et al. Effect of intravenous calcium and magnesium (IV CaMg) on oxaliplatin-induced sensory neurotoxicity (sNT) in adjuvant colon cancer: Results of the phase III placebo-controlled, double-blind NCCTG trial N04C7. Proc ASCO 2008; Abstract 4009.


Sargent DJ et al. Deficient mismatch repair as a predictive marker for lack of benefit from 5-FU based chemotherapy in adjuvant colon cancer. Proc ASCO 2008; Abstract 4008.


**TREATMENT OF METASTATIC COLON CANCER**

**DR ALBERTS:** As first-line therapy for metastatic disease, I generally recommend chemotherapy with bevacizumab. However, with the evolving data on K-ras and evidence from two large European studies, the CRYSTAL and OPUS trials — which evaluated FOLFIRI or FOLFOX with cetuximab — we have a good rationale for using cetuximab in the front-line setting, and I have done so recently.

**DR LEONARD B SALZ:** The CRYSTAL trial was a 1,200-patient study investigating the addition of cetuximab to FOLFIRI as first-line therapy — half of the patients received FOLFIRI, and half received FOLFOX with cetuximab. The outcome of that study was technically positive, but in my opinion it was disappointing.

Progression-free survival, the specified primary endpoint, was improved in the overall study to a statistically significant degree, with a \( p \)-value of 0.048. The actual improvement in progression-free survival, however, was 27 days. I believe this raises the question of what is a clinically significant versus a statistically significant improvement.

I’m concerned that the skin toxicity associated with cetuximab has been underappreciated in terms of the significant impediment it imparts on quality of life. The rash can be painful or itchy, and the paronychial cracking — the paper-cut feeling in the fingers and toes — can become painful.

The CRYSTAL study demonstrated that progression-free survival is statistically significantly better with the addition of cetuximab to front-line therapy. My interpretation, however, is that for the overall population, the incremental toxicity and probably the incremental costs are difficult to justify.

In 2008, Dr Van Cutsem’s group evaluated the outcomes in the CRYSTAL trial for the patients whose tumors had a wild-type K-ras gene versus those whose tumors had a mutant K-ras gene, based on archived tissue. The data suggest that for the patients whose tumors had a K-ras mutation, cetuximab added no value to FOLFIRI. The patients whose...
TREATMENT OF METASTATIC COLON CANCER

Tumors had wild-type K-ras — approximately 60 to 65 percent of patients in the study — derived more substantial benefit when cetuximab was added. These data can be interpreted in two ways. First, patients whose tumors have a K-ras mutation do not benefit from the addition of cetuximab and therefore ought not receive it in this scenario. Second, patients whose tumors have wild-type K-ras derive a greater degree of benefit from cetuximab. Instead of a 0.9-month progression-free survival benefit, it was a 1.2-month progression-free survival benefit. So now instead of 27 days, we’re up to 36 days. One must ask, should a median 36-day improvement in progression-free survival define a standard treatment? I don’t believe so.

My take-home message is that I am not compelled to recommend front-line cetuximab-based therapy. I believe it is an option that can be considered in select

FIGURE 14

**Do you generally check the K-ras mutation status of a tumor in patients with metastatic colon cancer?**

**If yes, approximately when did you begin checking this?**

![Graph showing the K-ras mutation status and the timing of checking.]

**FIGURE 15**

**CRYSTAL trial: A Phase III randomized study of FOLFIRI with or without cetuximab as first-line therapy for EGFR-expressing metastatic colorectal cancer**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>FOLFIRI + cetuximab (n = 599)</th>
<th>FOLFIRI (n = 599)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>8.9 months</td>
<td>8.0 months</td>
<td>0.048</td>
</tr>
<tr>
<td>One-year PFS rate</td>
<td>34%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td>Overall response rate*</td>
<td>46.9%</td>
<td>38.7%</td>
<td>0.0038</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety: Grade III/IV adverse events</th>
<th>FOLFIRI + cetuximab (n = 600)</th>
<th>FOLFIRI (n = 602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>26.7%</td>
<td>23.3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15.2%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Skin reactions†</td>
<td>18.7%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Infusion related</td>
<td>2.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

PFS = progression-free survival
* Complete response + partial response
† No Grade IV skin reactions

**SOURCE:** Van Cutsem E et al. *Proc ASCO* 2007;Abstract 4000.
Figure 16

Which systemic therapy would be your typical first-line choice for a chemotherapy-naive patient with metastatic colon cancer that is K-ras wild type?

65-year-old patient

<table>
<thead>
<tr>
<th>Systemic Therapy</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX + bevacizumab</td>
<td>76%</td>
</tr>
<tr>
<td>FOLFIRI + bevacizumab</td>
<td>16%</td>
</tr>
<tr>
<td>XELOX/CAPOX + bevacizumab</td>
<td>8%</td>
</tr>
<tr>
<td>FOLFOX + cetuximab</td>
<td>5%</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>0%</td>
</tr>
<tr>
<td>FOLFIRI + cetuximab</td>
<td>0%</td>
</tr>
<tr>
<td>Other systemic therapy</td>
<td>0%</td>
</tr>
</tbody>
</table>

85-year-old patient

<table>
<thead>
<tr>
<th>Systemic Therapy</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX + bevacizumab</td>
<td>40%</td>
</tr>
<tr>
<td>Capecitabine ± bevacizumab</td>
<td>24%</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>16%</td>
</tr>
<tr>
<td>5-FU/LV ± bevacizumab</td>
<td>12%</td>
</tr>
<tr>
<td>FOLFOX + cetuximab</td>
<td>5%</td>
</tr>
<tr>
<td>FOLFIRI + biologic*</td>
<td>4%</td>
</tr>
<tr>
<td>Other systemic therapy</td>
<td>4%</td>
</tr>
<tr>
<td>No systemic therapy</td>
<td>2%</td>
</tr>
</tbody>
</table>

* PO: FOLFIRI + bevacizumab 6%; FOLFIRI + cetuximab 4%

A quick family history will tell you if any family member has had problems receiving chemotherapy. If a family member has a dihydropyrimidine dehydrogenase (DPD) deficiency and cannot metabolize pyrimidines, usually everybody in the family has been alerted.

Another issue would be bevacizumab-specific contraindications. Recent (six months to one year) arteriovascular complications — myocardial infarction, stroke or active disease — are fairly significant contraindications to bevacizumab.

DR GOLDBERG: In the first-line setting, I initially attempt to enroll patients with metastatic disease on CALGB-C80405, a study of dealer’s choice of chemotherapy — FOLFOX or FOLFIRI — combined with cetuximab, bevacizumab or both.

If the patient is not interested, I explain that FOLFOX and FOLFIRI provide basically equivalent outcomes and that, in general, we’re adding bevacizumab to first-line therapy.

I don’t believe that the NO16966 data presented at ASCO will change my first-line approach off study. I will still offer people FOLFOX with bevacizumab as first-line therapy. The data populations for whom response is critical to management.

One might consider it for patients with contraindications to bevacizumab, which is a more standard addition to front-line chemotherapy.

Colorectal Cancer Update Issue 5, 2007

DR HERBERT I HURWITZ: The main issue when selecting first-line therapy in the metastatic setting is whether the patient is a candidate for systemic therapy.

The second issue is the presence of any major contraindications to the backbones of therapy, which would be either a fluoropyrimidine or bevacizumab.
from NO16966 — evaluating CAPOX versus FOLFOX with or without bevacizumab — indicated no difference in response rate when bevacizumab was added. Modest differences in survival of about a month were evident.

Does that mean bevacizumab is not worth adding? Not to me. I believe it’s worth adding bevacizumab to FOLFOX, but I have my eye on it. I’m watching for additional information to either reinforce or change my opinion.

Colorectal Cancer Update Issue 3, 2008

DR ALBERTS: EORTC-40983 was designed to determine whether we could administer three months of neoadjuvant chemotherapy to a patient with potentially resectable hepatic metastases and not hinder the ability to perform surgery, either by causing liver toxicity or by allowing disease progression to a point at which the tumor was no longer resectable.

Then, if the surgery was successful, three more months of chemotherapy were administered postoperatively. This regimen was compared to surgery alone.

A statistically significant progression-free survival advantage was observed with the perioperative chemotherapy. However, a bar was set for a hazard ratio of 0.71 or less, which was not reached. With some reservations about the outcomes, investigators are considering a trial of adjuvant therapy versus perioperative therapy.

Additionally, EORTC is evaluating the combination of biologic agents with chemotherapy to try to enhance the outcome with perioperative therapy.

Another point to consider is that the patients enrolled in the trial were generally at good risk in that they typically had only one or two liver metastases. In that group — particularly patients with only one liver metastasis —...
Treatment of Metastatic Colon Cancer (Continued)

FIGURE 18

Case 2: Metastatic Colon Cancer, No Prior Systemic Therapy

- A 65-year-old patient in otherwise average health
- Three years ago, treated for Stage II sigmoid cancer (no adjuvant chemotherapy)
- Now with 2 metastases in right lobe of liver that are considered to be surgically resectable (maximum diameter 3 centimeters)
- No evidence of extrahepatic metastases

Which of the following treatment strategies, if any, are you most likely to recommend for this patient with colon cancer?

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Perioperative FOLFOX4 + surgery</th>
<th>Surgery alone</th>
<th>HR (95.6% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection of liver mets → systemic therapy</td>
<td>60%</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop systemic therapy → resection → systemic therapy</td>
<td>24%</td>
<td>35%</td>
<td>0.79 (0.62-1.02)</td>
<td>0.058</td>
</tr>
<tr>
<td>Periop systemic therapy with 1/2 of cycles prior to resection and 1/2 after</td>
<td>16%</td>
<td>12%</td>
<td>0.73 (0.55-0.97)</td>
<td>0.025</td>
</tr>
<tr>
<td>Immediate resection of liver mets alone, no postop systemic therapy</td>
<td>0%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


FIGURE 19

Trial evaluating the benefit of perioperative FOLFOX4 for patients with potentially resectable colorectal cancer hepatic metastases

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

<table>
<thead>
<tr>
<th>Three-year progression-free survival</th>
<th>Perioperative FOLFOX4 + surgery</th>
<th>Surgery alone</th>
<th>HR (95.6% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients randomly assigned (n = 182, 182)</td>
<td>35.4%</td>
<td>28.1%</td>
<td>0.79 (0.62-1.02)</td>
<td>0.058</td>
</tr>
<tr>
<td>All patients who underwent resection (n = 152, 151)</td>
<td>42.4%</td>
<td>33.2%</td>
<td>0.73 (0.55-0.97)</td>
<td>0.025</td>
</tr>
<tr>
<td>Reversible postoperative complications (n = 159, 170)</td>
<td>25%</td>
<td>16%</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence interval


metastasis — the benefits of chemotherapy beyond surgery may be fairly small, depending on which agents the patient has received in the past. Had we evaluated patients with three to five liver metastases, among whom the rate of recurrence is much higher, we might have seen a better outcome with perioperative therapy.

MetResect? Issue 1, 2008

DR AXEL GROTHEY: Approximately 50,000 patients per year die of colon cancer, and about one third of them have liver-only disease. Of those, at least 25 to 40 percent can be considered for a resection.

PROF JOHN N PRIMROSE: If you evaluate the published reports — many are from older retrospective studies — 20 to 30 percent of patients will have liver metastases at the time of presentation of their primary. Of those that experience disease recurrence at some point, 30 to 40 percent will have liver-only metastases.

So, putting all of the bits and pieces of the data together, approximately 25,000 to 30,000 patients per year will have liver-only disease. Forty percent of those patients have resectable disease, or about 10,000 patients per year.

Colorectal Cancer Update Issue 2, 2008

PROF ERIC VAN CUTSEM: In EORTC-40983, patients with resectable liver metastases received six cycles of FOLFOX4 before and after resection (perioperative chemotherapy). The progression-free survival for the patients treated with perioperative chemotherapy was better than that for patients who underwent surgery alone.

We also saw slightly more postoperative complications among the patients who received perioperative chemotherapy than among those who underwent surgery alone. Although slightly more morbidity was observed in the patients treated with perioperative chemotherapy, the postoperative mortality was identical.

The three-month duration of preoperative treatment is important. In other
metastases may cease to appear on a CT scan, which can be a nightmare for the surgeons. Perhaps that’s an overstatement, but it’s extremely difficult for them to find the lesions if they don’t see the correlation on imaging. Upon resection, more than 80 percent of the areas in which a metastasis was initially present but later absent from a CT scan will still have microscopic lesions.

Formally, we do not have proof that preoperative therapy followed by postoperative therapy is better than postoperative therapy alone. However, for rectal cancer and many other types of cancer, preoperative treatment is better tolerated, and there are oncologic advantages.

At ASCO last year, Nick Petrelli suggested a randomized trial to evaluate these two options. I believe it would be extremely difficult to conduct such a trial, and more important questions must be answered to make progress for these patients.

Colorectal Cancer Update Issue 3, 2008

DR ALBERTS: For patients with liver-only metastases that I believe may be resectable after a response to systemic therapy, one of the critical steps is to evaluate them along with the surgeon. If the surgeon agrees that downsizing the tumor may make it resectable, then the data from two prospective clinical trials suggest FOLFOX and FOLFIRI are equivalent in terms of the response rates.

I believe most clinicians in the United States are more comfortable using FOLFOX. However, FOLFIRI is not any less efficacious in this setting. Probably the best option for downsizing the tumor rapidly would be FOLFOX and a biologic agent. Some data in patients with metastatic disease at any site, not just colorectal liver-only metastases, suggest that combining cetuximab with FOLFIRI or FOLFOX increases the response rate.

Obviously we need to take into account the tumor’s K-ras status. In my practice, if a patient is chemotherapy naïve, I use either FOLFOX or FOLFIRI — preferably FOLFOX — combined with cetuximen.
imab. If the tumor has a K-ras mutation, then I typically add bevacizumab instead.

Colorectal Cancer Update Issue 3, 2008

DR STEVEN A CURLEY: In the late 1980s and early 1990s, patients who presented with a synchronous primary and metastatic disease, more than three or four liver metastases or small-volume extrahepatic disease were considered incurable. Now we have data for each of those subsets that show an opportunity for long-term survival.

A number of groups have examined the issue of curative surgery for patients with more than four hepatic metastases, including Rene Adam at the Paul Brousse Hospital. With surgery alone, these patients have a five-year survival in the range of 20 to 25 percent.

However, if we add adjuvant or neoadjuvant chemotherapy, their five-year survival at MD Anderson is 51 percent. Approximately 20 percent are alive and disease free at five years, while the other 30 percent are alive with disease. Essentially, we have changed the landscape for these patients in that they are living longer.

Colorectal Cancer Update Issue 3, 2008

DR ALBERTS: One approach to converting liver metastases from unresectable to resectable is to try to maximize chemotherapy. Traditionally, trials have used either FOLFOX or FOLFIRI, but a recent European trial for metastatic colorectal cancer evaluated "FOLFIRINOX" — the combination of 5-FU, leucovorin, irinotecan and oxaliplatin.

A secondary endpoint in that trial was the rate of resection for patients with initially unresectable, liver-only disease. A high rate of downsizing leading to resectability was seen with FOLFIRINOX.
Another strategy is to combine biologic agents with chemotherapy. Based on the recent K-ras data, we may need to screen patients. If the tumor has a wild-type K-ras expression, we would consider an EGFR inhibitor, such as cetuximab or panitumumab, and if K-ras is mutated, we would consider an agent such as bevacizumab.

**Colorectal Cancer Update Issue 2, 2008**

**DR MEROPOL:** The first treatment option for a patient with unresectable liver metastases who has received adjuvant FOLFOX two years ago would be FOLFOX in combination with bevacizumab — considering she had a two-year disease-free interval. Another treatment option would be the combination of irinotecan, 5-FU and bevacizumab.

I would consider those to be the two standard treatment options. She had not received irinotecan or an antibody against the epidermal growth factor receptor (EGFR). Those were the drugs on the table, but in taking a sequential approach, I thought it made the most sense to offer chemotherapy in combination with bevacizumab.

**Colorectal Cancer Update Issue 2, 2008**

**DR VENOOK:** In CALGB-C80405, the choice of chemotherapy regimen — FOLFOX or FOLFIRI — is left up to the physician and the patient. Then patients are randomly assigned to cetuximab alone, cetuximab with bevacizumab or bevacizumab alone. Indeed, a patient who completed adjuvant FOLFOX more than a year earlier would be eligible for enrollment.

**Colorectal Cancer Update Issue 5, 2007**

**DR HURWITZ:** One approach to maximize the benefit from oxaliplatin in patients with metastatic disease is to be preemptive through the use of a calendar schedule. This is the OPTIMOX approach, by which stopping and starting treatment are based as much on the calendar as they are on the patient’s symptoms or disease control.

I find that adjustment based on the patient’s symptoms — as long as the threshold for symptoms is lowered —

---

**FIGURE 23**

**Case 4: Metastatic Colon Cancer, Previous Adjuvant Treatment**
- A 65-year-old patient in otherwise average health
- **One year ago,** completed treatment for a Stage III lesion with resection and adjuvant FOLFOX (5-FU + leucovorin + oxaliplatin) chemotherapy for 6 months
- Now presents with 12 liver metastases

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

![Therapy Options Graph](image)

- FOLFIRI + bevacizumab: 68%
- FOLFIRI: 50%
- FOLFOX + bevacizumab: 28%
- XELOX/CAPOX + bevacizumab: 24%
- Irinotecan + cetuximab: 16%
- Other: 12%

---

**FIGURE 24**

**Phase III randomized study of cetuximab and/or bevacizumab in combination with either FOLFOX or FOLFIRI**

Protocol IDs: CALGB-C80405, C80405, SWOG-C80405, NCT00265850
Target Accrual: 2,300 (Temporarily Closed)

Eligibility
- Previously untreated metastatic adenocarcinoma of the colon or rectum

Chemotherapy + cetuximab
Chemotherapy + cetuximab/bevacizumab
Chemotherapy + bevacizumab

Treatment of Metastatic Colon Cancer (Continued)

ends up being a nearly identical approach. I have a bias to try to adjust based on how the patient is faring rather than the calendar, but in practice, the two approaches are most likely similar.

Currently my algorithm is to reduce or stop only the problem agent and to continue the portions of therapy that seem to help, as long as they’re well tolerated.

For patients who need a break for personal reasons or for asthenia, I believe stopping even the fluoropyrimidine and bevacizumab for a period of several weeks to two months is a reasonable approach, as long as the disease burden and patient’s symptoms allow for the holiday.

**DR MARSHALL:** In OPTIMOX1, patients were randomly assigned to continuous FOLFOX or six cycles of FOLFOX followed by 5-FU/leucovorin alone with oxaliplatin restarted when their disease progressed. The data showed that the latter schedule was as effective and it was a little less toxic, with less neurotoxicity.

OPTIMOX2, presented at ASCO 2007, compared the winning arm from OPTIMOX1 to a complete drug holiday — stopping all drugs after six cycles of FOLFOX and the drugs not being restarted until the disease had regrown to the baseline status. Both a progression-free and an overall survival benefit were seen among the patients who continued to receive 5-FU/leucovorin through the holiday.

I am still surprised that OPTIMOX2 showed that four months or so of 5-FU/leucovorin affected overall survival. However, everyone left ASCO with the message that the patients have to receive something during the holiday.

Although the data indicate that a holiday may be valuable, we need to determine how to optimize that holiday. The data do tell us that waiting until tumors regrow to their baseline size is probably not the right thing to do. Clinically, we restart the chemotherapy at the first sign of disease progression.

**DR AIMERY DE GRAMONT:** Outside of a protocol, my management strategy for metastatic disease will be similar to OPTIMOX1. I start with the modified FOLFOX7 regimen, which is an optimized regimen that has a much lower toxicity than FOLFOX4. I administer bevacizumab to patients who meet the same inclusion criteria used in the clinical trials.

Bevacizumab is the drug that has most increased the progression-free sur-
vival in these patients. We learned from NO16966 that it’s important not to discontinu bevacizumab.

When you decide to start treatment with bevacizumab, patients know they will continue on bevacizumab. Results presented by Axel Grothey demonstrated that survival is much better in the patients who continue on bevacizumab after progression.

Oxaliplatin is stopped at six cycles. I’m sure that if I stop at six cycles, the patient will have no neuropathy. When the patient’s disease progresses, I reintroduce oxaliplatin.

In the OPTIMOX1 study, the median survival was 21 months. In our centers in which more than 40 percent of the patients have had oxaliplatin reintroduced, the median survival was more than two years.

The stop-and-go strategy for oxaliplatin is my strategy for all patients with advanced disease. If we add bevacizumab, it will be administered with FOLFOX, between the administrations of FOLFOX and continued with the reintroduction of FOLFOX.

Colorectal Cancer Update Think Tank Issue 1, 2007

DR GROTHEY: I try to educate everyone that I give talks to that we should stop treatment before patients develop toxicities, and for an oxaliplatin-based regimen this has become more common. It’s already now a standard treatment based on the Phase III data from the OPTIMOX 1 trial, which showed that we could safely discontinue oxaliplatin after some time before the majority of patients develop toxicity without compromising efficacy.

We have limited information based on an Italian trial presented at ASCO 2006 that even discontinuation of irinotecan-based therapy in an “on and off” schedule every two months — two months on FOLFIRI, two months off FOLFIRI — did not influence progression-free survival.

The data are more solid for an oxaliplatin-based regimen, which is typically what we use as first-line therapy in the United States.

Colorectal Cancer Update Issue 2, 2008

PROF VAN CUTSEM: An issue we don’t have a formal answer to is the continuation of bevacizumab after disease progression. Data from the BRiTE registry — presented at ASCO 2007 — suggested that for patients whose disease is progressing on chemotherapy and bevacizumab, switching the chemotherapy but continuing bevacizumab produces a better outcome.

It’s not a randomized trial, but the BRiTE data and some preclinical data suggest that the continuation of bevacizumab after disease progression may provide additional benefits.
For a patient who demonstrates stable disease on FOLFOX/bevacizumab and who is then continued on bevacizumab alone, how long do you generally continue bevacizumab if the patient is tolerating it well?

<table>
<thead>
<tr>
<th>Duration</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I don't use maintenance bev</td>
<td>60%</td>
</tr>
<tr>
<td>Until disease progression</td>
<td>32%</td>
</tr>
<tr>
<td>A specified number of cycles</td>
<td>13%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
</tr>
</tbody>
</table>

A 60-year-old patient has an excellent response to FOLFOX + bevacizumab as first-line therapy for metastatic disease and is continued on bevacizumab. At 14 months, the patient develops slow but definite disease progression. Outside of a protocol setting, the bevacizumab should generally be continued with the addition of another agent/regimen.

A German group is conducting a similar but more flexible study in that patients can be treated with any irinotecan- or oxaliplatin-based regimen with bevacizumab as first-line therapy, and then they change to another chemotherapy regimen with or without bevacizumab in the second-line setting.

Colorectal Cancer Update Issue 1, 2008

DR MARSHALL: At ASCO 2007, Axel Grothey presented data from the BRiTE registry demonstrating a significant improvement in survival for patients who received bevacizumab beyond disease progression compared to those who did not, and it’s a strikingly positive finding.

We’re all soft-pedaling the data, using the fact that these are registry data and not prospective randomized trial data as a rationale for enrolling patients on the iBET trial. Accrual to that trial is slow, and I believe a bias for continuing bevacizumab is already emerging.

Two of the three arms in the iBET trial include bevacizumab, and I predict that when the patients who do not receive bevacizumab develop disease progression, they’ll receive bevacizumab in the third line. In the end, all the patients will receive bevacizumab beyond progression.

Colorectal Cancer Update Issue 4, 2007

DR GROTHEY: The reason for the BRiTE registry was to obtain information on a large number of patients — eventually 1,953 patients — enrolled in a “real-life” setting. Oncologists who used bevacizumab in combination with whatever chemotherapy regimen they deemed appropriate documented the clinical course of their patients over a long period. We are developing a nice database on these patients.

When patients experienced their first disease progression on therapy, some physicians continued bevacizumab in combination with a different treatment regimen and others did not continue bevacizumab. Outcomes, progressive disease and overall survival data were documented in the BRiTE registry.

Of the 1,953 patients, approximately 1,450 experienced disease progression. Some patients did not receive any further therapy because of poor performance status. Some continued therapy without bevacizumab, and others continued bevacizumab in combination with other chemotherapies.

Although this was a nonrandom-
In the randomized setting, we tried to compare the outcomes for patients who continued bevacizumab to those who did not. The effects were quite profound, because patients who continued bevacizumab had a remarkably longer overall survival than the patients who did not.

The physicians may have decided to continue bevacizumab only for patients who had a better performance status or those who had experienced a better response to therapy.

Having said that, we tried to account for all of these factors in a multivariate analysis by considering age, performance status, the number of metastatic sites, some laboratory analyses, duration of first-line therapy, et cetera. Still, the continuation of bevacizumab beyond disease progression turned out to be a significant factor in this analysis.

If a profound effect appears, such as the difference in overall survival of 31 months versus 19 months using bevacizumab beyond disease progression, we need to validate this in a prospective clinical trial.

The iBET trial randomly assigns patients who have received first-line therapy with bevacizumab and oxaliplatin — either FOLFOX or XELOX — to second-line treatment with cetuximab in combination with FOLFIRI or irinotecan with cetuximab with or without bevacizumab at two different doses.

So patients on two of the three arms will receive bevacizumab beyond disease progression. I believe this is one of the most important trials we’re running in colorectal cancer because a considerable number of our physicians use bevacizumab beyond progression — 40 to 50 percent are using it as we speak.
TREATMENT OF METASTATIC COLON CANCER

Presented back in 2001, and it’s been corroborated by virtually every study with an anti-EGFR agent that’s been reported since. So it’s not realistic to think you might obtain benefit from cetuximab without experiencing a substantial rash. If you’re going to benefit from cetuximab, you’re going to experience a substantial rash.

DR ALBERTS: For cetuximab and panitumumab, one thought has been that rash may predict response. The EVEREST trial asked whether for a patient who has a mild rash you can increase the dose of cetuximab and therefore further increase the response.

Indeed, when they did an analysis of the patients with wild-type K-ras, an improvement in response and duration of response was observed for those in whom it was possible to escalate the dose of cetuximab to the development of a more severe rash.

DR GROTHEY: The PACCE trial had two cohorts — one received an oxaliplatin-based regimen, and the other cohort received an irinotecan-based regimen. The data from the cohort that received irinotecan-based chemotherapy were reported.

Approximately 200 patients were randomly assigned to irinotecan/5-FU/bevacizumab with or without panitumumab as first-line therapy. The data revealed the activity of panitumumab — an antibody that targets EGFR — in patients with tumors that had wild-type versus mutant K-ras.

Patients whose tumors had mutant K-ras received no benefit — in terms of response rate — from panitumumab in combination with irinotecan/5-FU/bevacizumab. In contrast, patients whose tumors had wild-type K-ras had a higher response rate when panitumumab was combined with irinotecan/5-FU/bevacizumab.

DR MAYER: The use of double antibody therapy for advanced colorectal cancer presented back in 2001, and it’s been corroborated by virtually every study with an anti-EGFR agent that’s been reported since. So it’s not realistic to think you might obtain benefit from cetuximab without experiencing a substantial rash. If you’re going to benefit from cetuximab, you’re going to experience a substantial rash.

Approximately how many patients with metastatic colon cancer have you treated with panitumumab?

Approximately how many patients with metastatic colon cancer have you treated with cetuximab?

Of the patients with metastatic colon cancer you have treated with cetuximab, approximately how many have developed significant infusion reactions?

The severity of skin toxicity in patients undergoing treatment with EGFR inhibitors such as cetuximab and panitumumab correlates with response.
is a controversial issue because of the results of the PACCE study presented at the 2008 ASCO GI meeting. The PACCE study was a randomized trial in which four out of five patients received FOLFOX, and the remaining patients received FOLFIRI.

Then they were randomly assigned to receive bevacizumab with or without panitumumab.

To everyone’s surprise, PACCE has shown seeming detriment and increased toxicity.

**SELECT PUBLICATIONS**


Purr CJ et al. Randomized phase III study of capcitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). Proc ASCO 2008;Abstract LBA4011


Van Cutsem E et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRISTAL experience. Proc ASCO 2008;Abstract 2.
We find that endoscopic ultrasound (EUS) is a user-friendly way to triage patients to the gastroenterologist fairly quickly and obtain an answer in terms of clinical staging. Clinical staging is important to us because in order to get on a protocol of preoperative therapy, the tumor needs to be transmural or node-positive. If those patients went to the OR, we would say up front that they need postoperative therapy.

So we’re comfortable with EUS staging, understanding it’s not perfect and it’s not 100 percent accurate. It is a good system to identify patients who will potentially benefit from preoperative therapy because typically they would need it postoperatively.

In most of the data, an overstaging rate of approximately 20 percent is present by the use of endoscopic ultrasound, even in experienced hands. I’m sure in inexperienced hands, the rate of overstaging is higher. An understaging rate also occurs for some patients who are viewed as having early-stage disease and in fact have higher-stage disease. That’s probably not as bad as the other, but there is an understaging rate also.
**Colorectal Cancer Update Issue 1, 2008**

**DR O’CONNELL:** The NSABP-R-04 study is evaluating different methods of combined-modality neoadjuvant treatment using continuous infusion 5-FU combined with radiation therapy preoperatively as the standard, and it’s investigating whether capecitabine would be equally effective as 5-FU in a noninferiority analysis.

The trial is also evaluating whether the addition of oxaliplatin in the preoperative setting might increase the pathological response rates and improve long-term local control.

We hope it will be possible to use an oral agent along with radiation therapy to be equally effective without the need for a central venous catheter and the ambulatory infusion pump. With the known radiation-sensitizing effect of oxaliplatin and its activity combined with fluorinated pyrimidines in colorectal cancer, I believe it’s reasonable that the addition of oxaliplatin might improve local control. Obviously we have to run the trial and examine the results.

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**Colorectal Cancer Update Issue 4, 2007**

**DR CHRISTOPHER H CRANE:** Oxaliplatin has been proven in the adjuvant setting, which makes it interesting to combine with radiation therapy. That’s why it’s being evaluated in the NSABP-R-04 study. Its value may be that it’s a radiosensitizer or that it’s being used earlier in the treatment.

It’s a worthwhile drug to study in the neoadjuvant setting, and the NSABP-R-04 protocol was improved when they added oxaliplatin as the second part of a two-by-two randomization. I believe it’s acceptable to use oxaliplatin-based chemoradiation therapy off protocol if it’s done selectively, carefully and with close monitoring because the rates of Grade III gastrointestinal toxicity, mainly diarrhea, will be higher.

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**Colorectal Cancer Update Issue 5, 2007**

**DR TEPPER:** After treating a number of patients with a fluoropyrimidine during radiation therapy, I don’t believe the side effects are much different between capecitabine and continuous infusion 5-FU. However, some questions related to timing remain regarding the combination of capecitabine with radiation therapy.

Based on some of the available pharmacokinetic data, we try to deliver the capecitabine approximately an hour and a half before the radiation therapy. I don’t know if that’s better, but it matches up with being at or slightly past the peak concentration of the agent.

The response data appear similar between the agents based on early results, but it’s possible that the NSABP-R-04 study will demonstrate the superiority of capecitabine.

---

**FIGURE 35**

When administering a fluoropyrimidine during radiation therapy, which regimen do you generally recommend?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CI (%)</th>
<th>PO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous infusion 5-FU/LV</td>
<td>68%</td>
<td>67%</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>32%</td>
<td>31%</td>
</tr>
<tr>
<td>Bolus 5-FU/LV</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Patients who receive 5-FU/LV with radiation therapy for neoadjuvant treatment of rectal cancer and have positive nodes in the resection specimen postoperatively should generally receive which of the following regimens?

<table>
<thead>
<tr>
<th>Regimen</th>
<th>CI (%)</th>
<th>PO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>FOLFOX + biologic (bev or cetuximab)</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>FOLFIRI</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

*Colorectal Cancer Update Issue 1, 2008*
Neoadjuvant and Adjuvant Treatment of Rectal Cancer (Continued)

Dr. Marshall: When deciding which fluoropyrimidine to administer with radiation therapy for rectal cancer, I am probably on the fringe, because I’ve been using capecitabine with radiation therapy in patients with rectal cancer for a long time.

In terms of ease of delivery and being able to dial the dose up or down, capecitabine is much better than 5-FU in the neoadjuvant setting. I am also biased in favor of including oxaliplatin, as it is effective in the adjuvant setting and it enhances radiation therapy. In the neoadjuvant setting, you increase the likelihood of reducing the tumor size, but you also begin systemic therapy.

For the subset of patients for whom I want to be more aggressive and have loftier therapeutic goals of performing sphincter-sparing surgery, I add oxaliplatin into the mix of capecitabine and radiation therapy.

Dr. Tepper: The major emphases in clinical trial development in rectal cancer are in two separate areas. One is trying to enhance local control to the point of being able to treat rectal cancer without a surgical resection. Virtually all those trials have included radiation therapy, and all include a fluoropyrimidine.

People are also interested in using other agents to enhance response to radiation therapy. The new cytotoxics have been
studied to a great extent. Irinotecan has been of some interest but is problematic due to the possibility of diarrhea associated with irinotecan being additive to the diarrhea already associated with radiation therapy and the fluoropyrimidine.

Much more interest has been shown in oxaliplatin, which has been evaluated in Phase I and II studies. We performed a Phase I study and the initial parts of a Phase II study, which then went into CALGB as a Phase II study.

The study’s aim was to deliver the oxaliplatin in such a way as to optimize radiation sensitization. We used a once-weekly schedule throughout the course of radiation therapy, which is somewhat different than the schedule typically used with oxaliplatin alone as a cytotoxic. The Phase I study suggested that a dose of 60 mg/m² per week would be most appropriate.

**Colorectal Cancer Update Issue 3, 2008**

**DR RAKESH K JAIN:** We conducted a Phase I/II neoadjuvant dose-escalation trial of chemoradiation therapy with bevacizumab for patients with locally advanced rectal cancer. The initial dose of bevacizumab was five milligrams per kilogram. The trial design was such that we could view the effect on tumor biology of bevacizumab alone or in combination with chemotherapy.

I do not know of any other trial in which so much information has been obtained from so few patients. The patients received bevacizumab initially by itself, followed by chemotherapy, radiation therapy and bevacizumab. Then a rest of seven to nine weeks was followed by surgical resection.

The results were presented at ASCO 2008. Three-year overall survival and three-year local control rates were 100 percent, and disease-free survival was approximately 90 percent at three years. We have to be cautious in interpreting the data because it was not a randomized trial.

**Colorectal Cancer Update Issue 5, 2007**

**DR TEPPER:** Bevacizumab is an interesting drug to consider combining with radiation therapy. You would expect that the last thing you would want to do would be to use an anti-angiogenic agent with radiation therapy because shutting down the blood supply could lead to worse results by producing more hypoxic cells and a decreased response to radiation therapy.

That does not appear to be the case because the preclinical data suggest that drugs such as bevacizumab have a beneficial effect when combined with radiation therapy. Work from Rakesh Jain has suggested that what is occurring in these tumors treated with bevacizumab is vascular normalization rather than overall vascular shutdown.

By changing intratumoral pressure, we might actually allow better blood flow, better delivery of chemotherapy and better oxygenation effects for radiation therapy. Few small studies have used bevacizumab with radiation therapy. Thus far, the toxicity appears to be acceptable, but I believe it’s too early to say how encouraged one should be with the results.

**Colorectal Cancer Update for Surgeons Issue 2, 2006**

**DR STEVEN D WEXNER:** It used to be said that if you could feel the rectal tumor on digital rectal exam, then an abdominoperineal resection was necessary. Clearly, that is not true. Some patients are undergoing sphincter extrication when the sphincter could have been saved, but the converse is also true.

Some tertiary care centers are attempting to spare every sphincter, and we’re now seeing margins of almost zero, which is clearly the wrong way to go. On some occasions you have to say to the patient, “You have received preoperative chemoradiation therapy and there may be no cancer remaining, but we will need to remove your sphincter anyway because when I first evaluated you this tumor was at your dentate line. We don’t have enough information on the curative effect of neoadjuvant therapy.”

An occasional patient will refuse surgery, and we have to follow those patients, but we know from our own data that even in the 30 percent of patients who demonstrated a complete response to neoadjuvant chemoradiation therapy, approximately 14 percent of those...
patients have tumor deposits through the mesorectum.

**Colorectal Cancer Update Issue 5, 2007**

**DR TEPPER:** The standard therapy for patients who have T3 and/or node-positive rectal cancer should probably be preoperative chemoradiation therapy followed after a rest period of between four and eight weeks of a total mesorectal excision with appropriate adjuvant chemotherapy. The details of the radiation therapy have been argued somewhat. The standard in the United States is to use a total dose of about 5,000 centigray administered over the course of about five and a half weeks. The standard chemotherapy is probably continuous infusion 5-fluorouracil or perhaps capecitabine.

The issue is, do subsets of patients exist with either earlier-stage disease who should undergo radiation therapy or patients with T3 node-positive disease who do not need radiation therapy?

If you analyze which patients are at high risk for both local and distant failure, you can subdivide groups into those with low risk — T1, T2, N0 disease, and by staging criteria into an intermediate-risk group — T1 or T2, with N1 disease, or T3N0 disease. As the T and N stages increase, the risk continues to increase.

So do all patients in the intermediate-risk group need radiation therapy? You need to be certain that you have some reasonable measure of the T and the N stage by ultrasound or by MRI, and you have to be able to trust that.

Another simple factor to consider is the location of the tumor in the rectum. Tumors that are located high in the rectum have a lower risk of local failure than tumors that are located low in the rectum, and oftentimes it’s difficult to know whether a tumor is truly in the rectum or not.

What’s important is whether the tumor is in the nonperitonealized portion of the large bowel. That varies by location in different patients, and if a tumor is in a nonperitonealized portion of the bowel, the risk of local failure should be decreased substantially.

Perhaps a number of the patients who have been said to have rectal cancer treated with surgery alone with low local failure rates may be those who don’t have rectal cancer. They have sigmoid colon cancer.

It becomes a little more complicated because there could be nodal spread that’s distal to the tumor and is located in the nonperitonealized portion of the large bowel. Tumors that are clearly above the peritoneal reflection probably don’t need radiation therapy. Tumors that are high up in the rectum and are T1, T2N1 or T3N0, especially small T3s, may not need radiation therapy.

At the present time, if I see a patient with minimal T3 disease by imaging studies, I can’t feel the tumor on a careful rectal exam and it’s thought to be fairly high up, I suggest primary surgical treatment for some of those patients and then further therapy based on the pathological findings.

**Colorectal Cancer Update for Surgeons Issue 2, 2007**

**DR BRUCE MINSKY:** Based on the randomized study from the Germans published in 2004 in *The New England*
Journal of Medicine, the standard treatment for patients with advanced T3 and/or node-positive disease is preoperative chemoradiation therapy followed by surgery and postoperative chemotherapy.

An interesting development from the German study is that the pendulum has swung toward preoperative treatment. However, patients in that study who had T3 node-negative disease and were randomly assigned to surgery first had T1, T2 disease with negative nodes, which meant that we would be overtreating approximately 20 percent of patients with unnecessary pelvic radiation therapy preoperatively.

Conversely, if patients undergo surgery first, approximately 20 to 40 percent will have positive lymph nodes that weren't detected at the initial preoperative workup and will need to receive postoperative chemoradiation therapy, which according to the German study results in higher local recurrence rates and toxicity.

So we have a real quandary, because both overtreatment and undertreatment occur. One of the major questions in colorectal cancer is how we identify patients with positive lymph nodes up front before preoperative therapy is administered. This is an area that is under intense investigation, and we will accomplish this with better molecular markers or imaging or a combination.

Adjuvant therapy after neoadjuvant chemoradiation therapy and surgery is another highly controversial area. The standard treatment is to administer six cycles or six months of chemotherapy, which is based on the adjuvant data we have in the postoperative setting.

So in the preoperative setting, two cycles of chemotherapy are administered with radiation therapy followed by surgery and four cycles or four months of postoperative chemotherapy. Until we prove that point otherwise, all patients should receive postoperative chemoradiation therapy for four months.

Dr Venook: Once you have administered neoadjuvant therapy for rectal cancer, the general belief is you are committed to administer postoperative therapy.

This is a question that I’m asked all the time: What if neoadjuvant therapy is administered and a pathologic complete response is evident at surgery? The patient still had disease initially, so I believe that once you commit to neoadjuvant therapy, you’ve committed to postoperative therapy.

It is important to remember because a subset of patients with rectal cancer probably don’t need neoadjuvant therapy.

Joel Tepper published data involving patients with high rectal tumors that may be at the peritoneal reflection, which aren’t apparently node-positive and probably don’t need radiation therapy. I believe a tendency exists to overtreat some of these patients with high rectal tumors, but that’s an evolving field.

The problem is defining the rectum. The rectum is generally said to be 12 centimeters from the anal verge, but anteriorly and posteriorly, we may come up with different measures, and it may be different in a big man compared to a more petite woman.
Colorectal Cancer Update for Surgeons
 ISSUE 1, 2007

DR LEE M ELLIS: Any patient who receives neoadjuvant chemoradiation therapy and has already documented T3 N0 or N1 disease receives postoperative adjuvant therapy, typically for a duration of about four months. If we’re going to be aggressive enough to treat with chemoradiation therapy, they’ll probably receive FOLFOX chemotherapy for four months. I can’t necessarily tell you that we have hard data to base that on, but we believe they have aggressive disease and we want to give them the benefit of the doubt.

Case 8: Rectal Cancer After Neoadjuvant Treatment and with Complete Pathologic Response Evident on Resection, Including Absence of Residual Nodal Disease

- Man in average health
- T3N1 rectal cancer (2 enlarged lymph nodes on endoscopic ultrasound)
- Lesion is 8 centimeters from the anal verge
- Undergoes neoadjuvant chemoradiation therapy with XELOX/CAPOX
- Complete pathologic response evident on resection

Which postoperative therapy are you most likely to recommend for this patient?

![Graph showing postoperative therapy recommendations]

SELECT PUBLICATIONS


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

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

<table>
<thead>
<tr>
<th></th>
<th>4 = Excellent</th>
<th>3 = Good</th>
<th>2 = Adequate</th>
<th>1 = Suboptimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community oncologist (CO) and clinical investigator (CI) preferred adjuvant therapy regimens for colon cancer in older and younger patients</td>
<td>4 3 2 1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CO and CI assessment of K-ras mutation status in patients with advanced colon cancer</td>
<td>4 3 2 1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CO and CI preferred first-line therapy choices for older and younger chemotherapy-naive patients with advanced colon cancer</td>
<td>4 3 2 1</td>
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<tr>
<td>CO and CI management of potentially resectable hepatic metastases</td>
<td>4 3 2 1</td>
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</tr>
<tr>
<td>CO and CI preferred postoperative adjuvant therapy for patients with high-risk rectal cancer</td>
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<td></td>
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<td></td>
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</tbody>
</table>

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

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<tr>
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</tr>
</tbody>
</table>

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

☐ Yes    ☐ No

If no, please explain:

Will this activity help you improve patient care?

☐ Yes    ☐ No    ☐ Not applicable

If no, please explain:

Did the activity meet your educational needs and expectations?

☐ Yes    ☐ No

If no, please explain:

Please respond to the following LEARNER statements by circling the appropriate selection:

<table>
<thead>
<tr>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = Learning objective not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
</table>

AS A RESULT OF THIS ACTIVITY, I WILL BE ABLE TO:

- Compare management strategies of community oncologists and cancer clinical investigators in the neoadjuvant, adjuvant and metastatic settings, and use this information to develop practical colorectal cancer treatment algorithms ................................................................. 4 3 2 1 N/M N/A

- Identify clinical scenarios for which relative agreement and heterogeneity exist in patterns of care for colorectal cancer, and apply these findings to individualized treatment plans for patients .................................................. 4 3 2 1 N/M N/A

- Counsel patients with colorectal cancer about the benefits and risks of multiple acceptable treatment options when they exist .................................................................................................................. 4 3 2 1 N/M N/A

- Recognize the rate at which practice-changing clinical research affects oncologists’ decision-making, and explain how this affects patient access to standard and novel therapeutics ........................................ 4 3 2 1 N/M N/A

- Recall the design and eligibility criteria for ongoing colorectal cancer clinical trials, and consider appropriate patients for study participation ................................................................. 4 3 2 1 N/M N/A
What other practice changes will you make or consider making as a result of this activity?

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

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

To what extent do you feel the faculty members’ comments were helpful or not helpful? Please be as specific as possible about individual faculty.

Please recommend additional faculty for future activities:

Other comments about the faculty for this activity:

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:
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☐ DO  ☐ RN  ☐ PA  ☐ Other

Medical License/ME Number: ................................................. Last 4 Digits of SSN (required):

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Management of Cancer of the Colon and Rectum in the Adjuvant and Metastatic Settings

Adjuvant Systemic Therapy for Colon Cancer
Treatment of Metastatic Colon Cancer
Neoadjuvant and Adjuvant Treatment of Rectal Cancer

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A Survey Comparing Practice Patterns of GI Clinical Investigators and Practicing Oncologists

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