Colorectal Cancer: All Hands on Deck

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OVERVIEW

The past 50 years has seen substantial progress in our understanding of and in the management of colorectal cancer (CRC). Surveillance colonoscopy with resection of premalignant polyps has led to a decreased incidence of CRC even though compliance with the recommendations is suboptimal. Epidemiologic and genetic information allow us to identify individuals at risk for cancer and should allow us to prevent the disease in many individuals. Patients diagnosed with metastatic CRC live much longer than in the past, and some with metastatic disease are cured. This is attributed to many factors, including cross-sectional imaging that identifies metastases earlier, new surgical and radiation techniques, and numerous new chemotherapies. Higher resolution imaging modalities have improved the ability to find limited and resectable metastatic disease; surgical advances include laparoscopic-assisted procedures and safer and more extensive hepatic resection; and radiation techniques allow for higher dose and less morbidity. Biologic therapies have not yet been maximized, but we are learning when and where some should be used. Soon we expect to be staging patients by biologic and genetic characteristics rather than by gross pathology—treating patients based on biologic features but preferably identifying people at risk and preventing CRC altogether.

When ASCO first convened in 1964, colorectal cancer (CRC) was a common cancer with surgery as the only real treatment. We knew little about its etiology and even less about its genetics, and the only chemotherapeutic in use for CRC was 5-fluorouracil (5FU), which was administered via intravenous bolus or orally. Response, rare as it was, might have been reported based on a decrease in liver size on physical exam or improvement in a nuclear medicine liver scan. Adding 5FU to external beam radiation therapy qualified as innovative, and metastatic disease was a death sentence.

Much has changed over 50 years. The initiation of epidemiologic studies would lead to insight on CRC etiology and natural history after individuals were followed for enough years. In 1973, the National Cancer Institute (NCI) funded the Gastrointestinal Tumor Study Group (GITSG), and in 1977 the National Surgical Adjuvant Breast Project (NSABP) launched studies C-01 and R-01. Not only did this add a second B (bowel) to NSABP, but it also helped create the precedent for addressing colon and rectal cancers differently. The flexible sigmoidoscope became a reality in 1967, and much later new techniques helped investigators interrogate the molecular events within cancers. Numerous other advances—such as imaging or surgical instruments—affected a range of cancers. And, of course, just as ASCO would go international, so too would cancer research. Progress would not depend solely on the U.S. research groups.

And progress there has been. By following cohorts of patients we have a better understanding of environmental risk factors (e.g., red meat) or potential protective factors (e.g., aspirin) for CRC, and pathologists and molecular biologists created a step-wise model for colon carcinogenesis.1 Gastroenterologists have shown that most cases of CRC can be avoided with the removal of polyps—if only enough of the right patients were screened.

These advances have led to a decreasing incidence of CRC; although nearly 150,000 people in the United States will still be diagnosed with CRC this year. The following sections will discuss the separate advances of surgery, chemotherapy, and radiation therapy and then highlight how the emergence of multidisciplinary care has led to changes in the treatment paradigm. Finally, this article speculates what we hope to discuss at ASCO’s next landmark anniversary.

SURGERY

When ASCO was founded, colon and rectal cancer had been the purview of surgeons for more than a century. A standard segmental resection of the involved colon had been defined, and it has remained unchanged over the ensuing years. Colon surgery was straightforward unless the cancer had invaded contiguous structures and local recurrence was unusual. On the other hand, we had already observed that local recurrence was a major problem for tumors arising in the rectum and from the Helen Diller Family Comprehensive Cancer Center University of California, San Francisco, San Francisco, CA; Memorial Sloan-Kettering Cancer Center and Weill Medical College of Cornell University, New York, NY; UNC/Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC.

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that systemic failure was all too common. The abdominal-perineal resection (APR) was the standard.

In the late 1970s, Heald and the Basingstoke Group began removing the mesorectum in its entirety in every patient with rectal cancer through sharp—rather than blunt—excision.\(^2\)\(^3\) Resection of the rectum with its cylindrical mesentery and associated nodal tissue was accomplished by precise dissection between the visceral and parietal sheets of the endopelvic fascia. The goal was sharp dissection to the pelvic floor and complete removal of the en bloc “package” contained within the “envelope” of the visceral sheet of the pelvic fascia. This technique, which Heald termed total mesorectal excision (TME), resulted in dramatically reduced rates of local recurrence, and it quickly became the surgical golden standard. In 1986, Quirke and colleagues demonstrated a lower rate of recurrence when the circumferential (radial) resection margin was free of tumor.\(^4\) These improvements in surgical technique, along with advances in instrumentation, perioperative technology, and postoperative care resulted in better recovery and survival. Intraoperative preservation of the autonomic pelvic nerves also became possible, lessening the prospect of long-term urinary and sexual dysfunction and improving patients’ quality of life.\(^5\)

By midcentury, a more sophisticated understanding of oncologic principles led to surgeons performing a low anterior resection (LAR) with coloanal anastomosis to treat tumors located 5 cm or more above the anal verge. This made sphincter preservation possible, with equivalent oncologic results and without the need for a permanent stoma. It soon became clear that even rectal tumors situated less than 5 cm from the anal verge were amenable to LAR with bowel anastomosis. As a rule of thumb, sphincter preservation was considered possible if a tumor-free distal margin of at least 2 cm could be obtained.

In the 1990s, investigators reported the results of intersphincteric resection of very low rectal cancers. Intersphincteric resection entails removing the internal sphincter to obtain a sufficient distal margin, preserving intestinal continuity. This made sphincter-sparing surgery possible for most patients, even in the setting of very distal rectal tumors.\(^6\)^\(^7\) It is now believed that tumor-free margins of 1 cm or less are oncologically sound. Abdominoperineal resection is reserved for a minority of cases.

The application of laparoscopic and robotic technology to rectal cancer surgery has resulted in less intraoperative blood loss, less postoperative pain, briefer hospital stay, and better short-term results for an increasing number of patients.\(^8\) However, given the organ’s anatomic location and blood supply, survival and relapse after surgery are associated not only with operative technique but also with tumor and nodal stage. Cancers that invade through the rectal wall (T3/T4) or involve locoregional lymph nodes (N1/N2) portend a greater risk of both local and distant recurrence than less extensive tumors.\(^9\)

### CHEMOTHERAPY

Considering the crowded field that represents the current chemotherapies active in CRC, two things stand out: 5FU is still a major component of every treatment setting and none of the other available therapies were in use before 2000. So although chemotherapy is at least partly responsible for improved survival across the adjuvant and metastatic settings, we will need more time to know if the gains from newer agents will diminish or increase over the long term.

### Adjuvant Therapy

The first major advance of chemotherapy in CRC was in 1989, when the NCI distributed an Advisory Letter that announced the “availability” of a treatment that “substantially reduces the risk of dying from recurrent colon cancer.” This alert heralded the combination of adjuvant levamisole (LV) and 5FU as the new standard, based on 5-year survival in patients with Dukes’ C of 49% compared with 37% for the combination compared to no therapy. This would represent the high point for LV: an “immune modulator” in humans and an anthelmintic in veterinary medicine. Shortly after this data became available, Dr. Charles Moertel spoke from an ASCO podium and excoriated the drug’s distributors for charging humans 100-fold the cost of a veterinary dose of the drug. Unfortunately, that issue would soon be moot when reports of LV-induced multifocal leukoencephalopathy surfaced and the NCI recalled the drug 3 years after the initial advisory.

That misstep was partly responsible for the slow pace, or lack, of progress in adjuvant therapies for colon cancer during the 1990s, when a large US intergroup trial had already been launched to ask a duration and dosing question with bolus 5FU and LV, as well as to explore the added benefits of folinic acid as a modulator to 5FU.\(^10\) Also problematic was the split decision across cooperative groups, who remain divided even today as to whether patients with stage II and stage III (stage C reclassified from the earlier staging systems) disease should be included in the same or different studies. In retrospect, regardless of the LV misfire and the staging question, the tools did not exist in those years to have made much more of an effect.

While the debate about standard adjuvant therapy for colon cancer in the United States boiled down to scheduling differences between the Mayo Clinic and Roswell Park, the next major advance would not be presented at ASCO until 2004, and it would come from French investigators.\(^11\) Willing to use the continuous infusion route for 5FU and with access

### Key Points

- Colorectal cancer (CRC) requires multidisciplinary care.
- Radiation therapy can be delivered more precisely than before.
- Systemic therapy is much improved even without biologics.
- Surgery alone is not enough to cure most patients.
- Even patients with metastatic CRC may be cured.
to oxaliplatin, de Gramont presented the results of the MOSAIC trial. The infusional 5FU and oxaliplatin combination—dubbed FOLFOX4—improved 3-year disease-free survival from 65.3% to 72.2% in patients with stage III disease and with longer follow-up would show a probability of survival at 6 years of 73.0% in patients with stage III disease and 86.9% in patients with stage II disease.

The U.S. Food and Drug Administration (FDA) quickly approved oxaliplatin for use in the United States, restricting it to patients with stage III disease. Although MOSAIC included patients with both stage II and III disease and while separate analyses by stage were not preplanned, the FDA—correctly it seems—took the unusual step of distinguishing patient eligibility post hoc. mFOLFOX6 (FOLFOX4 without bolus 5FU) has been modified by most practitioners, and it remains today’s standard. Capecitabine (an oral fluoropyrimidine prodrug) has been shown to be noninferior to bolus 5FU/LV in patients with stage III disease and represents a monotherapy option for patients deemed poor candidates for oxaliplatin or an acceptable substitute for infusional 5FU in FOLFOX. A pooling of the data from studies around the world currently comparing 12 to six cycles of mFOLFOX6 will tell us if less exposure to the neurotoxic oxaliplatin leads to similar survival results.

That an oxaliplatin-based therapy remains a standard is not alarming, but that it is the standard is a wake-up call. The past decade has seen numerous contemporary trials of adjuvant therapy for stage III disease come up short: irinotecan, bevacizumab, and cetuximab have all failed in large trials and with longer follow-up would show a probability of survival at 6 years of 73.0% in patients with stage III disease and 86.9% in patients with stage II disease.

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Combination therapy has become the default stance and it is noteworthy that every new agent introduced over the past two decades in CRC has been tested in combination with a fluoropyrimidine. Although more is usually assumed to be better, it has been shown that for patients with incurable disease, sequential therapy strategies lead to similar outcomes to combinations.

By most accounts, the last 15 years of drug development in CRC have been fruitful. Irinotecan and oxaliplatin were both approved with data in refractory and then first-line metastatic disease and when combined with 5FU as FOLFIRI and FOLFOX roughly equivalent. Bevacizumab showed dramatic additivity to an irinotecan/5FU bolus regimen (and was presented at the 2004 ASCO meeting at the same session as the MOSAIC data) although no subsequent study would show as dramatic an effect for the anti-vascular endothelial growth factor antibody. The epithelial growth factor receptor (EGF-R) antibodies advanced with meaningful combined monotherapy activity but are probably underused due to the unsightly acneiform rash and ziv-aflibercept and regorafenib are too new to critique.

To put the present treatment options into perspective, the National Comprehensive Cancer Network (NCCN) spends nine pages in its Guidelines and 20 pages of text defining the possible permutations for CRC management. The term “line” has been replaced by the phrase “continuum of care.” This uncertainty accurately reflects the findings of dozens of randomized trials around the world that have tested enumerable combinations. While research is good, too much research with too many angles does not lead to clarity. Nonetheless, recent studies suggest patients with metastatic CRC are now surviving an average of 30 months, compared to 6 to 8 months in the early days. While some of that can be attributed to chemotherapies, some is a function of earlier diagnosis of metastases and much is a function of improved staging and multidisciplinary management that may often use new if unproven technology to prolong lives in some if not most patients.

Metastatic Disease

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RADIATION THERAPY

Fifty years ago, CRCS, as well as many other adenocarcinomas, were thought to be radioresistant. Despite a few reports

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suggesting the utility of radiation therapy, there was certainly no thought of it having a general role. But despite the skepticism of surgeons it was becoming clear that local recurrence was a clinical problem, particularly for rectal tumors extending through the bowel wall as well as for those with node disease. In retrospect, with blunt dissections in the mesorectum in comparison to the sharp dissection used today, it is not surprising that local-regional recurrence rates were high. As radiation therapy is especially effective against small volume disease, there appeared to be great potential in its use to prevent local-regional failure.

Initially the emphasis was on postoperative radiation therapy as techniques to define preoperatively which patients were at high risk of local failure did not exist; transrectal ultrasound, pelvic CT scans and MRI were not even in the imagination of a forward thinking clinician in 1964. CT scans were first used clinically in the early 1970s, based on basic physics research in the 1960s that resulted in a Nobel Prize (Cormack and Hounsfield, 1979), and were very low quality and only used for brain lesions. MRI was a research tool until much later and ultrasound had a gradual evolution over many decades. Colonoscopy was also not available 50 years ago, as the needed fiberoptic techniques were just being developed. In fact, the diagnostic tools available for evaluation of a primary rectal tumor were limited to rigid endoscopy, barium enema, and the venerable digital rectal examination. The evaluation for metastatic disease included only chest X-ray, liver function tests, and nuclear liver-spleen scans (CEA was not yet developed). With these minimal diagnostic tools it is not surprising that investigators needed the pathologic examination of the surgical specimen to be able to define which patients were at high risk of recurrence—both local-regional and distant.

The technology for delivering radiation therapy was also undergoing dramatic changes that allowed for the safe delivery of higher doses of radiation therapy. Lest we forget, in the early trials of postoperative radiation therapy for rectal cancer, one cycle of chemotherapy was given before the initiation of radiation therapy. This was not based on biologic or scientific principles but reflected concern for the safe delivery of radiation and bought time while the radiation techniques could be centrally reviewed before initiation of therapy.

All aspects of radiation treatment planning and delivery have changed over the past 50 years. In the early 1960s, most radiation therapy was given with low energy sources such as cobalt-60 machines, Van de Graaf generators or orthovoltage machines. These delivered a much higher dose to the skin and other organs than present day machines, and produced more toxicity. Dose calculations were of one point at the center of the radiation fields which were primarily planned by using external anatomy: the radiation oncologist drew on the patient skin their impression of what was the correct location for radiation therapy delivery. The accuracy of radiation delivery was anybody’s guess.

Computers have changed everything about radiation treatment. Three-dimensional planning and the ability to incorporate imaging data from any modality allows for the radiation therapy field to be fully defined in all dimensions, with precise dose localization to the highest risk area and protection of normal tissues from the highest radiation doses. And today’s higher energy X-rays penetrate to deeper structures, with less dose to sensitive normal structures.

As if we need a reminder of the incredible insight of the earliest leaders in oncology, the laboratory data suggesting that tumor cell sensitization was produced with the concomitant use of fluoropyrimidines, such as 5FU and radiation therapy dates to the 1960s. Moertel et al at the Mayo Clinic showed efficacy of such a combination and a series of clinical trials done over the ensuing decades demonstrated convincingly that the combination of radiation therapy and chemotherapy decreased the local-regional recurrence rate in half compared to the use of surgery alone. Subsequent studies showed oral fluoropyrimidines to be as effective as their intravenous counterparts.

**MULTIMODALITY THERAPY: PUTTING THE PIECES TOGETHER**

The proper management of colon cancer requires coordination of care by surgeons and medical oncologists since there is little evidence that radiation plays a role in any but the most advanced cases. However, the subset of patients (about 1/4) with a cancer in the distal 12–15 cm of the bowel need the input of radiation oncologists as well. Indeed, the 50 years has resulted in the reordering of the roles of the modalities just discussed.

Radiation and chemoradiation were initially seen as postoperative maneuvers to control the local spread of cancer in the pelvis. A pooled analysis of five phase III North American rectal cancer trials (NSABP R01, NSABP R02, NCCTG 794751, NCCTG 864751, and US GI Intergroup 0114) assessed the impact of rectal cancer treatment on outcomes and these studies individually and taken together convincingly show a benefit for the three modalities in patients with high-risk tumors (T3N1 or greater). However, the aggregate analysis of 3,791 patients found that in the small subset of patients with intermediate-risk tumors (T1/2N1 and T3N0) there was no improvement in disease-free or overall survival when radiation was added to chemotherapy postoperatively.

Once it became clear that this approach could enable many patients to live a life cancer-free, the quality of that existence then mattered. As with many other cancers that became curable over these 50 years, the consequences of the “do not hold back” approach of oncology demanded attention. For rectal cancer, it would be personal and private matters such as bowel and sexual dysfunction that prompted the order of events to be revisited and just as colon cancer management changed when the French contributed FOLFOX, German investigators would lead the way in rectal cancer.

The NSABP launched its third rectal cancer trial (R-03) involving patients with clinical T3 or T4 node-positive rectal cancer to test the concept of employing surgery after rather than before chemoradiation. And while the study ultimately showed the apparent prognostic importance of a complete
pathologic response, it fell far short of its accrual goals. Only about 250 patients participated so the order of interventions could not be assessed.26 Luckily, the German CAO/ARO/AIO 94 trial accrued 823 patients over the similar time-frame.27,28 The preoperative group showed a statistically significant decrease in 5-year local recurrence (6% vs. 13%; p = 0.006) with less toxicity: the incidence of grade 3 or higher toxicity was 27% in the preoperative group, but 40% in the postoperative group (p = 0.001). These results were later validated; at a median follow-up of 11 years, decreased 10-year local recurrence in the preoperative group persisted (7.1% vs. 10.1%; p = 0.048). No differences were observed in the incidence of distant recurrence, disease-free survival, or overall survival.28 Since this landmark study, preoperative chemoradiation has been favored over adjuvant radiation therapy.

One thing that has not changed is the schedule of radiation: in the US it was at first, and remains, a 5.5-week course of therapy (with weekends off). Studies have explored short course preoperative radiation (25 Gy in 5 fractions) and therapy (with weekends off). Studies have explored short course preoperative radiation (25 Gy in 5 fractions) and while popular in portions of Europe, it has not been embraced in the United States.

Long-term follow-up demonstrated that patient subgroups characterized by nodal involvement, negative circumferential margins, and low-lying tumors (5–10 cm from the anal verge) benefited most from preoperative radiation.29,30 These findings suggest that some patients may not benefit from chemoradiation. Because TME with negative circumferential resection margins alone has achieved excellent local control in so many patients,31,32 the necessity of applying the three-pronged treatment paradigm to all patients has been questioned.

Several single-institution reports comparing trimodality therapy to surgical therapy alone suggest that, in select groups of patients, equivalent rates of recurrence-free and overall survival are possible with TME only.32 Pooled analyses of several large trials have provided a better understanding of risk stratification. Collective data from three phase III North American trials evaluating adjuvant treatment of rectal cancer (NCCTG 794751, NCCTG 864751, and US GI Intergroup 0114) show that T/N sub-classification offers superior prognostic accuracy.33 In this pooled analysis, all patients received postoperative radiation and were randomized to concurrent and maintenance chemotherapy. T/N stage was established according to risk of recurrence: low (T1/2N0), intermediate (T1/2N1, T3N0), moderately high (T1/2N2, T3N1, T4N0) and high (T3N2, T4N1/2). Patients with tumors classified as intermediate-risk had better outcomes than those with moderately-high and high-risk tumors, with lower rates of local recurrence (6% to 8% vs. 8% to 15% and 15% to 22%, respectively) and better overall survival (74% to 81% vs. 61% to 69% and 33% to 48%, respectively).33 This suggests that adjuvant radiotherapy may not be a routine requirement for patients with intermediate-risk tumors (T1/2N1 or T3N0) following TME resection with negative radial margins, although in this analysis all patients received radiation therapy, making conclusions difficult.34

INDIVIDUALIZING CARE

While the trimodality approach has been designed with the aim of curing nonmetastatic disease, a new meaning of the term metastatic disease has revolutionized how we manage metastatic tumors. Fifty years ago it was assumed that metastatic disease was an “all or none” phenomenon—patients either had local-regional disease only and had potential for cure, or they had metastatic disease and they had a tumor that was not curable. We now know that this is not true and that patients with localized metastatic disease, oligometastases, can be cured. The data on liver resections for metastatic CRC is compelling and show that a substantial percentage, perhaps 40%, of patients who have resection of isolated liver metastases can be cured of their disease with surgical resection alone.35 Other techniques such as radiofrequency or microwave ablation can also control small volume disease in the liver. The same is also true for limited metastatic disease in the lung or in nodal chains in the abdomen and pelvis. The situation has changed so much that at the present time the oncology team should always consider surgical or ablative approaches as the initial and primary management for patients with localized metastatic disease.

Although the data are not as compelling as for surgical resection, radiation therapy also has a role in the management of patients with limited metastases. There was little thought 5 decades ago about treating isolated disease in the liver with radiation therapy as the liver is known to be quite sensitive to relatively low doses of radiation therapy. However, as radiographic tumor localization improved, as radiation dose localization became much better, and as there became better means for accounting for the movement of the liver during the respiratory cycle, radiosurgical ablation of liver and lung metastases (stereotactic radiation therapy) has become a viable treatment alternative that can produce local tumor control at the metastatic site, when other approaches are not appropriate.36 Depending on the situation, we now can combine resection, RFA or microwave ablation, and radiosurgical approaches to provide a realistic chance of cure for the patient with oligometastatic disease.

FUTURE DIRECTIONS

It is impossible to predict how the roles of the components of trimodality therapy will evolve over the next decade, let alone over the next 5 decades, but we do know what the research directions are at the present time. Assuming chemotherapy is a constant, current studies are attempting to determine whether radiation can be omitted for some patients with rectal cancer, with equivalent oncologic results. A recent exploratory prospective trial at Memorial Sloan Kettering Cancer Center of 32 patients with rectal cancer (22 with clinical node-positive disease) evaluated the impact of replacing preoperative fluorouracil-based chemoradiation with neoadjuvant FOLFOX (6 cycles) and bevacizumab (4 cycles). Thirty patients completed neoadjuvant therapy, followed by margin-negative (R0) TME resection; eight patients (27%)
had a complete pathologic response and remained free of local disease.37

This established the basis for a multi-institutional phase II/III randomized, prospective trial (NCCTG-N1048, NCT01515787) comparing neoadjuvant FOLFOX with selective use of chemoradiation. Only patients in the selective arm who have histologically positive circumferential resection margins undergo chemoradiation, because of their increased risk of local recurrence.

Refinements in radiation are constant but it seems unlikely that improved dose localization will have much further incremental impact until we have better imaging localization of minimal disease. When that occurs, focal high-dose radiation therapy could have an enormous impact in tumor control of both localized and metastatic tumors. Similarly, enhanced tumor profiling will likely allow us to be able to do a far better job of stratifying patients into high-risk and low-risk groups, and this will impact both local and systemic therapies. Whether this categorization will be from mutational analysis, expression profiling, miRNA panels, proteomics, circulating tumor cell analysis, or some other technique is totally unclear, but it seems quite likely that it will occur.

Last, we now know that radiation therapy with concurrent fluoropyrimidine treatment can control some percentage, perhaps 20%, of patients without surgical resection.38 Although much investigation into better radiation sensitizers has not as yet been successful, there is a reasonable likelihood that such sensitizers will be developed in the coming decade. Improved sensitization could occur from a better understanding of the biology and mechanisms of cellular repair mechanisms or other biologic approaches. It could also occur from better drug delivery through nanoparticle formulations that are selective in drug delivery to tumor. If these developments do occur, the role of radiation therapy in rectal cancer could be transformed to a definitive therapy, much as is the case in anal cancer at the present and the role of surgery could be dramatically altered.

The role of adjuvant chemotherapy will also likely evolve. There are data that for patients with rectal cancer who receive neoadjuvant radiochemotherapy (and especially if a good response is obtained) further chemotherapy may not be needed. Advances in tumor and normal tissue analysis are likely to define a subset of patients who either do not require adjuvant chemotherapy or, as in the case of microsatellite instability, may benefit only from specific drug regimens or perhaps from no drug treatment at all.

## THIS YEAR AND THE NEXT 50

The hard-earned multimodality paradigm for rectal cancer and the series of studies in colon cancer represent major accomplishments of the past 50 years. As noted above, more may not be better and the possibility of avoiding one or another of the modalities is a real one. The proper use of surgery and radiation is under study.

But at the risk of overstating the promise of personalized oncology in CRC, systemic therapy is still the major shortcoming for these diseases. Advances just recorded during ASCO’s 50th year shine a light on where we may be headed. The observation that any RAS mutation—and not just KRAS—make patients resistant to EGF-R antibodies further defines the patient population to be treated with these agents. And while not yet ready for prime time, early returns suggest that strategies to target BRAF may have substantial upside.

We may also be ready to clarify the confusion of first line options. CALGB 80405 is a study that directly compares cetuximab to bevacizumab in combination with chemotherapy. Expecting those results this year, we may learn when and where to use those agents. But perhaps more promising, employing the newest technology—bioinformatics and molecular—to tissue and blood specimens, we may be able to categorize cancers and shine a light on where we are and where we are going.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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