A Multidisciplinary Approach to the Treatment of Early Colorectal Cancer

Including a Clinical Discussion on Audio CD

Edited by

Edward Chu, MD
Yale Cancer Center
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Monograph
Activity release date: September 1, 2007
Activity expiration date: September 1, 2008

About the Activity
The CME activity is based on the information learned from the book component of A Multidisciplinary Approach to the Treatment of Early Colorectal Cancer, Including a Clinical Discussion on Audio CD. It was developed from an identified educational need for information about practical management issues in the practice of medical, surgical, and radiation oncology.

This activity has been developed and approved under the direction of Beam Institute.

Activity Learning Objectives
After reading A Multidisciplinary Approach to the Treatment of Early Colorectal Cancer, participants should be able to:

- Assess protocols to harvest and analyze lymph nodes and other tissues of individuals suspected of having colon cancer to accurately stage disease and provide maximal benefit of therapy.
- Describe various surgical techniques used to resect colorectal cancer lesions, consider their advantages and disadvantages, and understand outcomes and morbidities related to their use.
- Compare clinical results of current surgical, chemotherapeutic, and radiotherapeutic methods to treat colorectal cancer and its recurrence.
- Realize advances in identifying and characterizing the many molecular pathologic variables of colorectal tumors and how they affect patient management.
- Examine current standards of colorectal cancer, treatment, controversies concerning adjuvant treatment of the disease, and neoadjuvant approaches that combine chemotherapy with radiotherapy prior to surgical resection.
**Credit Designation**

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Dr. Chu is a consultant for Bristol-Myers Squibb/ImClone, Roche, and Sanofi-Aventis; he receives grants/research support from Bristol-Myers Squibb/ImClone, Genentech, Pfizer, Roche, and Sanofi-Aventis. Dr. Saif receives grants/research support from Avalon, Biogen, Bristol-Myers Squibb/ImClone, Roche, Samyang, and Taiho; he serves on the speakers bureau for Amgen, Genentech, Pfizer, Roche, and Sanofi-Aventis. Drs. Cha, Costa, Duffy, Lee, Longo, McGowan, and Walther have indicated they have no financial relationships with any manufacturers or providers.

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**Roundtable on Audio CD**

Activity release date: September 1, 2007  
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This activity has been developed and approved under the direction of Beam Institute.

**Activity Learning Objectives**

After listening to the audio portion, entitled *A Multidisciplinary Approach to the Treatment of Early Colorectal Cancer*, participants should be able to:

- Discuss current surgical, chemotherapeutic, and radiotherapeutic methods to treat colorectal cancer and its recurrence, as well as new therapies currently being tested against this malignancy.
• Assess protocols to harvest and analyze malignant tumor tissue and lymph nodes of individuals suspected of having new or recurrent colorectal cancer.

• Describe the advantages and disadvantages of surgical techniques used to resect colorectal cancer lesions.

• Review the staging of colorectal tumors, considering the utility of immunohistochemistry and of prognostic and predictive markers of the disease.

• Examine current standards of treatment and controversies concerning adjuvant treatment of colorectal cancer.

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Target Audience
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[Logo]
Colorectal cancer (CRC) is a major public health problem in the United States and throughout the world. Each year, this disease affects nearly 150,000 new patients, and it is the second leading cause of mortality, accounting for almost 50,000 deaths in the United States. Worldwide, CRC afflicts nearly 800,000 individuals and is associated with 500,000 deaths. Over the past 10 years, significant advances have been made in the screening for and early detection of CRC as well as in the different treatment approaches—including surgery, radiation therapy, and chemotherapy—that are now available for patients with early-stage CRC and more advanced stages of the disease. Without question, CRC has now become a highly preventable and curable disease through regular screenings and early detection, and highly treatable when diagnosed at an even more advanced stage.

In this book, we have condensed and summarized a wealth of essential information on the multidisciplinary treatment approach for patients with early-stage CRC, and presented it in a practical and readable format. It is critical that a team of physicians from various specialties—including surgery, radiation oncology, medical oncology, pathology, and radiology—provide their particular expertise in developing individual treatment plans for patients with CRC. With this in mind, the first three chapters review various key aspects relating to the surgical management of patients with CRC. The subsequent two chapters are focused on pathologic staging and the role of prognostic and predictive biomarkers in pathologic assessment. The final three chapters are devoted to an update on the role of adjuvant chemotherapy for colon cancer, the integration of biologic agents in adjuvant treatment regimens, and the combined-modality approach to treating rectal cancer.

My hope is that this book will serve as a source of practical information that can be used by physicians and other health-care professionals actively involved in the daily care of patients with CRC. This book should be viewed as a work in progress; our hope is to update it in the future to incorporate new drugs and treatment strategies that reflect the rapid advances in the field of CRC.

—Edward Chu, MD
Chapter 1: Early Colorectal Cancer: Nodal Evaluation and Sentinel Lymph Node Mapping

Charles Cha, MD

As is the case with a growing number of malignancies, the quantity and accuracy of lymph node retrieval has become a topic of much debate for patients with colorectal cancer (CRC). Colorectal cancer is the most common malignancy of the gastrointestinal tract, with an estimated 153,000 new cases expected to be diagnosed in the United States in 2007.[1] Nearly all patients with early CRC will undergo resection for attempted cure; an adequate lymph node assessment is critical to provide both accurate staging as well as maximal therapeutic benefit. It has therefore been the goal of numerous investigators to evaluate whether the traditional resection of the node-bearing mesentery along with the colorectal surgical specimen is sufficient. If so, how much of the mesentery should be removed and how many lymph nodes must be assessed? Furthermore, are newer technologies such as sentinel lymph node mapping, immunohistochemistry (IHC), and polymerase chain reaction (PCR) of any added benefit to our standard techniques?

Adequate lymph node analysis is a critical factor for making a therapeutic decision in CRC; the presence or absence of nodal metastases will predict long-term survival for patients more accurately than any other prognostic factor. Because of the high rate of recurrence, adjuvant chemotherapy is recommended for all patients with lymph node metastases (stage III). Furthermore, even in node-negative stage II patients, the risk of developing recurrent disease remains in the range of 20% to 30%.[2] As a result, selected patients with stage II disease and adverse histologic features will receive adjuvant chemotherapy.[3] Will better sampling or improved analysis of lymph nodes lead to a more targeted approach to treating high-risk stage II patients, helping to stratify high-risk patients and prevent unnecessary adjuvant therapy in patients with a low risk of progression?

A recent systematic review of available multicenter randomized trials, population-based observational studies, and single-institution cohort studies concluded that the number of lymph nodes evaluated after surgical resection was positively associated with...
survival in stage II and III colon cancer patients.[4] It is unclear whether this effect reflects a true therapeutic benefit or rather more accurate staging with concomitant stage migration (also known as the Will Rogers effect). In either case, what is clear is that accurate staging is a crucial component determining both therapy and prognosis.

History of Nodal Staging in Colorectal Cancer

Much of our knowledge about the nodal spread of colorectal cancer is due to the anatomic studies of Cuthbert Dukes, a pathologist at St. Mark’s Hospital and the originator of the Dukes staging classification, in 1932. Recognizing the pathologic importance of lymphatic spread, Dukes created a system where involvement of regional lymph nodes was designated stage C, regardless of depth of tumor invasion into the bowel wall. This system was further modified into the Astler-Coller “modified Dukes” system, which stratified node-positive patients according to depth of tumor penetration in 1954.[5]

The TNM system in use today was first introduced in 1953 and is loosely based on the Dukes staging system with varying degrees of modifications. The current TNM staging system for colorectal cancer was jointly developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC).[6] A significant change in the most recent sixth edition of the AJCC Cancer Staging Manual was the stratification of stage III into IIIa (T1/2, N1), IIIb (T3/4, N1), and IIIc (N2), as significant differences in survival were seen among node-positive patients who were previously grouped together into a single group in the fifth edition (T, any N1, M0).[7]

Although the current staging system has been validated by a number of studies, including two that analyze over 56,000 colorectal cancer patients with stage III disease,[8,9] some inconsistencies have arisen, highlighting the problem of understaging nodal disease. In a study of the Surveillance, Epidemiology and End Results (SEER) database, O’Connell et al compared survival using the sixth edition of the AJCC Cancer Staging Manual.[10] In their analysis, they found that survival in patients with stage IIb (T4, N0, M0) disease was actually worse than in those presenting with stage IIIa (T1/2, N1, M0) disease. Furthermore, a recent population-based analysis found that only 37% of patients receive adequate lymph node evaluation.[11] These findings suggest that patients with stage IIb disease are either inadequately staged or that they may benefit from the same chemotherapy that stage IIIa patients routinely receive.

Proper Nodal Evaluation in Colorectal Cancer

Standard surgical techniques for resection of colorectal cancer have evolved over the past few decades and improvements in technique have contributed to better tumor clearances and a decrease in local recurrence rates, particularly in rectal cancer (see Chapter 3,
“Surgical Management of Rectal Cancer and Its Variants”). The importance of an adequate lymph node retrieval has become increasingly apparent, and current guidelines require that at least 12 nodes be assessed in order to consider a patient truly node-negative. This recommendation was established by a number of governing bodies, including the AJCC, the UICC, the World Congress of Gastroenterology, and a National Cancer Institute (NCI)-sponsored panel of experts specifically gathered to ensure adequate lymph node assessment.\[12-15\] However, it should be noted that this final recommendation evolved over time and is based on numerous studies that have suggested that as few as 6 to as many as 40 nodes were an ideal minimum obtained during resection.\[16-18\]

Early studies of patients with stage II disease found that those with six or fewer lymph nodes assessed had a lower survival than patients with more than six removed.\[16\] Removal of only six nodes was eventually determined to be inadequate for accurate staging by Caplin et al.\[19\] A report by Wong et al\[17\] analyzing the National Cancer Database concluded that a minimum of 14 nodes would lead to accurate staging for T2/3 patients. Another group studied 2,427 patients with T3 tumors and found a 75.8% 5-year overall survival when 17 nodes were assessed compared to 62.2% for those with 7 or fewer nodes in their surgical specimen.\[20,21\] Some authors utilized mathematical modeling using the Poisson paradigm and the Bayes theorem to mathematically confirm whether node-negative patients were adequately staged.\[22\]

Eventually, an international consensus of a minimum of 12 lymph nodes was decided on, though interestingly, none of the available trials at the time used 12 nodes as a cutoff. Subsequent analysis of actual lymph node retrieval noted that in the United States, the median number of lymph nodes recovered following colorectal resection was only 9, and that only 37% of patients actually had 12 or more nodes recovered. By 2002, this percentage improved to 44% of patients who were adequately staged with 12 or more lymph nodes.\[11\] These results were not unique to the United States, as a number of trials from the Netherlands, Canada, France, and Sweden found the median number of lymph nodes examined at surgery to be seven to nine.\[23-25\] It is significant to note that the assessment of at least 12 lymph nodes is one of the quality measures that have been targeted by the NCI-sponsored National Quality Forum on colorectal cancer care. As part of the American College of Surgeons quality assurance program, the number of nodes recovered following colorectal resection will be tracked nationwide.\[26\]

**Factors That Affect Number of Lymph Nodes Recovered**

There are a variety of factors that influence the number of lymph nodes recovered in patients with colon cancer, including the quality of the surgical resection, the quality of the pathologic evaluation, patient factors, and tumor factors.
Surgical Factors

The first variable that must be considered is the quality of surgical resection. The surgeon must provide an adequate specimen that is composed of the segment of bowel containing the tumor and its associated mesentery to the level of the origin of the draining vessels. Long-term survival and local failure rates after surgical treatment of colorectal cancer and other malignancies have been associated with surgeon and hospital volume, suggesting that surgeon or hospital volume may be a surrogate indicator of surgical quality.[27-29] Surgeons performing a high volume of colorectal resections may be performing a more complete resection of the primary tumor with a more complete resection of the lymph node–containing mesentery. In fact, surgeon volume has been associated with lymph node recovery as well.[30] Furthermore, resections occurring in teaching hospitals have been observed to have a higher recovery of lymph nodes as well.[31-33] Overall hospital volume is also associated with an increased number of lymph nodes recovered and reflects influences by both the surgeon and pathologist.[34] Patients in low-volume hospitals were more likely to have fewer than seven lymph nodes evaluated and less likely to have positive lymph nodes detected.

Pathologist-Related Factors

High hospital volume also leads to increased experience and expertise on the part of the pathologist. Much like the surgeon who specializes in colorectal disease, pathologists who develop a special interest in colorectal cancer will identify a larger number of lymph nodes in a given specimen. In a multicenter trial from the Netherlands, after adjustments for relevant factors such as stage and adjuvant therapy, there was variation in patient survival between departments of pathology, based on the ability to recover lymph nodes.[35] As evidence that pathologic assessment was as important as surgery, in the Dutch study, there was no difference in the number of lymph nodes recovered between hospitals that were covered by the same department of pathology. Furthermore, hospitals covered by two separate pathology groups had lymph node recovery rates dictated by pathology group rather than surgeon. These results suggest that pathologic rather than surgical practice patterns may be more important in lymph node recovery.

The College of American Pathologists has established guidelines[36] for the pathologic evaluation of colorectal cancer resection specimens, including the recommendation that if fewer than 12 lymph nodes are found, additional techniques for visual enhancement should be considered. The most straightforward is to increase the time of fixation in formaldehyde for an additional 24 hours, as well as the practice of embedding of the mesenteric fat and the use of fat clearance techniques.[37] The experience of the pathologist and the technique of pathologic evaluation, including the use of templates,
have been shown to be important in lymph node recovery after adjusting for surgeon- and tumor-related factors.\[30,38\] Thus, both surgeon and pathologist factors associated with lymph node recovery may influence the relationship between hospital volume and colon cancer outcome.

**Patient Factors**

There are a number of patient-related factors that can influence the number of nodes recovered following surgery. A fibrotic response occurs in patients who have received preoperative chemoradiotherapy, making it difficult to identify nodes on pathologic evaluation; the size of both normal and involved lymph nodes decreases. Because the average lymph node harvest for patients following preoperative therapy is significantly lower, the AJCC has concluded that a pathologic N0 designation was justifiable in patients following chemoradiation even when the optimum number of 12 nodes were not available for analysis.\[6\]

Another patient factor that affects lymph node recovery is the anatomic location of resection. Right hemicolectomy and subtotal colectomy appear to give the highest yield of lymph nodes compared to transverse colectomy and abdominal-perineal resection, where a 33% to 48% reduction in the number of lymph nodes is seen.\[39\] Other patient factors include older age and obesity, which decrease lymph node recovery (a 6.8% reduction in lymph node recovery for every 10-year increase in age).\[11,32,40\] However, some surgeons may perform less extensive or palliative operations on older patients, which may explain the association between age and the number of lymph nodes recovered.

**Increasing the Sensitivity of Detecting Lymphatic Involvement**

A more thorough scrutiny, as well as a more sensitive analysis, of lymph nodes that are recovered with surgical resection of colorectal cancer represent strategies to more accurately stage a patient. The standard assessment of lymph nodes is to bisect and embed each half of all identified nodes larger than 2 mm in size. Simply increasing the number of sections taken of individual nodes could increase the sensitivity of detecting lymphatic metastases. However, this approach would also increase the workload of pathology departments significantly.

In a study of 100 colorectal cancer specimens, three sections of each node were taken vs the normal single section. Twelve extra metastases to lymph nodes were discovered in 11 patients, which was statistically significant; however, only two patients were actually upstaged according to TNM classification.\[41\] This technique represents the least technologically challenging but logistically difficult method of increasing detection of lymph node metastases.
The use of immunohistochemical evaluation of lymph nodes using anticytokeratin antibodies can also detect micrometastasis with greater sensitivity than standard H&E evaluation of lymph nodes. At this time, however, the clinical significance of micrometastatic disease that is not detectable by conventional means is unclear. The suggestion that patients with node-negative disease have a significantly poorer outcome with micrometastatic disease detected by IHC is a matter of debate. Some investigators have identified a higher risk of recurrence as well as adverse outcome with micrometastases to the regional lymph nodes and have recommended the routine IHC evaluation of stage II patients, though other authors have suggested there is little to no clinical significance to micrometastases. Given the increased workload and lack of clear-cut benefit, routine immunohistochemistry is not recommended on all lymph nodes and should be used selectively.

An even more sensitive test for micrometastases is using reverse transcriptase–polymerase chain reaction (RT-PCR) to detect three epithelial markers (carcinoembryonic antigen, guanylyl cyclase, and cytokeratin 20) in histologically node-negative patients. Reverse transcriptase–polymerase chain reaction is highly sensitive at detecting micrometastases in 24.5% of patients previously categorized as node-negative and increasing the detection rate of micrometastases in lymph nodes by a reported 66%. Similar to the results of IHC, the clinical value of PCR-positive micrometastases remains unclear, and its use in routine practice is not currently recommended.

**Sentinel Lymph Node Biopsy**

Given the success of sentinel lymph node (SLN) biopsy techniques in breast cancer and melanoma, a significant amount of research has been directed toward assessing its applicability and usefulness in colorectal cancer. Unlike breast cancer and melanoma, sentinel node biopsy in colorectal cancer does not reduce the extent of surgical resection, but instead allows for a more focused analysis of a few lymph nodes, often using IHC or RT-PCR techniques. Furthermore, SLN may identify unusual or unconventional lymph node drainage patterns and allow these areas to be removed with the surgical specimen. Though uncommon, direct drainage into the para-aortic basin or opposite side of the colon has been reported.

The sentinel node is defined as the first lymph node receiving lymphatic drainage from the primary tumor. If this node is positive for metastases, it suggests other nodes in the lymphatic basin are positive as well. The technique for SLN mapping in colon cancer involves injection (either percutaneously or via colonoscope) of 0.5 to 1 mL of isosulfan blue dye into either the submucosa or subserosa around the periphery of the tumor. A radiocolloid (1mCi of 99mTc) may also be used as an adjunct to facilitate the detection
of the sentinel node. Timing of dissection is not standardized, but approximately 30 to 60 seconds following injection, dissection of the mesentery is performed to trace the blue lymphatic path to the blue-stained SLN. A gamma probe may be used to guide the dissection if 99mTc is used.[50]

An alternative ex vivo method has been proposed by Wong et al.[51,52] Following resection, the surgical specimen is placed on a back table and 1 to 2 mL of isosulfan blue dye is injected into the subserosa around the tumor. Again, ex vivo, the lymphatic path is carefully dissected to the sentinel node which is marked for further pathologic review. This technique has demonstrated success both as a primary means of identifying the SLN, but also as salvage when in vivo mapping is unsuccessful. However, ex vivo mapping obviously does not allow for the identification of atypical lymphatic drainage patterns.

The initial results of SLN biopsy for colon cancer demonstrated a high success rate of identifying sentinel nodes and good accuracy in predicting nodal disease. Bilchik et al reported results of a phase II multicenter trial where SLN were identified 100% of the time with an 88% sensitivity.[53] Of note, 24% of patients with stage II disease were upstaged by SLN biopsy and IHC.

In contrast, Bertagnolli et al reported on the results of a prospective, randomized multicenter trial of SLN biopsy for colon cancer and found a 92% localization rate, an accuracy of 80%, but a high false-negative rate of 58% using standard H&E staining. The authors then reanalyzed the data using IHC and improved their false-negative rate to 12%, using a definition of a positive single tumor cell seen on IHC. Using this criterion, 70% of node-negative patients were upstaged to have nodal disease—a far greater percentage than the 25% recurrence rate typically seen in stage II patients.[54,55] Giving adjuvant chemotherapy to this entire cohort of patients with a single positive cell in regional lymph nodes would likely overtreat this group of patients. Clearly, a balance must be struck between sensitivity and accuracy of SLN biopsy and what is considered clinically relevant in colon cancer.

Rectal cancer SLN biopsy is technically more difficult than colon SLN biopsy due to the inability to access tumors that are not visible from the peritoneal side of the rectum. A posterior tumor could only be visualized by disrupting the mesocolon, which would violate standard oncologic and surgical principles of resection. Despite these issues, investigators are demonstrating the ability to identify the sentinel node up to 91% of the time.[50] However, because many patients are receiving neoadjuvant therapy for rectal cancer, investigators have reported a decrease in sensitivity from approximately 90% for colon cancers to nearly 40% for rectal cancers treated with preoperative chemoradiation.[56] It is likely that the same issues of a high false-negative rate that arise for colon SLN biopsy would apply for rectal cancers as well, and with the accurate nodal staging
modality of endorectal ultrasound in rectal cancer dictating neoadjuvant therapy, use of SLN biopsy for rectal cancer is likely to be limited.

Although SLN biopsy for colon cancer appears to be of reasonable accuracy, its limitations are twofold. First, it does not change the morbidity of nodal dissection or surgical technique in terms of excision of local tumor or nodal drainage, except in the rare case of atypical nodal basins. Second, the true impact of SLN biopsy will not be realized unless micrometastatic disease, as detected by PCR or IHC, is demonstrated to have a clinical significance—then the detection of micrometastases to the lymph nodes, directed by SLN biopsy in node-negative patients, will be much more useful. The current literature suggests that micrometastases contribute to a slightly poorer prognosis than node-negative disease, but is not quite equivalent to true node-positive disease. Initial results for both breast cancer and melanoma SLN biopsy were less than ideal as well; perhaps as more prospective data are accumulated and surgical technique improves, SLN biopsy for colon cancer will slowly be adopted. For now, it is a technique that provides a modicum of additional information compared to a standard resection with adequate nodal sampling.

Summary

The number of lymph nodes recovered from a patient with colon cancer has been identified as a potentially important measure of the quality of cancer care by the American College of Surgeons, the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the National Quality Forum, and health insurance providers. The recovery of at least 12 lymph nodes has become the international standard of care for patients with colorectal cancer. Based on the literature, it is clear that inadequate lymph node recovery leads to poorer outcome due to a missed opportunity to give adjuvant therapy to a patient who actually has node-positive disease, as well the theoretic possibility of leaving gross disease behind that could progress.

Since the institution of the 12 lymph node standard, an additional clinical dilemma has arisen: what to do with colorectal cancer patients who are clearly understaged with significantly less than 12 nodes assessed and no evidence of nodal disease? Whether these patients should receive adjuvant therapy is a matter of ongoing debate; this issue will be further addressed in chapter 6 of this book.

Of less significance than the number of nodes recovered is the technique used to assess the nodes. Intensive sectioning, immunohistochemical analysis, and molecular-based testing do not appear to have a large clinical impact. Additionally, the role for sentinel node biopsy in colorectal cancer appears less useful than in other malignancies such as breast cancer and melanoma, where the SLN biopsy offers accurate staging and dictates extent of resection.
It remains to be determined whether obtaining substantially more than 12 lymph nodes is beneficial, or what significance a single cell found by IHC in a lymph node represents. As molecular profiling of tumors with gene and protein microarrays becomes more commonplace in predicting and directing treatment options for individual patients, many of these issues and technologies may become obsolete.[57] Until then, physicians will continue to use technology that has not changed for decades, namely, light microscopy, with the precise counting and staining of nodes.

References
15. Sobin LH, Greene FL: TNM classification—Clarification of number of regional lymph nodes


Surgical removal of a primary colon tumor is essential for treatment with curative intent. The importance of successful surgery in colon cancer outcome means that any variations in surgical techniques or treatment plan must be at least equivalent to the historical standards of care.

There is now increasing patient and physician emphasis on minimally invasive, and in some cases, endoscopic therapies for malignancy and complicated gastrointestinal disease. These treatment modalities have been and are currently undergoing rigorous clinical trials to ensure that any perceived patient benefit is not at the expense of sound oncologic principles. These studies are carefully evaluating laparoscopic techniques for colon cancer with regard to standard endpoints such as disease-free survival. In addition, concerns about tumor recurrence at surgical wounds and metastatic potential from effects of pneumoperitoneum are also being examined. Increasingly, attention is being focused on the extent of the mesenteric lymphadenectomy during colon cancer surgery, laparoscopic or open, and their respective prognostic and potential curative value.

**Terminology**

There are a number of variations of the technique of laparoscopic colectomy, and several terms are used with, at times, subtle distinctions:

*Laparoscopic colectomy* refers to complete mobilization of the colon, its mesenteric attachments, and intracorporeal transection of the bowel. The specimen is extracted through a small incision. This technique is the most technically demanding but results in the smallest possible extraction incision. This procedure can be performed with either an intracorporeal or extracorporeal anastomosis.

*Laparoscopic-assisted colectomy* refers to mobilization of the colon intracorporeally and extraction of the undivided bowel through a somewhat larger incision. The bowel and
mesenteric attachments are divided through the extraction incision. The anastomosis is constructed extracorporeally.

**Hand-assisted laparoscopic colectomy** is a hybrid procedure that involves the introduction of one of the surgeon’s hands through a gas-tight seal. The intracorporeal hand is used to assist in retraction and mobilization of the colon. The introduction site of the hand is used, with its accompanying wound barrier, as the extraction site. The size of the hand incision is generally related to the size of the surgeon’s hand and wrist and results in the largest incision of the three variations of this procedure.

**Operative Technique and Considerations**

For most patients with colon cancer, the diagnosis is established preoperatively, usually with a tissue diagnosis from colonoscopy. One of the most important steps preoperatively for laparoscopic colon surgery is to ensure the location of the target lesion. This is particularly true in cases where cancer was detected in a polyp that was partially or completely resected endoscopically. Except in hand-assisted laparoscopy, the surgeon is not able to directly palpate the bowel to locate lesions. When tumors are located preoperatively, it is essential for the endoscopist to ensure the location is clearly marked. Endoscopic tattooing of the area in multiple locations around the circumference of the bowel is the most effective method. For polyps at clear landmarks, such as the appendiceal orifice or ileocecal valve, endoscopic marking is not required if adequate documentation of the lesion’s position is provided. If a tattoo mark is not visible at the time of surgery despite careful inspection of the entire colon, intraoperative colonoscopy may be a useful tool. Inability to locate the lesion may result in conversion to a hand-assisted or an open procedure for full manual palpation of the bowel.

Any abdominal cancer operation includes a complete inspection of the peritoneum and the liver. Again, as in most laparoscopic procedures, the liver cannot be directly palpated. A preoperative abdominal and pelvic CT scan is routine for colon cancer patients undergoing laparoscopic resection to help direct the intra-abdominal visual inspection. Intraoperative ultrasound with a laparoscopic ultrasound probe is also a useful tool to evaluate suspicious liver lesions.

Laparoscopic procedures are routinely performed with the patient endotracheally intubated, under a general anesthetic. Paralytic agents are utilized throughout the case to ensure adequate abdominal wall relaxation for intraperitoneal gas insufflation.

After the administration of the appropriate anesthetic agents, the abdominal cavity is accessed directly through a small incision, or with a specialized needle placement (Veress needle). The peritoneal space is expanded, in most cases, with carbon dioxide gas (CO₂). The gas pressure routinely used is between 12 and 15 mm Hg. In order to reach
this pressure, most patients require 2 to 3 L of gas insufflation. CO₂ is most commonly used because it is noncombustible and rapidly absorbed into the bloodstream. This latter characteristic speeds absorption at the conclusion of the procedure and helps minimize patient discomfort from residual gas.

The absorbed CO₂ is solubilized in the bloodstream. The increased pCO₂, if uncorrected, will result in acidosis, with the accompanying physiologic derangements. The anesthesiologist compensates for the CO₂ absorption by increasing the minute ventilation during the period of insufflation. Patients with significant pulmonary disease and CO₂ retention at baseline may not tolerate prolonged pneumoperitoneum.

The positive intra-abdominal pressure required to complete the procedure can present some challenges for perioperative fluid management. Especially in cases of bowel resection where a preoperative bowel preparation is used, many patients are relatively dehydrated at the onset of the procedure. If the abdominal pressure is significantly higher than the central venous pressure, venous return to the heart and cardiac function can be impeded. Careful pre- and intraoperative hydration usually counteracts these effects.

Intraoperative and postoperative fluid requirements for laparoscopic abdominal surgery are significantly lower than those for open surgery. This is related to multiple factors including decreased evaporative losses during the procedure and less blood loss, as further discussed below.

The space realized by insufflation is adequate for most procedures in most patients. Only in rare cases of extreme bowel distention is abdominal exposure technically not feasible. Obesity and prior surgery are not contraindications to laparoscopy in general or

**TABLE 1. Indications and contraindications for laparoscopic colon resection for cancer**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
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<tbody>
<tr>
<td>Same as for open</td>
<td>Inability to tolerate general anesthesia or pneumoperitoneum</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>Lack of appropriate equipment, support staff, or credentialed surgeon</td>
</tr>
<tr>
<td>• Resection for cure</td>
<td>Obesity and prior surgery are <strong>not</strong> contraindications</td>
</tr>
<tr>
<td>• Palliative resection for advanced disease</td>
<td></td>
</tr>
<tr>
<td>Endoscopically unresectable polyps</td>
<td></td>
</tr>
</tbody>
</table>
laparoscopic bowel resection, although both can present technical challenges. See Table 1 for a list of indications and contraindications for laparoscopic colon surgery for cancer.

After establishing pneumoperitoneum, several small incisions are made in the abdominal skin. Laparoscopic access ports are placed through these incisions to allow instruments access to the space. These ports include valves to facilitate instrument exchange and movement without gas loss. The ports protect the exposed edges of the insertion wounds and function as gas-tight seals at the abdominal wall. As technology has developed, the incisions required have decreased in size. Most instruments and laparoscopes now require
5-mm incisions, and most techniques of laparoscopic colon resection require four incisions. Incisions of 12 mm in size are generally required for most stapling devices.

In place of standard retractors to maneuver the bowel, bed positioning during surgery is critical. Positioning the patient in the Trendelenberg position helps keep the small intestine out of the surgical field for pelvic and lower abdominal procedures. Rolling the patient to the right and left side down positions, similarly, assists in exposure where manual and mechanical retraction would be used in open procedures. During complex cases, the bed may be repositioned several times during the course of the case to optimize exposure for various areas of the abdominal cavity (Figure 1).

During cases when a specimen is to be extracted, it can either be withdrawn through an existing port, or directly through one of the small incisions. For procedures such as colectomy, one incision needs to be enlarged to accommodate the cross-sectional area of the specimen. Most colon specimens require either enlarging an existing incision or making a separate incision for specimen extraction. For example, for a left colectomy many surgeons will perform a left lower quadrant, muscle-splitting incision through which to perform the extraction.[1] This incision is usually between 2.5 and 6 cm in length. It is now the standard of care to exclude the specimen from the wound, either with the use of a wound protector or a specimen retrieval bag, as seen in Figure 2.[2] Transanal extrac-

![FIGURE 2. A left colon specimen is removed through a 2.5-cm left lower quadrant incision. A plastic drape is placed to protect the wound from contamination from the specimen.](image)
Minimally Invasive Colon Cancer Resection

Taking of specimens may also be performed during left colon surgery and rectal procedures. This technique eliminates the need for abdominal incision expansion.

**Evolution of Laparoscopic Surgery for Colon Disease**

The widespread use of laparoscopic techniques for abdominal surgery began in the late 1980s. Gynecologic procedures were a starting point, but the techniques were applied to common general surgical procedures, including cholecystectomy and appendectomy. Laparoscopic cholecystectomy is now considered the standard of care for gallbladder surgery by patients and physicians alike. The benefits to the patient are indisputable and include shorter hospital stays, less postoperative pain, and faster return to work and full activity.

The lessons learned from the development of laparoscopic cholecystectomy have been applied to more complex abdominal and gastrointestinal procedures including laparoscopic variations of procedures for colon diseases, reflux, achalasia, hernias, solid organ disease, and morbid obesity.

As of 2007, most open abdominal procedures have a laparoscopic alternative. Laparoscopic techniques are increasingly commonplace for malignant disease including colon and rectal cancer, gastric cancer, and early-stage esophageal cancer. Training for these techniques is widely sought after by surgeons in training and is an essential component of premier minimally invasive, colorectal, and surgical oncology fellowship programs.

The first laparoscopic colon procedures were performed in 1990. Dennis Fowler and Moises Jacobs, individually, published their initial experiences in the same issue of the journal *Surgical Laparoscopy and Endoscopy* in September 1991.[1,3] These articles demonstrated that laparoscopic techniques could be safely applied to colonic resections for both left-[1,3] and right-sided diseases.[3] The development of colon surgery procedures, as with other advanced laparoscopic surgery procedures, was very dependent on the development of novel technology to facilitate the safe completion of these procedures.

Specifically, laparoscopic analogs of open surgical stapling devices were developed to ensure reliable, reproducible ligation and division of the mesenteric vascular pedicle, and to transect the bowel specimen. Other devices have subsequently reached the market to aid in dissection and vessel ligation, provide protection to the wound used for specimen extraction, and allow the intraperitoneal introduction of one of the surgeon’s hands without losing the peritoneal gas pressure.
Potential Advantages of the Laparoscopic Approach

In addition to demonstrating that laparoscopic colon surgery is feasible, Fowler, Jacobs, and others have gone on to demonstrate that the benefits to the patient of laparoscopy can be applied to major bowel resections. These benefits come at the expense of increased operative and anesthesia time in all major reports on laparoscopic bowel resection.

Some of the potential benefits for patients are hard to quantify, such as improved wound cosmesis and less adhesion formation. The latter may translate into lower long-term rates of bowel obstruction, but significant data to support this are lacking. Many other potential advantages of the laparoscopic approach are enumerated below.

Postoperative Pain

Multiple authors have attempted to quantify postoperative pain after laparoscopic colectomy with Visual Analog Scores (VAS) and tracking of narcotic requirements. The results have consistently demonstrated an significant overall reduction in both when compared to patients who have undergone an open colectomy.[2,4,5] Initial narcotic requirements are similar for the first 12 hours after surgery, but rapidly diverge on the first postoperative day. Over the subsequent hospital stay, narcotic requirements are roughly half of that required following open colectomy.[4] In addition to the clear effects on patient comfort, minimizing postoperative narcotic requirements may contribute to faster return of bowel function and shorter length of stay (LOS).

Length of Stay

Multiple authors have commented on the duration of stay after laparoscopic colon resection, for both benign and malignant disease. Hospital LOS is usually related to the time to return of bowel function and ability to tolerate a diet. Practice patterns vary between Europe and the United States but multiple prospective studies demonstrate significantly shorter stays following laparoscopic surgery.[6-8] The largest and most rigorously constructed multicenter, prospective trials comparing laparoscopic and open colon surgery for cancer have all published their short-term outcomes data. The North American trial (the COST trial, see page 26) noted an average hospital stay of 5.1 days for laparoscopic vs 6.4 days for patients who underwent open surgery.[9] Two European trials (COLOR and MRC-CLASICC, see page 27) reported 8.2 vs 9.3 and 9 vs 11 days, respectively.[5,10,11]
Return to Work

This outcome measure is harder to accurately quantify than LOS but may be equally important to the patient and the employer. Any analysis of the costs of surgery, including lost worker productivity, will be incomplete without assessing this relevant endpoint.[10] In a nonrandomized fashion, Fowler and Franklin have reported an average of 2 to 2.5 weeks for patients’ return to work after surgery.[8,12] This timeline compares to an average of 7 weeks after open resection in Franklin’s 1996 series.[8] These data translate into a one-third to one-half reduction in the time to return to full duty.

Blood Loss

Reduced intraoperative blood loss is an often overlooked benefit of laparoscopic surgery. For many operations performed laparoscopically, there is significantly less blood loss than the equivalent open procedure. As demonstrated in the COLOR trial and others, there is significantly less blood loss in laparoscopic colon surgery.[9]

A surgeon’s ability to successfully perform laparoscopic surgery is limited by the quality of the view and the contrast between tissue planes. Even small amounts of hemorrhage will significantly impair the surgical exposure. As a result, very meticulous dissection is required to minimize tissue trauma and bleeding. The pneumoperitoneum may assist by helping to tamponade small, low-pressure bleeding sources. An abdominal incision, with the accompanying abdominal wall injury, is often the significant source of intraoperative blood loss during open procedures and is generally minimized with laparoscopic techniques.

Port Site Recurrence

The early reports of technical feasibility, combined with favorable short-term outcome data in the early and mid-1990s, encouraged the application of laparoscopic techniques to the treatment of colon cancer. Indeed, many publications at that time included patients who underwent surgery for benign or malignant disease.[3,7,12] However, in 1994 concerns were raised about tumor recurrence at the surgical port sites at rates higher than noted for wound recurrences after open surgery.[13,14] Although these recurrences can be effectively controlled by local excision, the prevalence of this problem raised concerns about the techniques of laparoscopic colectomy, the removal of a tumor-laden specimen through a small incision, and the effects of CO2 pneumoperitoneum on tumor biology and metastatic potential. The incidence of port site metastases was variable and some series did not demonstrate increased prevalence of wound recurrences,[8] suggesting that surgical technique is an important factor in this process. The overall rate of port
site wound recurrences has been reported between 0% [15] and 21%. [16] The concerns about port site metastasis have led to further basic science research and renewed emphasis on prospective, randomized clinical data on short- and long-term outcomes of these procedures.

Several studies have been performed in animal models evaluating the effects of local treatment at the time of surgery of port sites. Numerous substances have been utilized, including chemotherapeutic agents such as oxaliplatin (Eloxatin). Although a trend to decreased tumor implants at port sites has been noted with oxaliplatin in a rat model, statistical significance was not obtained.

Perhaps the most interesting finding of this and other similar studies is that in this immunocompromised rat model, peritoneal injection of colon cancer cells in the presence of unprotected wounds and positive pressure pneumoperitoneum resulted in a 68% rate of tumor implantation in controls. [17] This model highlights the need for rigorous surgical technique including trocar site protection, careful venting of insufflation gas, and careful handling of the tumor specimen.

Effects of Pneumoperitoneum and Oncologic Implications

Metastatic spread—locally throughout the peritoneum or distant via hematogenous or lymphatic channels—is a primary concern in colon cancer diagnosis and treatment. Mechanical factors from tissue handling, spillage of luminal contents, or direct injury to the tumor can lead to exfoliated cells in the bowel lumen and free cells in the peritoneal cavity. The “no touch technique” of cancer surgery has long been espoused as a key oncologic principle. This dictum emphasizes minimizing direct mechanical trauma to the tissues, especially the areas containing a malignancy. As such, this issue may be more important in laparoscopy than open surgery given the inherent limitations of laparoscopic instrumentation and the loss of direct tactile feedback from the operative field.

On a cellular level, any effects of direct manipulation of the tumor or otherwise exfoliated cells may be magnified by some of the effects of the CO₂ pneumoperitoneum. Local effects of increased pressure, acidosis, and hypoxia have been demonstrated to affect the adhesion molecules expressed in human colon cancer cell lines. [18, 19] These findings translate to potential increased friability of colon cancers during laparoscopic surgery and emphasize the value of surgeon experience, instrument quality, and rigid adherence to surgical oncologic principles.

In addition to potential direct effects on tumor cells, the pneumoperitoneum and altered stress response of laparoscopic surgery induces inflammatory effects that vary significantly from open abdominal surgery. Multiple human and animal studies have demonstrated improved preservation of delayed-type hypersensitivity immune responses
in the immediate postoperative period in patients who have undergone laparoscopic surgery when compared to equivalent open procedures.[20-23] In these studies, the degree of surgical trauma and incision length correlated with the degree of depression of the T-cell-mediated responses.

Cellular immunity is affected in other ways. Surgery-related depression of natural killer cell function is less marked in laparoscopy. Neutrophil and lymphocyte chemotaxis is less inhibited and monocytes are more responsive to subsequent stimuli. Similarly, antigen presenting cell HLA-DR expression is better preserved following laparoscopic procedures.

All significant surgery triggers a systemic inflammatory response, with the net effect often being significant postoperative immunosuppression. In contrast to laparotomy, laparoscopy results in smaller postoperative increases in serum levels of the interleukins IL-6 and IL-1β, tumor necrosis factor–alpha (TNF-α), C-reactive protein (CRP), and vascular endothelial growth factor (VEGF).

VEGF is a potent inducer of angiogenesis and helps support tumor growth. At baseline, preoperatively, VEGF levels are higher in patients with colon cancer. Postoperatively, less additional elevation was noted in laparoscopic patients.[24] The higher postoperative increases seen in open surgery may constitute a detrimental oncologic effect following laparotomy but this effect requires more study.

The upregulation of many inflammatory mediators also correlates with a substantial serum decrease of insulin-like growth factor–binding protein-3 (IGFBP-3) in open surgery patients, when compared with matched laparoscopic patients.[25] IGFBP-3 has tumor suppressor effects. Plasma from patients who undergo major open surgical procedures induces significant in vitro tumor growth when compared to the same patient’s plasma preoperatively.[26] The combined effects of variations in serum proteins, inflammatory mediators, and immune cell function may have significant effects on the ability of postoperative patients to respond to infections, eliminate micrometastatic tumor cells, and on their overall recovery after surgery. Possible oncologic benefits of laparoscopic surgery require further exploration.

**Clinical Trials Evaluating Laparoscopic Colon Cancer Surgery**

Prior to 2004, Curet et al and Lacy et al completed and published randomized, prospective trials of laparoscopic vs open colectomy in cancer. In 2000, Curet et al reported a mean of 4.9 years follow-up on 43 patients randomized to open or laparoscopic procedures. There was a 28% conversion rate to open surgery. Benefits were seen in length of stay and blood loss for the laparoscopic group. A median of 11 lymph nodes were harvested in the laparoscopic group vs 10 in the open surgery group. No port site metastases occurred in
### TABLE 2. Short- and long-term results of laparoscopic colectomy for cancer trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Procedure Type</th>
<th>Patients</th>
<th>LOS (d)</th>
<th>Conversion Rate</th>
<th>Lymph Nodes</th>
<th>Median Follow-Up</th>
<th>Long-Term Oncologic Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>COST</td>
<td>Laparoscopic</td>
<td>435</td>
<td>5.1</td>
<td>12</td>
<td>12</td>
<td>Equivalent</td>
<td>Equivalent</td>
</tr>
<tr>
<td>MRC-CLASICC</td>
<td>Laparoscopic</td>
<td>526</td>
<td>9</td>
<td>21%</td>
<td>12</td>
<td>3 yr</td>
<td>Equivalent</td>
</tr>
<tr>
<td>COLOR</td>
<td>Laparoscopic</td>
<td>627</td>
<td>8.2</td>
<td>25%</td>
<td>10</td>
<td>Pending</td>
<td>Pending</td>
</tr>
</tbody>
</table>

LOS = length of stay.

*aSummary of the major, multicenter, prospective randomized trials published as of July 2007. The length-of-stay data differences are statistically significant in all three trials. Long-term follow-up and oncologic outcomes data are pending for the COLOR trial.*
this series. Oncologic outcomes over the study duration were equivalent.\[15\]

In 2002, Lacy published a single-institution, randomized prospective trial for laparoscopic colon cancer surgery. This study included 219 patients. There was an 11% conversion rate to open surgery in the laparoscopic group. The patients assigned to the laparoscopic arm required shorter length of stay and had faster return of bowel function postoperatively. There was an overall lower complication rate in this group. Most interestingly, a survival advantage was noted in stage III patients who underwent laparoscopic surgery. The authors concluded that laparoscopic colectomy conferred an oncologic and survival advantage over open surgery for colon cancer.\[27\]

To date, the effects noted for stage III patients in the Lacy trial have not been reproduced and this study has been criticized for yielding suboptimal lymph nodes numbers for analysis, a mean of 11.1 in both the open and laparoscopic arms.

A number of case series and prospective trials have since been published, and satisfactory results and equivalency to open surgery have been universally reported.\[28-33\] One recently reported study, a prospective randomized trial from Taiwan, was designed to investigate possible long-term clinical advantages for patients with stage III, left-sided colon cancers. All patients underwent a formal left hemicolectomy with splenic flexure mobilization. Patients with unsuspected metastatic disease discovered at surgery were excluded from the final analysis. In this study, lymph node retrieval was sufficient in both the open and laparoscopic groups, 15.6 and 16.0, respectively. There was a 3% conversion rate to open surgery in the laparoscopic groups. These patients were included in the laparoscopic group for the statistical analysis. With a median follow-up of 40 months, survival and recurrence rates were equivalent in both groups.\[30\]

While these results have been reassuring, most surgeons who perform laparoscopic colon surgery for cancer have been awaiting the results of the largest North American and European randomized, prospective trials. The results that have been reported to date are summarized below and are outlined in Table 2.

The COST Trial

In 1994, at the request of the American Society of Colon and Rectal Surgeons (ASCRS), a voluntary moratorium on laparoscopic colectomy for cancer outside of clinical trials was instituted. This moratorium was coordinated with the formation of the Clinical Outcomes of Surgical Therapy Study Group (COST). The major intent of this study was to test the hypothesis that laparoscopic surgery for cancer was equivalent in long-term outcome (3 years) to open surgery.

The trial enrolled 872 patients with adenocarcinoma of the right or left colon at
48 institutions in North America. Patients were randomized into laparoscopic or open treatment paths. Throughout this study, there was a 21% conversion rate from laparoscopic to open surgery. For the purposes of the study, these patients were included in the laparoscopy arm of this intention-to-treat analysis.

At the participating institutions, 66 surgeons were enrolled as providers. As variability in technique is considered the most likely contributing factor to port site recurrences, strict technical requirements were implemented for the duration of the study. All contributing surgeons were required to document a minimum of 20 laparoscopic colorectal resections. In addition, an expert panel reviewed representative case video to assess each surgeon’s adherence to oncologic techniques. Throughout the study, all surgeon participants were subject to a random audit of case video and pathologic specimens for adequacy of bowel margins.

The oncologic techniques required for certification for the study included a thorough abdominal exploration, identification of critical adjacent structures such as the ureters and major vessels, avoidance of direct tumor manipulation, and a high level of mesenteric vessel ligation. High ligation of the mesenteric pedicle is necessary to ensure adequate lymphadenectomy during the procedure.

The short-term outcome data from the COST trial was published in 2002, confirming many of the findings regarding the patient benefits of laparoscopy during the early postoperative period. The long-term data and conclusions were published in the New England Journal of Medicine in 2004. With a median follow-up of 4.4 years, the authors noted no differences in recurrence rate, survival, or the rate of wound recurrences between the laparoscopic and open arms. Patients with lymph node–positive cancers displayed equivalent survival between the groups. In both the open and laparoscopic groups in this trial, the median number of lymph nodes harvested and analyzed was 12.

This study concluded that laparoscopic colectomy is equivalent to open surgery in the hands of appropriately trained and experienced surgeons for the treatment of colon cancer.

The MRC-CLASICC and COLOR Trials

In Europe, two major prospective randomized trials were established shortly after the COST trial. The British Medical Research Council Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (MRC-CLASICC) trial includes surgery for rectal cancer. Preliminary data were published in May 2005. The short-term outcomes were similar to those published by the COST group, with the notable exception of increased positive margins for laparoscopic low anterior resection. This issue was not noted for...
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abdominal perineal resections. The mean number of lymph nodes obtained in the open arm was 13.5 vs 12 in the laparoscopic group. This finding suggests that adequate oncologic resection can be obtained in both groups.

The long-term data from this trial were published in July 2007.[34] The increased rate of positive circumferential margins for laparoscopic low anterior resections did not correlate with increased local recurrence rates. The overall long-term outcomes at 3 years were equivalent between the open and laparoscopic groups. Further trials focusing on laparoscopy in rectal cancer are required and are ongoing.

The COlon cancer Laparoscopic or Open Resection study group (COLOR) published its short-term outcomes in July 2005. This trial does not include rectal cancer patients but, unlike the COST trial, did include hand-assisted laparoscopic cases. There were no short-term differences in outcome, length of stay, blood loss, and postoperative pain scores were decreased in the laparoscopic arm.[5] The extent of lymph node harvest in this trial is somewhat less than the other major studies at a median of 10 for each arm of the study. Long-term outcome data are pending.

In March 2007, the authors of COST, COLOR, and CLASICC trials jointly published a meta-analysis of the available 3-year follow-up data. Cumulatively, 796 patients were included in the laparoscopic arm of the analysis, 740 in the open arm. This analysis confirmed the independent findings of the COST and CLASICC trials in that laparoscopic and open colectomy are equivalent in long-term outcomes for colon cancer.[35]

In an interesting offshoot from the COLOR trial, the Swedish contribution to the cohort was independently analyzed for cost differences between the open and laparoscopic approaches. Although laparoscopic resection resulted in increased costs to the health-care system, this difference was recouped by 12 weeks from productivity savings from earlier returns to work. There was no significant societal cost difference when all aspects were considered.[36]

Numerous other reports are now available reporting on case series with increasing follow-up, including a number or retrospective series with 5-year follow-up.[31,32,37] The reports to date demonstrate similar short- and long-term outcomes to the larger prospective randomized trials.[38]

Most of the studies published to date have limited enrollment to patients with right- or left-sided malignancies, the MRC-CLASICC trial being the exception as it also includes rectal cancer. Cancers of the transverse colon and splenic flexure are the focus of a retrospective analysis of 285 patients treated with potentially curative laparoscopic resection. The procedures involved included 22 transverse colon lesions treated with either an extended right colectomy, a transverse colectomy, or an extended left colectomy. At a median follow-up of 17.2 months, patients with transverse colon lesions had similar rates
of conversion to open surgery, perioperative complications, and cancer recurrence. The authors concluded that patients who undergo laparoscopic resection of transverse colon cancers will have equivalent oncologic outcomes and will benefit from the short-term advantages of laparoscopy.

The Role of Lymphadenectomy

In 2000, a National Cancer Institute (NCI) consensus conference made a number of recommendations regarding standards for colon cancer surgery. This conference reinforced key oncologic principles such as high ligation of the primary feeding vessel at its origin with accompanying removal of the associated lymph nodes. Any additional suspicious lymph nodes should also be removed. Specimen analysis in the pathology suite was also emphasized. Meticulous examination, with fat-removal tissue processing techniques is mandated.

This emphasis on lymph node retrieval by surgeons and identification and analysis by pathologists is required to maximize the number of excised and examined sites for potential nodal metastasis. A minimum target number of lymph nodes to be retrieved was set at 12 for a colon resection. This number confers a greater than 90% accuracy in lymph node and overall tumor staging. If fewer than 12 lymph nodes are retrieved, a referral to a medical oncologist is recommended. More recent data suggest that the number of lymph nodes retrieved during colectomy may impart more of a benefit than just more accurate staging. Retrieval of greater than 18 lymph nodes at surgery improves survival in some analyses. Lymph node retrieval is clearly a key benchmark to help guide subsequent treatment, and the same high standards should be maintained whether the colectomy is performed open or laparoscopically.

The Learning Curve

In 1991, it was projected that laparoscopic colectomy would rapidly become as ubiquitous as laparoscopic cholecystectomy through a combination of patient preference, and surgeon ability and availability. The initial projections, as with other increasingly complex laparoscopic procedures, were overstated. Complex laparoscopic procedures are technically more complex than the equivalent open procedures, and are harder to learn and to teach. Open surgical skills and experience do not translate to laparoscopic procedures. These factors, combined with the oncologic concerns, inhibited the development and training of these skills. Laparoscopic colectomy training experience is now widely sought as a key component of minimally invasive, surgical oncology, and colorectal fellowship programs.

The experience required to become an appropriately trained laparoscopic colon
surgeon has been reported in a number of publications. Patient outcomes, oncologic and otherwise, are emphasized as key benchmarks of skill development. Fowler notes in his initial series of 60 patients that LOS, operating room time, and complications all improved dramatically with experience. He concludes that there is a steep learning curve in learning laparoscopic colectomy. [12] Wishner noted in 1995 that operative times for laparoscopic colectomy dropped to a mean of 150 minutes per case after an initial experience of 35 to 50 cases. After 50 cases, the operative time plateaued at 140 minutes. [44]

In 2007, Kang described a single-surgeon, hand-assisted experience that required between 21 and 25 cases to traverse the learning curve. The endpoints of operating room time, return of bowel function, intraoperative blood loss, and LOS all leveled off in this case range. [45]

Based on this experience, the most recent revision of NCI guidelines for colorectal cancer surgery, published in November 2006, mandates a requirement that at least 20 laparoscopic colorectal resections be successfully completed by an individual surgeon either during training, by proctoring, or for benign disease before proceeding to laparoscopic colorectal resection for cancer. [41] This recommendation is made to ensure that surgeon experience and skill do not negatively impact the oncologic outcomes of patients with potentially curable colorectal malignancies.

**Surgeon Credentialing**

Surgeon credentialing is becoming an increasingly important topic as surgeon practices become more specialized. Hospitals and surgical facilities have evolving standards, patients increasingly inquire about surgeon experience, and major insurance carriers are becoming more inquisitive about individual surgeon outcome data.

Current guidelines on credentialing surgeons for advanced laparoscopic procedures in general and specifically for laparoscopic colorectal surgery are derived from the consensus guidelines of major surgical organizations. The experience and standards of practice required for admittance to the COST trial is the basis for these guidelines. The long-term outcome data of this trial supports the conclusion that with these standards enforced, oncologic outcomes of laparoscopy are equivalent to open procedures. The authors of the COST study have concluded that to maintain excellent oncologic outcomes, appropriate credentialing based on surgeon skill and experience is essential for routine application of laparoscopic colon surgery for cancer while maintaining safe outcomes and high oncologic standards. [46]

In 2004, the Society of American Gastrointestinal and Endoscopic Surgeons and the ASCRS co-endorsed the credentialing standards that have subsequently been adopted by the NCI. A minimum of 20 laparoscopic colorectal resections for benign disease or
metastatic cancer (noncurative intent) with anastomosis should be completed prior to granting of privileges for potentially curative colorectal cancer excisions.

**Conclusions**

The COST trial and other studies have established the effectiveness and safety of laparoscopic colectomy for colon cancer. Since the development of the techniques and equipment that enable laparoscopic colon surgery, significant insight has been gained into the skills required, the standards to be set, and the surgical principles to be adhered to for safe and effective resections for curable colon cancer. Appropriate training and experience is required to achieve oncologically appropriate patient outcomes. The technical difficulty of the procedure with the concomitant rigid oncologic standards require thoughtful surgeon operative credentialing at institutional levels that adhere to national standards.

Continued efforts are required to maximize disease-free survival, which necessarily include ongoing and future medical and surgical clinical trials, continued efforts to strive for excellence in training surgical residents and fellows, and close monitoring of outcomes and quality markers to standardize care among practitioners and centers. Similar methods of technical evaluation need to be applied to rectal cancer and other gastrointestinal malignacies. The continued emphasis on a coordinated multidisciplinary approach that emphasizes early detection through colon cancer screening programs, excellence in surgical management, rigorous pathologic evaluation, and adjuvant treatment, when appropriate, will help ensure continued progress and uniformity in improving long-term outcomes and survival.

**References**


Minimally Invasive Colon Cancer Resection

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Chapter 3: Surgical Management of Rectal Cancer and Its Variants

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John of Arderne, the 14th century surgeon, is credited with the recognition of the signs, symptoms, and natural history of rectal cancer. However, no form of excisional surgery was performed for nearly the next 400 years. The surgical treatment of rectal cancer has evolved significantly over the past 250 years, paralleling the evolution of the art and science of surgery. The first procedures were local excisions and were nearly always palliative in nature. The earliest radical procedures were essentially an amputation of the anus and distal rectum with an incontinent perineal anus.[1] Nevertheless, these procedures were associated with substantial morbidity, and mortality was often due to sepsis. Improvements in anesthesia and antisepsis allowed the development of radical extirpative procedures done with curative intent. Perineal approaches, trans-sacral resections, and abdominal sacral resections were in vogue as radical resections, but again, complications were frequent (more than 50%), and just as important, quality of life (QOL) was poor.

In the current “modern era” of rectal cancer treatment, the management of rectal cancer has progressed tremendously over the past 80 years. Due to an increased understanding of the pathology and natural history of the disease, surgical management includes a spectrum of operative procedures ranging from radical operations to innovative sphincter-preserving techniques including local therapy.[2]

Today, physicians managing this condition have a number of perioperative and operative techniques at their disposal for the better treatment of these patients. If any disease treatment can be classified as purely “individualized,” it is rectal cancer. There are four main goals in the treatment of a patient with rectal cancer: (1) local control; (2) long-term survival; (3) preservation of anal sphincter, bladder, and sexual function; and (4) maintenance or improvement in quality of life.[3] This chapter will review preoperative local staging, neoadjuvant therapy, refinements in operative technique such as total mesorectal excision and negative radial margins, and the use of the circular stapler and...
perianal suturing techniques, all of which have improved oncologic outcome and quality of life in patients with early (T1/T2 and N0) as well as locally advanced (T3/T4 and/or N1) rectal cancer. The use of sentinel lymph node mapping and the role of laparoscopy are discussed in other chapters in this book.

Preoperative Staging

Information regarding the depth of tumor penetration through the rectal wall, lymph node involvement, and the presence of distant metastatic disease is crucial when planning rectal cancer treatment. A number of rectal tumors can be detected by digital rectal examination. Results are often reported as “mobile,” “tethered,” or “fixed.” Many tumors are obviously beyond the reach of the finger, making clinical staging impossible. Current imaging modalities are superior to that of digital examination. Endorectal ultrasound (ERUS) is currently a well-established method and appears to be the “gold standard” for the preoperative assessment of most rectal cancers. Currently, the accuracy of ERUS in evaluating perirectal neoplastic infiltration varies between 81% and 96%, while the accuracy in demonstrating perirectal lymph node involvement ranges between 60% and 83%. High rectal tumors, lesions close to the anal verge and bulky, and stenotic tumor hamper accurate placement of the probe and diminish accuracy. The accuracy of ERUS is also affected by tumor stage where early lesions are often overstaged. Mesorectal lymph node staging is less accurate than perirectal wall infiltration. When they are evident, metastatic lymph nodes are typically hypoechoic, usually comparatively larger than inflammatory nodes (frequently 4 mm in diameter), and irregular with sharply defined borders. Technical improvements to increase accuracy have employed endoluminal scanning with color Doppler imaging and the use of water enema transvaginal ultrasound.

Magnetic resonance (MR) imaging, initially popularized in the late 1980s, has evolved into a useful tool in an effort to stage rectal cancer accurately. Initial studies have shown accuracy rates similar to those obtained with ERUS and significantly better than those with standard MRI, CT, and clinical assessment. The traditional body-coil MR is less accurate than ERUS and is rarely used for locoregional staging of rectal cancer. The use of MR imaging employing an endorectal surface coil has been extensively reported in the assessment of rectal cancer, and is becoming the preferred modality for the definition of local pelvic spread and in identifying extrapelvic metastatic disease. These newer techniques of endorectal coil MR and phased-array MR have been reported to be 66% to 92% accurate in determining T stage and can reliably determine extent of tumor mesorectal involvement in up to 100% of cases. Magnetic resonance is limited by its relatively small field of view, expense, and patient tolerance.

The potential role of CT scanning in patients with rectal cancer is twofold. First,
this staging evaluation can help to assess the local extent of the tumor, any involvement of regional lymph nodes, and any local extension into surrounding structures. Second, CT scans can detect the presence of metastatic disease outside the local confines of the primary tumor. However, it is important to emphasize that the accuracy of CT scanning in local staging is inferior to that of ERUS or MR. As such, the primary role of CT scanning is to determine if the primary tumor has metastasized to the liver, adrenal glands, ovaries, kidneys, or lungs. The accuracy of detection of liver metastases is 90%. Positron emission tomography scanning is often used in the postoperative evaluation of recurrent disease. Its role in determining response to neoadjuvant therapy is currently under investigation.[7]

**Curative Treatment of Rectal Cancer**

There are many factors involved in determining the optimal treatment of patients with potentially curable rectal cancer. Factors such as stage of disease, location of the tumor from the anal verge, age and preoperative continence, the potential need for a permanent colostomy, the role for preoperative neoadjuvant therapy, and above all, the patient’s wishes and expectations, are all crucial. A thorough and detailed explanation of all options including morbidity and quality of life are paramount. This is especially true if a patient chooses an option that deviates from the standard of care or that is associated with a poor oncologic outcome.

Today, the majority of patients are treated with one form of radical surgery or another. However, prior to embarking on this form of operative endeavor, the decision as to whether to employ preoperative neoadjuvant therapy is routinely discussed based on the results of preoperative local staging. This combined-modality approach, along with “optimized surgery,” has dramatically improved outcomes of patients with rectal cancer. The benefits of preoperative chemoradiation have evolved from the results of two large multicenter trials that demonstrated that postoperative chemoradiation was beneficial for patients with transmural or node-positive rectal cancer.[8] Many centers now employ preoperative chemoradiation to enhance chances of tumor resectability, decrease local recurrence, increase rate of sphincter preservation, and diminish treatment toxicity. In patients treated with preoperative neoadjuvant therapy, they are often restaged and surgical resection is often deferred for 6 to 8 weeks to allow for maximum tumor response as well as patient recuperation. Among this group of patients who may prove most challenging are those with distal third lesions who have achieved either a complete or near complete pathologic response. The key issue is to determine whether these patients should then undergo definitive surgical treatment.
Treatment of Early Rectal Cancer

Treatment of rectal cancer determined to be “early” upon preoperative imaging remains a controversial issue. For the most part, T1/T2, N0 proximal third lesions, accurately staged, often undergo immediate sphincter-sparing proctosigmoidectomy with colorectal anastomosis. This approach is often taken of “true” T1 middle third lesions. However, in centers utilizing transanal endoscopic microsurgery (TEM) capabilities, this peranal modality has been used for proximal and middle third T1 lesions. Conventional local excision of early distal third rectal cancer is attractive in that it can be performed with minimal morbidity and satisfactory functional results. It obviates any question of sphincter preservation, but its oncologic benefit continues to be brought into question. This is especially true in “high-risk” lesions that are poorly differentiated or have other adverse histopathologic features. It must be kept in mind and completely understood that recent evidence suggests that patients treated with local therapy have higher local recurrence rates than those treated with radical resection. Because local excision does not remove the lymph node-bearing tissue of the mesorectum, accuracy of curative resection may be, at best, speculative. Local recurrence rates vary between 7% and 40% following local excision for rectal cancer. This rather wide range in local recurrence is due to the fact that lymph node involvement is 0% to 12% for T1 tumors, 12% to 28% for T2 tumors, and 36% to 79% for T3 tumors. Overall survival has been reported to be 70% to 89% in properly selected patients.[9] However, most reported series suffer from small sample size and follow-up of often less than 5 years.

Patient Selection for Local Therapy

Ideally, tumors that are suitable for local treatment are less than 4 cm in diameter, mobile on digital rectal examination, located within 7 cm from the anal verge, involve less than 30% of the rectal circumference, have no associated palpable perirectal lymph nodes, and have favorable histology. Either ERUS or MR imaging can assist tremendously in selecting patients for local therapy. Regardless, patients often weigh in on the final decision, especially when local therapy is utilized for nonideal tumor characteristics. There are situations when adjuvant chemotherapy and radiation are administered to further improve surgical results.

Local Excision

In 1977, Morson[10] advocated transanal local excision as definitive treatment in select patients. This procedure often involves a full thickness “disc excision” performed in the prone jack-knife position, ideally employing a 2-cm margin around the tumor. The
defect in the rectal wall is either left open or closed with absorbable sutures. The specimen is carefully pinned on a piece of cardboard and marked for orientation. A detailed review with the pathologist is highly recommended for orientation and clinical correlation. The procedure carries a low morbidity, with the most frequent complications being bleeding, hematoma, urinary retention, and transient defecatory disability. Although initial results were quite encouraging, local recurrence rates, even in the setting of T1 lesions, have ranged between 10% and 25%.[9,11,12]

Transanal Endoscopic Microsurgery

Transanal endoscopic microsurgery was developed and popularized in the mid-1980s. Patient selection is nearly identical to local excision barring distance from the anal verge. It may be utilized for tumors located 10 cm anteriorly, 15 cm laterally, and 20 cm posteriorly. It employs a highly sophisticated 40-mm-diameter endoscope with four work channels allowing the use of different instruments. The instruments are similar to those used in laparoscopic surgery. The limitations of TEM are a substantial learning curve and specialized training, expensive equipment that may sit dormant due to patient availability, risk of anastomotic disruption resulting in peritonitis and a stoma, and potential intraperitoneal dissemination of cancer for upper third lesions. Transanal endoscopic microsurgery in properly selected patients may achieve similar oncologic results to that of radical surgery.[13]

Contact Radiotherapy

The long-term effects of endocavitary contact radiotherapy for rectal tumors were reported by Papillon.[14] This is a nonsurgical alternative to local excision. Criteria for this therapy are similar to that of local excision. It is performed on an outpatient basis with local anesthesia and consists of four endorectal applications (20 to 30 Gy) over a 6-week period. It may be supplemented with interstitial iridium implants. Morbidity is minimal and consists of tenesmus, diarrhea, and bleeding. This procedure is performed in only a few centers able to offer this therapy. Local recurrence rates have ranged from 8% to 30%.

Papillon’s series of 312 patients reported a 5-year disease-free survival of 74%.[14] This procedure suffers from the limitation of no pathologic specimen being obtained.
Electrocoagulation

Initially electrocoagulation was used as a palliative measure for patients with disseminated cancer or those who were felt to be high surgical risk. The surprising success of this technique in achieving local control has fostered surgeons to utilize electrocautery in treating early and curable tumors. Selection criteria are similar to other local treatments; however, because of the potential for extensive thermal injury, care must be taken not to injure adjacent structures such as the prostate or vagina. The results from the few published series resulted in survival rates varying from 58% to 82%. There remains significant morbidity (20%) with this procedure, and perioperative deaths have also been reported.

Adjuvant Therapy After Local Treatment

For T1 tumors, most authors report a local control rate of 80% to 90%, which drops off to about 70% for T2 lesions and for T3 lesions, this may be at best 50%. Recurrence appears to be related to several factors such as depth of tumor invasion, resection margin status, and any unfavorable histology. The addition of chemotherapy or radiation therapy to local therapy appears to have some benefit in certain subset of patients. The key to potentially curative local treatment for rectal cancer is patient selection by identifying the best candidates with preoperative tumor staging and clinical and pathologic assessment of favorable features. Low-risk T1 is suitable for local excision alone. Limited data suggest that adjuvant chemoradiation therapy may be helpful in patients with unfavorable T1 and T2 lesions, achieving a local recurrence rate of less than 20%.

Salvage Following Failed Local Therapy

Meticulous follow-up following local therapy is paramount in detecting local recurrence that is salvageable for cure. Salvage with a radical resection is possible, with several small series reporting a 50% to 88% disease-free survival. In the largest series published to date, 49 patients who underwent successful surgical salvage of local recurrence after T1 local excision, 58% had recurred or died of disease within 33 months. Currently local excision for cure is recommended only for carefully selected T1 tumors without high-risk features. Patients must be followed closely for a prolonged period, since nearly one-third of recurrences occur 5 years or more after local excision. The role of postoperative adjuvant chemotherapy and radiation is being utilized, although no standard currently exists.
Treatment of Locally Advanced Rectal Cancer

Over the past 30 years, a number of critical surgical management issues regarding the radical treatment of rectal cancer have come to the forefront. These include (1) total mesorectal excision (TME), (2) autonomic nerve preservation (ANP), (3) circumferential resection margin (CRM), (4) distal resection margin, (5) abdominoperineal resection, (6) sphincter preservation, (7) minimally invasive approaches, and (8) postoperative quality of life. Although each of these factors, by themselves and collectively, are important, the ultimate goal should be oncologic cure.

Total Mesorectal Excision

Historically, using traditional operative technique without adjuvant therapy, oncologic outcomes were poor and associated with significant morbidity. Local recurrence rates consistently exceeded 20% and 5-year survival ranged from 27% to 42%. One of the most important advances in operative technique has been the advent of TME, which is commonly used in the management of mid- and distal third rectal tumors. Most patients with rectal cancer have full thickness penetration into the perirectal fat or involvement of regional mesorectal lymph nodes situated along the route of the blood supply to the rectum. This regional spread is virtually all confined within the mesorectum, which comprises fat, vessels, and lymphatics contained within the visceral pelvic fascia. Pathologic evaluation of resected specimens has identified mesorectal spread in a significant percentage of patients. These studies identified mesorectal spread extending 4 cm distal and 10 cm proximal to the primary tumor. Conventional rectal cancer surgery often employs a blunt technique along unidentifiable tissue planes with a tendency to “cone in.” It was felt that leaving behind the mesorectal involvement greatly contributed to local recurrence, which in fact, is probably persistent disease.

The technique of TME uses precise, sharp dissection in the areolar tissue between the visceral and parietal layers of the pelvic fascia. In 1998, Heald and colleagues reported on the use of TME with a local recurrence rate of 2.6% and a 5-year actuarial local recurrence rate of 3.5% in 152 curative anterior resections[20]; this was a follow-up to their initial 1992 report. Their updated series demonstrated local recurrence rates with or without distant metastases of 6% at 5 years and 8% at 10 years. Nine percent of patients received preoperative radiation therapy for fixed tumors. Several reports have demonstrated continued improvements in local recurrence (4% to 8%) and cancer-specific survival with TME (70% to 80% at 5 years). The importance of TME cannot be underestimated. When compared to historical controls of patients undergoing blunt mesorectal excision, patients treated with TME have lower local recurrence rates.[20-22] This surgical approach emphasizes the achievement of negative circumferential and distal margins and
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optimizing oncologic outcome. The reported morbidity of TME has been variable with anastomotic leak rates higher than conventional resections. However, this particular side effect is largely avoidable with the use of proximal diversion.

Autonomic Nerve Preservation

Injury to the pelvic autonomic nerves during rectal dissection impacts postoperative quality of life. Sexual and urinary tract dysfunction continues to plague even the most experienced rectal cancer surgeon. However, the incidence of these morbidities is dramatically lower than 40 years ago. It should be emphasized that other factors unrelated to the pelvic dissection, such as a history of chemoradiation, patient comorbidities, medications, and alcohol, contribute to genitourinary and sexual dysfunction. One of the added benefits of TME is that it facilitates autonomic nerve preservation. In the anterior component of TME, the dissection is in the plane between the seminal vesicles and Denovillier’s fascia. Under direct vision, precise dissection leaves the gonadal vessels, ureters, iliac vessels, sacral veins, pelvic autonomic nerves, and pelvic wall musculature beneath the parietal fascia and minimizes the risk of damage to these structures. Erectile potency has been reported to be 37% to 68% after conventional rectal resection, with significant impairment of urinary function. Utilizing careful autonomic nerve preservation, postoperative genitourinary and sexual dysfunction can be reduced from 25% and 75% to as low as 10% and 25%.[23] The combination of TME with autonomic nerve preservation is essential to reducing the long-term genitourinary morbidity of rectal cancer resection. It seems intuitive that the addition of external beam radiation to TME should further reduce local recurrence.

Circumferential Resection Margin and Distal Resection Margin

Local recurrence is defined as regrowth of tumor in or around the tumor bed after previous removal of all visible tumor. Careful assessment of the CRM of a rectal cancer specimen allows prediction of local recurrence. CRM status is an independent prognostic variable in rectal cancer, with involvement of this margin by tumor predicting a 12-fold increased risk of local recurrence and 3-fold increased risk of death. Tumors at or within 1 mm of the CRM histologically should be regarded as being incompletely excised. Involvement need not necessarily be the result of direct or discontinuous spread of the primary tumor, but may be because of tumor within a lymph node or vessel approaching to within 1 mm of the margin. A recent series of 686 patients with rectal cancer treated with TME after a median follow-up of 29 months documented a 5% local recurrence rate for patients with CRM > 1 mm and a 20% local recurrence rate for CRM < 1 mm.[24] These
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results have led to the treatment strategy of administering postoperative radiotherapy to patients with involved circumferential margins.

Several studies have shown that rectal cancers may extend further distally than their surface appearance would suggest. This spread may occur either within the wall of the rectum (distal intramural spread) or within the mesorectal tissues (distal mesorectal spread). Distal spread greater than 1 cm beyond the mucosal edge of rectal cancer has been documented in only 10% of cases—all in poorly differentiated, node-positive tumors. In a recent study from Memorial Sloan-Kettering Cancer Center, the recurrence-free survival and local recurrence rates within 3 years of follow-up after preoperative chemoradiation and TME resection were not significantly different in patients with margins less than or equal to 1 cm compared to those greater than 1 cm.[3] Regardless, the surgeon should strive to obtain a 2-cm grossly tumor-free margin in a fresh unfixed unpinned state. If a larger margin can be obtained without changing the type of operation being performed, efforts should then be made to gain additional margin.

Abdominoperineal Resection

The number of abdominoperineal resections carried out has decreased over the past 3 decades. Our current understanding of the routes of spread of rectal cancer, combined with technical innovations such as the circular stapler, intrarectal ultrasound, and “ultralow” anastomotic techniques, has contributed to this decline. Nevertheless, abdominoperineal resection has an important role in the treatment of patients with distal rectal cancer and, for many of them, remains the best option to achieve cure.[25] A number of factors influence the decision to perform an abdominoperineal resection. Although the distance of the tumor from the anal verge helps guide surgical therapy, it is not an absolute indication for or against abdominoperineal resection. It is often not until complete mobilization and assessment of tumor margins that a decision for or against a sphincter-preserving procedure can be performed. Regardless, cure of the cancer should be the guiding principle.

In patients with anal sphincter dysfunction and fecal incontinence, abdominoperineal resection is preferred to restoring bowel continuity.[26] In institutionalized or bedridden patients, a colostomy is usually easier to care for and preferred to a constantly incontinent patient. Regardless, colostomy complications are not infrequent and can adversely affect quality of life. Abdominoperineal resection remains an essential procedure in the management of rectal cancer. The inability to perform a sphincter-preserving procedure should not be perceived by the patient or family as failure. There will continue to be a select group of patients where this procedure will be the patient’s best oncologic and functional outcome.
Restorative Procedures

Restorative procedures (anterior resection, low anterior resection, and coloanal anastomosis) are performed more frequently than ever before. In patients with acceptable preoperative anorectal function and ideal body habitus and pelvic anatomy, restorative procedures that preserve sphincter function are possible for rectal tumors within 1 to 2 cm from the upper portion of the anorectal ring. However, location of the tumor is not the only limiting factor. Restorative procedures may not be able to be performed technically in obese patients, males with a long narrow pelvis, or those with an enlarged prostate. The anterior resection applies to lesions in the upper rectum (11 to 16 cm from the anal verge) and restoring intestinal continuity is not significantly different from the sigmoid resection. The low anterior resection for lesions of the middle third of the rectum and the coloanal anastomotic procedures where the entire rectum is removed just above the anorectal ring continue to be challenging procedures. Once the rectum, along with the tumor, is removed, the method of restoring intestinal continuity is ascertained.

Classically, bowel continuity following either a low anterior resection or completion proctectomy was restored with either a straight colorectal or coloanal anastomosis. In 1986, the J-pouch coloanal anastomosis was developed in an effort to increase colonic reservoir function and improve quality of life. Such an approach involves folding the distal 8- to 10-cm segment of the distal descending colon on itself and forming a J-shaped reservoir where the most dependent part is anastomosed to the anal sphincter, using either a circular stapler or hand-sewn anastomosis. The anastomosis should be protected in nearly all instances with a diverting loop ileostomy. Anastomosis and pouch integrity are evaluated at 8 to 12 weeks with a water-soluble enema prior to stoma closure.

Quality-of-life studies evaluating straight coloanal and coloanal J-pouch reconstructions in a prospective randomized fashion have demonstrated the superiority of the J-pouch procedure, especially during the first year following surgery.[27] One disadvantage of this procedure is the potential for the bulky colonic J-pouch to fit into the pelvis. In 1997 an alternative to the colonic J-pouch, the transverse coloplasty, was introduced to create a distal colonic reservoir. The results of the transverse coloplasty vs the colonic J-pouch have been mixed, where the risk of anastomotic leakage and bowel function favor the colonic J-pouch. However, when the colonic J-pouch reservoir is not technically feasible, the transverse coloplasty is a reasonable option.[28]

Management of Complete Responders Following Chemoradiation

Neoadjuvant chemoradiation therapy (CRT) is the preferred treatment option for distal rectal cancer. Complete pathologic response after CRT has led to the proposal of a nonoperative approach as an alternative treatment for highly selected patients with
complete clinical response. Many of these patients would have only an abdominoperineal resection as an alternative. However, patterns of failure following this strategy remain undetermined.

Habr-Gama[29] reported on 361 patients with distal rectal cancer who were managed by neoadjuvant CRT including fluorouracil (5-FU), leucovorin, and 5,040 cGy. Tumor response assessment was performed at 8 weeks following CRT. Patients with complete clinical response were not immediately operated on and were closely followed. A total of 122 patients were considered to have complete clinical response after the first tumor response assessment. Of these, only 99 patients sustained complete clinical response for at least 12 months and were considered stage c0 (27.4%) and managed nonoperatively. Mean follow-up was 59.9 months. There were 13 (13.1%) recurrences: 5 (5%) endorectal, 7 (7.1%) systemic, and 1 (1%) combined recurrence. All five isolated endorectal recurrences were salvaged. The mean recurrence interval was 52 months for local failure and 29.5 months for systemic failure. There were five cancer-related deaths after systemic recurrences. Overall and 5-year disease-free survivals were 93% and 85%, respectively. Although surgery remains the standard treatment for rectal cancer, nonoperative treatment after complete clinical response following neoadjuvant CRT may be safe and associated with good survival rates in a highly selected group of patients. Survival in these patients is significantly affected by systemic failure. Exclusive local failure occurs late after CRT completion and is frequently amenable to salvage therapy.

Quality of Life

The science of QOL has evolved during the 1990s. A great deal of effort has been devoted to developing QOL questionnaires that have a satisfactory reliability and validity. A potential solution to the problem of identifying the best instrument for the collection of QOL data has been introduced by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Study Group and the Eastern Cooperative Oncology Group. This relates to the use of a modular approach that requires the combined use of a core questionnaire with the addition of a site-specific module to address symptoms that are either not included or included only in general terms by the core questionnaire. A complimentary colorectal module has been developed by these study groups. Although improved outcome is the ultimate goal for the surgical treatment of rectal cancer, there has been increased interest in QOL following radical resection.[30]

A recent 4-year prospective study of 329 patients using the EORTC QLQ-30 and CR-38 questionnaires reported that patients undergoing low anterior resection have improved quality of life compared to patients undergoing abdominoperineal resection. In addition, patients who had no stoma, or had their stoma reversed, reported a substantially
improved postoperative quality of life compared to patients with a permanent stoma.\[31\] Another large series using the same QOL instruments reported opposite results: patients with a permanent stoma reported significantly better social function, less anxiety, and higher self-esteem than those who underwent restoration of bowel continuity.\[32\] There appear to be conflicting data with respect to postoperative quality of life, which is often associated with other factors such as patient comorbidities, anorectal function, location of tumor related to the anal verge, and the level of the anastomosis. The palliative aspect of QOL as it relates to rectal cancer treatment and issues such as pain, cachexia-anorexia, ascites, nausea and vomiting, and dyspnea often centers not only on the patient, but on families and caregivers as well.

Follow-up After Potentially Curative Therapy

In approximately 70% of patients, colorectal cancer is surgically treated for cure. However, 30% to 50% eventually develop recurrence and die of their disease. Today, physicians have at their disposal a variety of laboratory and diagnostic imaging modalities to aid in their efforts in detecting these recurrences while they are still potentially curable. When discussing follow-up after potentially curative treatment for rectal cancer, most preexisting data center around patients with both colon and rectal cancer. However, there are certain follow-up issues that are unique to rectal cancer. First is the fact that the pelvis represents a common site of recurrence, and second is that local full thickness excision represents a unique way to treat rectal cancer, but not colon cancer. A number of strategies often centering on either an “intense vs casual” follow-up schema employing data points such as the frequency of office visits, certain laboratory testing, schedules of diagnostic imaging, and colonoscopy have all yielded confusing results. Factors such as the age of the physician following the patient, the specialty of the physician, geographic variations, and even years since completion of training have all been variable as evidenced by questionnaires sent to specialty societies.\[33\] Unfortunately, the real issue is that once recurrent disease is detected, the percentage of patients able to be salvaged for cure is quite small. Better treatment and outcome of recurrent disease would provide a strong rationale for vigorous postoperative surveillance. Follow-up continues to have the benefit of detection of new primary tumors either of colorectal origin or elsewhere.

Less Common Rectal Tumors

Although the overwhelming majority of malignancies of the rectum are adenocarcinomas, a number of rare histologic types are seen in clinical practice. Carcinoids, lymphomas, and sarcomas are the most common lesions encountered. The treatment of rectal carcinoids remains controversial; however, the size of the lesion dictates treatment.
The majority of lesions are less than 1 cm in diameter with a low (3% to 5%) incidence of metastatic disease. If the lesion is less than 1 cm, either endoscopic removal, fulguration, or local excision is adequate. Lesions between 1 and 1.9 cm are initially approached locally. If the lesion is confined to the submucosa, local excision is adequate. If there is muscle invasion, radical surgery is recommended as invasion of the tumor into the muscularis appears to be an important prognosticator of malignant potential. Radical surgery is recommended for all lesions greater than 2 cm. These large bulky lesions are associated with a 10-year mortality of 60%. ERUS is a valuable tool in staging and follow-up. The carcinoid syndrome is a rare occurrence for rectal lesions.

Lymphoma of the rectum may represent a primary malignancy or metastases from elsewhere in the gastrointestinal tract. Primary rectal lymphoma is best treated by radical surgery with adjuvant chemoradiation. Overall 5-year survival for primary colorectal lymphoma is 30% to 50%, with better survival for patients presenting with localized disease. Secondary rectal lymphoma is best palliated surgically and chemotherapy given for metastatic disease. Leiomyosarcoma comprises 95% of colorectal sarcomas. This tumor has a high recurrence rate and a less favorable prognosis than adenocarcinoma. Wide local excision has a high recurrence rate (60% to 70%), while radical surgery is associated with a 20% recurrence rate. Regardless of treatment, this tumor carries a 5-year survival rate of less than 40%.

Conclusions

Rectal cancer continues to be a challenging entity for the surgeon. Prevention of local recurrence, sphincter preservation, cure, and quality of life remain the essentials to optimal treatment. Initial local staging, supplemented with evaluation for the presence of distant metastases, remains critical during the initial evaluation. The overwhelming majority of patients will have radical surgery. Prior to this, preoperative neoadjuvant therapy will be recommended to those patients with full thickness penetration of the tumor or those with metastatic disease suggested in the perirectal lymph nodes. It will also be offered to patients to increase the risk of sphincter preservation. Most patients will undergo a restorative operation, with fewer requiring an abdominoperineal resection. The utility of a laparoscopic resection continues to evolve, but should only be performed by an experienced minimally invasive surgeon. Emphasis on circumferential radial margins and total mesorectal excision will continue to also improve oncologic results. Sexual and urinary dysfunction are continued potential morbidities, but less so than in the past. A highly select group of patients will be offered local excision. However, informed consent should be emphasized regarding local recurrence, even for mucosally based tumors. The optimal way to manage patients who are complete responders where there is no
evidence of residual tumor after neoadjuvant therapy will need to be individualized. The continued advances in adjuvant chemotherapy may lead to new follow-up protocols. Regardless, there is no substitute for early detection where ultimate survival continues to be determined by stage at diagnosis.

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The complete surgical removal of malignant colorectal lesions is critical for both therapeutic and prognostic purposes. However, if the full benefits of colorectal cancer (CRC) surgery are to be realized for individual patients, a thorough pathologic assessment of each resected specimen is essential. The information gathered from pathologic staging of CRC specimens reveals the extent of disease at the site of origin of the tumor and within the local lymphovascular system, and it elucidates the histologic features of the neoplasm that correlate with aggressiveness and response to therapy. Thus, pathologic staging is the basis that allows the identification of patients who may benefit from postoperative adjuvant chemotherapy, as well as the stratification of patients into groups at varying levels of risk for tumor recurrence and/or distant metastasis.

The TNM Staging System

The TNM (tumor, node, metastasis) system of pathologic cancer staging was introduced in the 1950s by the French surgeon Pierre Denoix. Since then, the system has undergone continual improvement and refinement. The most popular TNM system currently in use worldwide has been developed by the American Joint Committee on Cancer (AJCC, http://www.cancerstaging.org/index.html) in conjunction with the International Union Against Cancer (UICC, http://www.uicc.org/) and is updated every few years upon evaluation of outcome data from large cancer patient clinical databases. Current guidelines for the determination and reporting of TNM pathologic stage can be found in the sixth editions of the *AJCC Cancer Staging Manual* [1] and the *UICC TNM Classification of Malignant Tumours*. [2]

The AJCC-UICC TNM pathologic staging system applies to all types of colorectal carcinoma; it is not applicable, however, to carcinoid tumors, lymphoma, or mesenchymal neoplasms such as gastrointestinal stromal tumors. In general terms, the TNM system works similarly at all sites in the body. In the specific case of CRC, the T designation...
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indicates the depth of invasion of the primary tumor from its site of origin in the colonic epithelium into the underlying intestinal wall. The absolute depth of tumor invasion, in centimeters, is not recorded, as it is of little biologic significance. Instead, the numerical progression of T-stage values describes the involvement of successive histologic layers of the intestinal wall, going from “inside to outside” (mucosa to serosa or perirectal fat). The N-stage designation refers to the degree of regional lymph node involvement. An accurate determination of the N stage depends upon the histologic examination of a sufficient number of lymph nodes. In current standard practice, a minimum of 12 regional lymph nodes must be examined microscopically, with routine histologic techniques, to ensure the correct assessment of N stage.[3] Lastly, the M-stage designation indicates the presence or absence of distant metastasis.

The natural progression of colon cancer has traditionally been divided into four stages. As in other organs, stage I represents limited invasion at the primary site, stage II represents more extensive tumor invasion at the primary site, stage III indicates spread of the tumor to nearby lymph nodes but not to distant sites, and stage IV signifies metastasis of the tumor to distant sites. This spatiotemporal sequence of colorectal cancer progression and its correlation with patient prognosis was first observed by the Scottish pathologist Cuthbert Dukes in 1932. In the Dukes classification, successive stages were labeled alphabetically, such that Dukes stages A through D corresponded to stages I through IV in the general scheme described above.

In the current TNM staging system, overall CRC stage is a direct function of TNM values and is determined by reference to the tabulated stage groupings defined in the AJCC-UICC pathologic staging guidelines. The most up-to-date TNM groupings have been refined to allow for a more precise stratification (substaging) of patients into as many meaningful prognostic groups as possible. For example, patients presenting with a small number (1–3) of local lymph node metastases (N1), whose disease stage would have been classified as the same as those with a heavier local nodal tumor burden involving four or more regional lymph nodes (N2) in the original Dukes system, are now considered to have earlier-stage disease (stage IIIA or IIIB, depending on the T stage) than those with a greater number of regional lymph node metastases (4 or more positive lymph nodes = N2, stage IIIC). This subclassification of stage III into IIIA, IIIB, and IIIC is highly significant in prognosticating patient survival.

For all patients with nodal metastases (stage IIIA, B, and C), postsurgical adjuvant chemotherapy is known to improve 5-year survival and is the current standard of care. Although systemic adjuvant therapy is not recommended routinely for stage II colon cancer, there are some stage II patients who would likely benefit from it. Among the poor prognostic features that would support the use of adjuvant therapy for a stage II CRC
is the presence of microscopic lymphatic or vascular invasion by the tumor, identified upon histopathologic examination of the surgical resection specimen. This finding would indicate an increased likelihood that nodal metastasis, although not detected directly, had in fact occurred. Although lymphatic invasion (L) or vascular invasion (V) does not change the N-stage designation or the overall stage, it is reported as a modifier of the T stage (eg, T3L1 or T3V1) and should be taken into account when considering treatment options for these patients.

**TNM-Independent Elements of Pathologic Staging: Margins**

The histopathologic examination of colorectal cancer specimens provides a few critical pieces of information that are not reflected in the TNM stage designation. One of these is the evaluation of the surgical margins of resection. The importance of histologic analysis of resection margins lies in the fact that the status of the margins is the best indicator of the presence or absence of “residual disease”—ie, tumor that remains in the patient after surgery. For colonic resection specimens, the proximal and distal margins are typically far away (at least several centimeters) from the primary tumor. The resection of rectal tumors, however, sometimes requires a surgical approach that removes only a minimal portion of grossly noninvolved tissue that is contiguous with the tumor. In such cases, a rapid microscopic assessment of the tissue at the margin of resection is often requested by the surgeon during the operative procedure, by means of “frozen section” analysis. Thus, it is unusual for the final pathologic evaluation to reveal proximal or distal margin positivity for colorectal cancer in cases in which potentially curative resection has been attempted.

The radial (circumferential) surface of a colonic resection specimen consists of the serosal surfaces, which cover the bowel and its attached mesentery, and the surgically cut surface of the mesentery at the site of its prior attachment to the abdominal wall. Only the latter surface, the mesenteric margin, is a true surgical margin. Microscopic positivity for tumor at this radial margin is indicative of residual disease, usually in the retroperitoneum. A different type of radial margin exists when a colonic tumor invades transmurally through the bowel wall and causes adhesion to an adjacent organ (eg, another loop of bowel, the urinary bladder, etc). The presence or absence of tumor, confirmed histologically, in the adherent structure determines the T stage (T3 vs T4), whereas the presence or absence of histologically confirmed tumor at the surgical margins of the resected adherent structure indicates the presence or absence of residual disease in the invaded organ.

Because the perirectal fatty tissues lack a serosal covering, the entire radial (circumferential) surface of the rectal component of a distal CRC resection specimen represents a true surgical margin. On occasion, the histologic analysis of a specimen that is the product of a surgical “gross total resection” (no macroscopic evidence of residual tumor
upon completion of surgery) reveals microscopic tumor positivity at the perirectal radial margin. As in the case of mesenteric margin positivity in a colonic resection specimen, this perirectal radial margin positivity indicates the presence of residual microscopic disease in the patient.

The reporting of residual tumor is an essential component of the pathologic diagnosis and is indicated by the R classification. R0 signifies the absence of residual disease (gross total resection and histologically tumor-negative surgical margins) and R1 indicates microscopic residual disease, as evidenced by histologically tumor-positive surgical margins. R2 denotes macroscopic residual disease (grossly positive surgical margins and/or macroscopic evidence of residual tumor after surgery). Often an accurate pathological evaluation of the margin requires a close collaboration between surgeon and pathologist. Tissue planes and structures may move after the specimen is excised and it behooves the surgeon to judge when the pathologist will benefit from direct guidance in determining how best to sample the margin for optimal patient care.

**TNM-Independent Elements of Pathologic Staging: Histology**

Some histologic features of colorectal carcinomas have prognostic significance and are routinely reported, but do not affect the TNM stage designation. These include the tumor type (histologic growth pattern) and the histologic grade.

The majority of CRCs show a characteristic glandular growth pattern that is easily recognizable as “intestinal type” adenocarcinoma. A few less common histologic types are worthy of mention here because they tend to follow either a more aggressive or a more benign course than the histologically typical adenocarcinomas. Primary colorectal signet-ring cell carcinomas are rare and have long been recognized as particularly aggressive. Recent data continue to support the designation of signet-ring morphology as a poor prognostic factor.[4,5] Although many colorectal cancers show focal neuroendocrine differentiation, pure neuroendocrine carcinomas are also rare in the large intestine. Like signet-ring cell cancers, these tumors, which include small-cell carcinomas and large-cell neuroendocrine carcinomas (but which by definition do not include carcinoid tumors) have a worse prognosis than adenocarcinomas.[6]

Mucinous carcinoma is a histologic subtype characterized by abundant extracellular mucin production. Sometimes these tumors show focal signet-ring cell morphology as well, and this has clouded the issue of the prognostic significance of mucinous histology, because many studies have not distinguished between tumors with and those without a signet-ring cell component. Another complicating issue is that mucinous histology is one of several features that have been found to correlate with microsatellite instability, which is a favorable prognostic factor (discussed in Chapter 5, “Role of Prognostic and Predic-
The standard pathologic analysis of colorectal cancer specimens is designed to gather as much information of critical prognostic relevance as possible. The essential parameters that should be elucidated by pathologic examination of every CRC specimen include: the location and size of the lesion, the TNM stage, the status of the surgical margins, the presence or absence of lymphovascular invasion, and the tumor's histopathologic type and grade.

In routine practice, large-bowel resection specimens are delivered to the surgical pathology laboratory on the day of surgery, usually within a few hours of removal. The pathologic assessment begins with visual inspection and palpation, and certain fundamental pieces of data are recorded, such as the anatomical components of the specimen.
Pathologic staging of colorectal cancer involves examining the specimen for various features, such as whether the tumor is grossly evident, the configuration of the specimen, and the presence of adhesions or perforation. Ink is applied to the outside of the specimen in the region of palpable tumor. This is usually a serosal surface and therefore not a true surgical margin. The ink serves as a marker in histologic sections for the serosal surface, which can otherwise be inconspicuous.

Colonic resection specimens are opened longitudinally with scissors, along an axis that avoids the tumor if possible. For fully circumferential lesions, however, it is not possible to avoid cutting through the tumor. Once the mucosal surface is exposed, the gross features of the lesion are recorded, such as the size of the tumor (maximum dimension in centimeters), its location relative to the surgical margins and any other anatomical landmarks (e.g., the ileocecal valve), and its gross morphology (i.e., polypoid, exophytic, ulcerated, etc.). All mucosal surfaces are examined for additional lesions such as polyps or incidental findings such as diverticuli. The specimen may be photographed at this point, and it is usually pinned to a substrate for formalin fixation prior to further processing.

Proximal and distal surgical margins are obtained by first shaving off any surgical staples and then removing a thin, circular (completely circumferential) cross section of the bowel from each end of the specimen. These tissue slices are processed and examined microscopically; the presence of carcinoma indicates a positive surgical margin. The main tumor mass is then sectioned and the cut surfaces are examined visually to determine the area of deepest tumor invasion. Sampling of the tumor for microscopic analysis must include the region(s) of deepest tumor invasion and should incorporate at least one section containing the inked surface of the specimen. In early CRC cases in which the lesion is predominantly adenomatous and/or in which tumor invasion is difficult to assess grossly, it may be necessary to submit the entire tumor for histologic analysis. In rare cases in which the tumor approaches the surgical mesenteric (radial) margin, this margin should be differentially inked so that it can be identified as a surgical margin in histologic slides. The fat can be removed from the bowel and “cleared” with the use of a special fixative, to aid in the identification of small lymph nodes. All lymph nodes are processed for histologic examination. Because it is important to report the total number of recovered lymph nodes, care must be taken not to count bisected lymph nodes twice during the microscopic analysis.

The pathologic examination and processing of rectal cancer specimens is similar to that of colonic carcinomas. The main differences concern the identification and handling of the surgical margins of resection. The peritoneal reflection, if present in the specimen,
should be identified and marked (either with ink or by labeling of sections) so that the position and extent of the tumor relative to the peritoneal cavity may be determined. As in colonic resections, the surface of the specimen in the region of tumor is inked. In rectal resections, this inked surface represents a true surgical (radial) margin.

Pathologic Analysis in Special Cases

Staging Cancer in a Polyp

Unsuspected CRC is sometimes discovered upon histopathologic examination of a polyp that has been removed endoscopically. The T staging of such lesions can be difficult and depends upon factors such as the polyp shape, size, and fragmentation. Pedunculated polyps that have been removed by transection of the stalk are the least problematic because the relationship between the cancer and the cauterized resection margin can be readily determined in histologic sections. Ink can be used to mark the cut margin of the polyp stalk before embedding and sectioning; however, the histologic artifact induced by tissue cauterization often serves to identify the polypectomy margin in microscopic slides. Pedunculated polyps that contain only intramucosal carcinoma and have a negative resection margin require no additional treatment after polypectomy. T1 lesions, in which the tumor invades the submucosa of the polyp, are also adequately treated with polypectomy alone provided that (1) the resection margin is free of tumor, (2) no lymphovascular invasion is identified, and (3) the tumor is histologically low-grade (ie, well or moderately differentiated). If any of these three conditions are not met, the polyp is considered high-risk, and surgical resection of the region of polypectomy should be considered. In fact, resection is both for therapeutic purposes and to allow assessment of the regional lymph nodes (N stage).[8]

If a polyp is removed piecemeal, as is sometimes necessary for sessile lesions, it becomes impossible for the pathologist to determine which of the cauterized areas are true resection margins. This sometimes necessitates surgical resection of the segment containing the polypectomy site when CRC is discovered in a sessile polyp.

Synchronous or Recurrent Tumors

If more than one cancer is found in a colorectal resection specimen, an attempt is made to stage each lesion independently; this is usually possible for T staging but may not be possible for N staging. However, if tumor is found in any regional lymph nodes, the overall CRC stage is stage III. In this case, systemic therapy would be appropriate, regardless of which particular primary lesion gave rise to the regional metastasis identified on pathologic examination.
Tumors that recur at the primary site after surgery, if resected, can be staged using the standard TNM system. The prefix “r” is used in the pathologic reporting of recurrent tumor stage (ie, rTNM).

Staging CRC After Preoperative Therapy

It has been demonstrated that many patients with locally advanced rectal cancer, as assessed clinically and radiologically, benefit from neoadjuvant therapy. The pathologic evaluation of surgical resection specimens from patients who have received preoperative treatment is similar to that of specimens from patients who have had surgery without prior therapy. The only difference is that in addition to providing information about any residual tumor that may be present, the pathologic assessment of a pretreated CRC specimen can often provide clues about the prior local extent of disease and the robustness of the response to therapy. Treatment response can often be detected histologically (as ulceration, fibrosis, inflammation, and sometimes foci of necrotic tumor), and the inferred pretreatment extent of disease (T and N stages) can be correlated with clinical and radiologic findings. The pathologic staging of pretreated CRC, however, refers only to histologically viable-appearing residual tumor and is designated with the prefix “y” (ie, yTNM).

Special Techniques for Evaluation of Lymph Nodes

The fact that a significant proportion of patients with stage II colorectal cancer suffer recurrence of their disease after complete surgical resection (R0) implies that these patients harbor occult, probably microscopic metastases. It is reasonable to hypothesize that such stage II patients with occult residual disease are more likely than those without occult residual disease to have undetected metastases in the lymph nodes of their primary resection specimens. For this reason, much effort in recent years has been focused on the development of highly sensitive methods for the improved detection of microscopic lymph node metastases in colorectal cancer surgical specimens. These methods include serial sectioning of lymph nodes for standard histologic analysis, immunohistochemistry (IHC) for the detection of protein CRC markers, and reverse transcriptase–polymerase chain reaction (RT-PCR) for the detection of CRC-specific mRNA transcripts.

Serial sectioning improves the sensitivity of routine histologic examination for the detection of small metastases simply by increasing the degree of sampling of each serially sectioned lymph node. Although not performed often during the pathologic evaluation of regional lymph nodes in CRC specimens, IHC can be useful for confirming the identity of very small clusters of cancer cells within lymph nodes, when such small clusters are identified on routine sections. However, the sensitivity of IHC is such that it also
allows for the detection of isolated tumor cells (ITCs), which should not be confused with micrometastasis.[9] The current AJCC-UICC staging guidelines recommend that nodal micrometastases (defined as histologic foci of tumor smaller than 2 mm in greatest dimension) should be included in the N classification (N1), but that isolated tumor cells detected on pathologic analysis should not be considered nodal metastasis (N0). The rationale for this recommendation is that ITCs observed in lymph nodes cannot be distinguished from circulating ITCs in the vascular and lymphatic systems. Only a small percentage of circulating cancer cells take up residence in the tissues and proliferate to form a metastatic tumor deposit; many circulating ITCs are simply lost and therefore are presumably of no clinical consequence. Even genuine micrometastases within regional lymph nodes, despite their inclusion in the N1 classification, are of unproven prognostic significance. This is because of variability in the techniques that have been used to detect micrometastases and because of a dearth of outcome data from large-scale studies in which micrometastasis has been evaluated systematically.

RT-PCR, because of its high sensitivity, is capable of detecting very minute amounts of tumor-derived RNA. In theory, quantitative RT-PCR assays might be able to distinguish nodal micrometastases from single ITCs in a lymph node. However, this approach has not yet been adequately developed and validated for clinical application, and the prognostic significance of the additional information it would provide (beyond that provided by standard histologic techniques) is as of yet uncertain.

Sentinel lymph node analysis, which has proven useful in the management of breast cancer as well as melanoma, is currently being evaluated as a tool for improving colorectal cancer N staging.[10] Colorectal sentinel nodes can be identified by peritumoral injection of a dye or tracer, either during surgery (in vivo) or immediately after resection (ex vivo), followed by visual observation or tracer detection to determine which lymph nodes have most quickly and avidly accumulated the dye or tracer.

The aim of identifying sentinel nodes in CRC would be to direct the attention of the pathologist to a small number of lymph nodes most likely to harbor metastases. Once identified, such sentinel nodes could be examined thoroughly with one or more high-sensitivity techniques (eg, multilevel sectioning combined with IHC) for the improved detection of micrometastases. Nonsentinel nodes would be examined histologically in the usual manner. The rationale for limiting the use of high-sensitivity techniques to the analysis of sentinel nodes, rather than applying them to all of the lymph nodes present in a CRC resection specimen, is that they are labor intensive and may be unnecessary, if sentinel node analysis is found to provide information of equivalent prognostic value. However, the protocols for studies of this kind have not been standardized and results are therefore difficult to compare.[11,12] Furthermore, there are conflicting data in the literature regarding the correlation between sentinel lymph node status and overall nodal
status in CRC, in terms of both conventional metastases and micrometastases.[13-16] Nevertheless, at least one recent prospective study has demonstrated a lower recurrence rate in CRC patients staged using sentinel node mapping and analysis compared with CRC patients staged by standard methods.[17]

Ultimately, it is likely that N staging of colorectal cancer will become more accurate through the standardization of high-sensitivity methods for the detection of micrometastatic disease. Whether sentinel node analysis proves useful and whether the assessment of regional nodal micrometastasis turns out to be a powerful prognostic tool are questions that will likely be resolved within the next few years.

References


In recent years, tremendous advances have been made in elucidating the molecular genetic basis of colorectal cancer (CRC). This work has led to the identification and characterization of an enormous number of molecular pathologic variables displayed by colorectal tumors. At present, a major goal of clinical investigation in this field is to determine which of these variables correlate with tumor behavior, both in the untreated patient and in response to therapy. The benefits of developing such prognostic and predictive markers are potentially great, as they would enable clinicians to more accurately assess the needs of individual patients and more precisely tailor treatments to the specific pathophysiologies of these tumors.[1] However, because large numbers of patients must be enrolled in diagnostic and therapeutic trials that incorporate such prognostic/predictive tests before the value of these markers is fully established, these efforts, on the whole, have not yet come to fruition.

In this chapter we review the most promising tumor markers now under development. It should be noted, however, that the number of prognostic/predictive pathologic markers currently used in daily practice is still relatively small.

**Prognostic Markers**

Currently, the most powerful prognostic tool available for guiding treatment decisions in early colorectal cancer is the pathologic TNM (tumor, node, metastasis) stage of the primary tumor, as determined by analysis of the surgical resection specimen. However, TNM stage is far from a perfectly accurate prognosticator. Even with improved methods for determining the pathologic N stage (discussed in Chapter 4, "Pathologic Staging of Colorectal Cancer"), it is unlikely that stage alone will permit a completely accurate prediction of tumor behavior.

Stage II CRC is cured by surgical resection alone in approximately 75% of cases, and surgery plus adjuvant therapy appears to increase the rate of cure by only 1% to 6%. [2]
Because of the significant morbidity associated with adjuvant therapy, an important goal of current research is to identify and validate prognostic markers that will help to stratify stage II CRC patients with respect to their risk of disease recurrence after surgery. Adjuvant therapy could then be more appropriately targeted toward those patients most likely to derive clinical benefit.

Several elements of the pathologic diagnosis are already well established as prognostic factors in CRC. In 1999, the College of American Pathologists (CAP) assembled an interdisciplinary expert committee to review the published data regarding prognostic and predictive markers in CRC. In their Consensus Statement,[3] this panel assigned individual pathologic variables to a series of categories to indicate the strength of the scientific data supporting the prognostic significance of those variables.

Category I factors were those whose prognostic importance had been conclusively demonstrated in multiple large clinical trials. Category II factors were those that had shown considerable promise in multiple studies but had not yet been fully validated in large clinical trials. Category III factors were those deemed insufficiently studied to determine their prognostic importance, and category IV comprised those factors that had been conclusively shown not to carry prognostic significance. Pathologic TNM stage, lymphovascular invasion, and the status of the surgical margins (completeness of resection, or R designation) were all established as category I factors. Elevation of the preoperative carcinoembryonic antigen (CEA) serum level (> 5 ng/mL) was the only other factor whose prognostic implications (as an unfavorable marker) were felt to have been demonstrated with sufficient rigor for inclusion in category I. The pathologic variables assigned to prognostic category II included tumor grade and histopathologic type (discussed in Chapter 4), as well as the molecular genetic variables of microsatellite instability and loss of chromosome 18q.

Microsatellite Instability

Sporadic colorectal cancer is thought to arise through two alternative genetic pathways.[4] The most common pathway is characterized by early mutation of the APC gene with consequent activation of the Wnt signaling pathway and progression to malignant tumors that display chromosomal abnormalities on cytogenetic analysis. This process has been termed the chromosomal instability (CIN) pathway and is thought to give rise to approximately 85% of sporadic CRC. An alternative molecular pathway involves inactivation of certain normal DNA repair mechanisms, specifically, the DNA mismatch repair system (MMR), which leads to tumors that show a form of genomic abnormality called microsatellite instability (MSI).

Microsatellite sequences are regions of repetitive DNA with very short repeat units
(usually di- or trinucleotide repeats) that are scattered throughout the genome. During mitosis, these microsatellite regions are prone to a type of DNA replication error that is normally repaired by the MMR enzymes. Tumor cells that have lost their MMR capability begin to accumulate characteristic changes in their microsatellite sequences: the lengths of the microsatellite sequences are altered such that they are either slightly longer (more repeat units) or slightly shorter (fewer repeat units) than the same microsatellite region in the normal cells of that individual. Microsatellite sequence lengths are determined by polymerase chain reaction (PCR) using genomic DNA derived from formalin-fixed, paraffin-embedded tissues. Approximately 15% of sporadic CRCs are found to harbor microsatellite alterations indicative of MSI.

The two major genetic pathways of colorectal carcinogenesis—the CIN pathway and the MSI pathway—appear largely distinct and nonoverlapping: tumors with MSI usually do not show CIN and tumors with CIN generally do not show MSI.

Ten years ago, the National Cancer Institute (NCI) sponsored a Workshop on Microsatellite Instability with the goal of standardizing definitions and methodologies for detecting MSI in CRC, as well as to review the evidence for correlations between MSI status, tumor histology, and patient prognosis.[5] This group recommended a standard panel of five specific microsatellite loci to be analyzed as markers of MSI and defined tumors with alterations of two or more of the five markers as displaying high levels of MSI, or MSI-H. Tumors showing alteration of only one of the five markers were designated MSI-L (low), and those without microsatellite alteration were designated microsatellite-stable, or MSS.

At the time this NCI workshop was convened, retrospective studies had already shown that MSI-H colorectal tumors are associated with certain clinicopathologic characteristics including proximal (right-sided) location, large size, mucinous or medullary histologic type, fewer nodal metastases, and a less aggressive clinical course when compared with stage-matched MSI-L or MSS controls.

Since that time, additional retrospective studies have provided further evidence that MSI-H status is a favorable prognostic marker, independent of stage, in CRC.[6-8] The analysis of this issue, however, has been complicated by the existence of data from preclinical studies suggesting that MSI-H status correlates with nonresponsiveness of tumor cells to the standard chemotherapeutic agent, fluorouracil (5-FU). As discussed below, retrospective analyses of clinical trial data have generally found that 5-FU does not improve outcome in patients with MSI-H tumors. Thus, somewhat paradoxically, MSI-H status may be both a favorable prognostic marker overall and an unfavorable predictive marker with respect to the efficacy of standard chemotherapy. However, it must be cautioned that the American Society of Clinical Oncology (ASCO), which has recently published evidence-based guidelines for the use of tumor markers in CRC clinical decision-making,[9] recom-
mends that MSI status not be used as an independent prognostic test to guide treatment because the data supporting such a use are as of yet insufficiently robust.

Hereditary nonpolyposis colon cancer (HNPCC) is a familial cancer syndrome caused by germline mutations in the genes governing DNA mismatch repair. The colorectal cancers that arise in the context of HNPCC invariably show MSI, and these tumors share the pathologic characteristics of sporadic MSI-H tumors (large size, mucinous or medullary histology, right-sided location, etc). However, HNPCC-associated tumors usually present at a younger age than sporadic MSI-H tumors. As a prognostic marker, MSI-H status is thought to hold the same significance in HNPCC as in sporadic cases; however, the overall outcome in HNPCC appears better, probably because of the younger average patient age and fewer comorbidities.

In most sporadic MSI-H colorectal tumors, DNA mismatch repair is defective as a result of the inactivation of either the hMLH1 gene or the hMSH2 gene. These genes encode key enzymes required for normal DNA MMR, and their inactivation leads to loss of the encoded enzyme from the nuclei of tumor cells. Immunohistochemistry (IHC) can be used to test for the presence of the MLH1 and MSH2 proteins in tumor sections. It has been suggested that IHC for MLH1/MSH2 might be useful as a surrogate for MSI-H status in CRC and therefore may have prognostic utility. However, PCR testing for MSI-H status is a more sensitive and better-established technique, and current large-scale, prospective trials that incorporate MSI-H as a tumor marker use PCR-based MSI determination methods. Several such ongoing trials are now testing the prognostic utility of MSI status in CRC.

Loss of Chromosome 18q and/or the DCC Gene

The loss of genetic material from the long arm of chromosome 18q occurs frequently in CRC and was among the first molecular defects found to be implicated in the progression of colon cancer. Several genes with possible tumor suppressor activity reside on chromosome 18q, including DCC (a gene named for the fact that it is frequently “deleted in colon cancer”), SMAD2, and SMAD4. The DCC gene encodes a netrin-1 receptor that is involved in the regulation of cell-cell contact and apoptosis. Recent basic research suggests that the loss of this receptor may increase the invasiveness and apoptosis-resistance of colorectal tumor cells. The SMAD4 and SMAD2 genes are involved in transforming growth factor–beta signaling, and they may therefore also play key roles in tumor suppression.

A number of retrospective studies published over the past 10 years have provided evidence that chromosome 18q loss or deletion (18q−) is a poor prognostic factor in CRC (reviewed in References 9 and 15). However, a significant proportion of such studies have
failed to find evidence for this association. This lack of consensus may be due in part to the variability in definitions of 18q-status (ie, 18q was defined as loss of heterozygosity for a variable number of marker loci on 18q). A small number of studies have examined the expression of DCC directly, using immunohistochemistry to detect the netrin-1 receptor protein in tumor tissues, and have searched for correlations between DCC expression and patient outcome. Although the data from some of these studies supports the hypothesis that loss of DCC expression in CRC correlates with poor patient survival, this question must be addressed in more studies and in larger patient populations before conclusions strong enough to influence clinical practice can be drawn.

Current ASCO guidelines do not recommend the use of chromosome 18q LOH or DCC expression analysis as prognostic markers for CRC in routine practice at this time. However, ASCO does suggest that further study is warranted into the potential future utility of chromosome 18q alterations as prognostic and/or predictive markers in CRC.

Other Histopathologic and Molecular Markers

Tumor microvessel density (MVD) and perineural invasion are two histopathologic features that have been suggested as potential prognostic markers in CRC. Perineural invasion can be detected upon routine histologic examination of colorectal cancer specimens and requires no special staining techniques. However, the CAP Consensus Statement published in 2000[3] judged the clinical data at that time to be insufficient for a determination of the prognostic value of perineural invasion in colorectal tumors (ie, perineural invasion was a category III factor). To date, there is scant additional information available on the usefulness of perineural invasion as an independent prognostic factor in colon cancer. A few recent studies have included perineural invasion among the variables tested for correlation with outcome in rectal cancer that had been treated with neoadjuvant therapy and total mesorectal excision.[16-18] These studies suggest that perineural invasion, along with other pathologic variables such as T and N stages and lymphovascular invasion, may indeed have some prognostic meaning in rectal cancer after pretreatment and excision. However, these data require confirmation in larger patient cohorts.

Angiogenesis within tumors plays a critical role in cancer progression. For this reason, microvessel density, as a quantitative measure of intratumoral angiogenesis, has been explored as a possible prognostic marker in a number of malignancies, including CRC.[19,20] The methodologies used for assessing MVD are not completely uniform, but most studies have employed IHC for endothelial markers (typically CD31) to highlight microvessels in tumor histologic sections and then have used morphometric procedures to quantitate vessel density in areas judged by eye to show maximal staining. The CAP Consensus Statement on prognostic factors in CRC lists tumor MVD as a category III
variable and recommends further study.[3] Although only a small number of reports published since that time provide data on MVD as a prognostic marker in CRC, these studies continue to support its potential utility.[21-23] Nevertheless, MVD measurement is still an investigational tool, and it is only one of several measures of tumor angiogenesis currently being evaluated for prognostic/predictive clinical applicability.

The DNA content (ploidy) and proliferation rate (percentage of cells in S phase) of colorectal cancers are variables that can be assessed by flow cytometric analysis of tumor tissue. In the chromosomal instability pathway of colorectal carcinogenesis, progression along the adenoma-carcinoma sequence is characterized by the accumulation of cytogenetic abnormalities, commonly leading to aneuploidy. It has long been recognized that chromosomal instability and consequent aneuploidy are hallmarks of CRC, and tumor ploidy is one of the better-studied potential prognostic markers. However, studies that have examined the prognostic value of tumor ploidy have yielded conflicting results.[24] Because S-phase analysis of tumors can be performed by the same technique as ploidy determination, these two parameters are often examined concurrently. Unfortunately, tumor proliferative rate, as determined by flow cytometry, has thus far proven to be no more consistently reliable as a prognostic marker than ploidy. The 2006 ASCO report on CRC tumor markers recommends against the use of either DNA content/ploidy or tumor proliferation index (percentage in S phase) as prognostic indicators in early colorectal cancer.[9]

A large number of molecular tumor markers have been investigated preliminarily for prognostic significance in CRC.[25,26] These include mutations of the tumor suppressor gene, p53, and the oncogene, K-ras. Methodologies for detecting mutations in tumor tissues are variable and differ according to the types of mutation most commonly found in the particular genes being tested. Although this remains an active area of investigation, results thus far have been generally disappointing. The most promising avenue of investigation now appears to be the search for combinations of molecular markers that may provide increased prognostic power. In addition, microarray analysis is being used to explore differential gene expression in tumors in an effort to find molecular “signatures” of tumor subtypes that differ in terms of prognosis.[27,28] It is hoped that significant advances will be made in this area over the next few years, ultimately leading to the incorporation of prognostic molecular markers into standard practice in the treatment of CRC.

Host Inflammatory Response

It has long been recognized that invasive colorectal tumors elicit local immune responses, and the influence of antitumor immunity on cancer progression is currently a subject of considerable interest and active investigation. Several different histologic
patterns of inflammation are recognized in CRC (reviewed in Reference 29). Medullary carcinoma is characterized by a particularly prominent host inflammatory response that includes peritumoral lymphocytic aggregates (a “Crohn’s disease–like” pattern) as well as large numbers of tumor-infiltrating lymphocytes (TILs). Medullary carcinoma in the intestine virtually always shows high-level MSI, and it has recently been recognized that the presence of numerous TILs is a general feature of MSI-H tumors. Thus, the histologic finding of abundant TILs in CRC is a marker that, as a correlate of MSI-H status, may have prognostic significance on that basis.

In addition, a recent study[30] provides provocative data implying that quantitation of TILs, specifically certain immunohistochemically defined subsets of intratumoral T cells (eg, CD45RO-positive), may be a powerful prognostic tool in CRC regardless of tumor type. This study provides startling evidence that the intratumoral T-cell profiles of primary colorectal tumors are not only independent prognosticators but are in fact better predictors of overall survival than is TNM stage. The techniques used for TIL quantitation in this report are quite sophisticated, requiring computerized image analysis of tissue microarray data. While the work is certainly promising, it requires validation by other groups in prospective clinical studies, and the methodology will likely need to be standardized and simplified. Ultimately, perhaps the most useful application would be in the identification of stage I/II patients with very high-risk intratumoral T-cell profiles who may benefit from adjuvant therapy.

Markers Predictive of Response to Therapy

Fluorouracil and other fluoropyrimidines exert their cytotoxic effects in large part by inhibiting the folate-dependent enzyme thymidylate synthase (TS). This enzyme catalyzes the reaction that provides for the sole intracellular de novo source of thymidylate, an essential nucleotide precursor required for DNA replication and repair. As such, TS has served as an important target for cancer chemotherapy. Preclinically, it is well established that the overexpression of TS in vitro and in vivo renders tumor cells resistant to 5-FU. For this reason, it has been of great interest to explore the relationship between TS expression level in colorectal cancer and responsiveness to 5-FU–based chemotherapy. Colorectal tumors demonstrate considerable heterogeneity with respect to the levels of TS expression, and tumor TS levels can be assessed by either semiquantitative IHC or quantitative RT-PCR. Although some early clinical studies supported the hypothesis that tumors expressing high levels of TS are associated with poor response to adjuvant 5-FU–based chemotherapy, overall results have been mixed,[31] and several recent studies have failed to confirm these initial findings.[32-34] At this time, ASCO does not support the routine use of tumor TS expression level.

Studies are also actively investigating the expression of dihydropyrimidine dehyd-
genase (DPD) and thymidine phosphorylase (TP), two other enzymes involved in 5-FU metabolism as potential predictors of response to chemotherapy in CRC. However, this work should also be viewed as experimental and not yet applicable for daily clinical practice. Areas of active research in this field include investigation of the prognostic and predictive significance of TS gene polymorphisms in CRC patients, as well as efforts to identify combinations of markers relevant to folate metabolism that would allow a more accurate prediction of tumor response to 5-FU–based adjuvant chemotherapy.

As mentioned above in the section on prognostic markers, MSI status in CRC may have value both as a stage-independent prognosticator and as a factor predictive of tumor responsiveness to 5-FU. In vitro, MSI-H tumor cells are less sensitive to fluoropyrimidines than are MSS cells. This effect is thought to be a direct result of the DNA MMR defect in MSI-H cells. In addition to inhibiting TS, 5-FU causes DNA damage of a type normally recognized by the MMR system. Cells with normal MMR enzymes (MSS cells) respond to severe 5-FU–induced DNA damage by undergoing apoptosis. However, in cells with defective MMR, 5-FU–associated DNA damage is not recognized, and therefore, apoptosis is not triggered. Whether this mechanism holds true in vivo for CRC in the adjuvant setting is still under investigation. Some clinical studies, but not all, have provided evidence that MSI-H colorectal tumors, in fact, show poor response to standard 5-FU–based chemotherapy, as judged by patient outcome measures. This continues to be an area of intensive study, and large prospective clinical trials that are currently underway will undoubtedly clarify the implications of MSI status in CRC prognosis and therapy in the near future.

The past several years have witnessed an explosion of research into novel targeted therapies for CRC. Two biologic agents have been shown to have activity in CRC and to improve the survival of patients with metastatic disease when administered in combination with standard chemotherapy. These are the monoclonal antibody therapies directed against the angiogenic mediator, vascular endothelial growth factor (VEGF) and those that target the epidermal growth factor receptor (EGFR). Although these therapies have proven to be efficacious in the treatment of metastatic CRC, their role in adjuvant therapy of early-stage disease is not yet established. Furthermore, there are as of yet no markers that can predict tumor responsiveness to either of these therapies.

EGFR expression level, as judged by IHC on tumor sections, has been examined as a possible predictive marker for anti-EGFR (cetuximab [Erbitux]) therapy, but has been found not to correlate with response. Similarly, there does not appear to be a clear relationship between the level of VEGF expression and other molecular markers relating to angiogenesis in tumor tissue and response to antiangiogenic therapy. The possibility that EGFR gene amplification might be associated with cetuximab response rate has also been explored. However, it appears that EGFR, unlike the HER2/neu gene in breast cancer, is almost never amplified in CRC. Current research in the fields of
tumor angiogenesis and growth factor signaling pathways is progressing at a remarkably rapid rate.

The elucidation of these critical biologic processes will continue to provide a wealth of new potential targets for biologic therapies, as well as novel potential biomarkers for assessing and predicting patient responses to those therapies.

Conclusions

In current practice, traditional histopathologic TNM staging of CRC offers the most reliable and accurate means of estimating patient prognosis. A few molecular pathologic markers have shown great promise in preclinical and preliminary studies and are in the late stages of validation as prognostic/predictive factors in large-scale, prospective clinical trials. These include tumor MSI status and loss of chromosome 18q. Other molecular and histopathologic factors that may prove useful as prognostic/predictive markers in the future, but that are further from clinical validation, have been identified through TIL immunoprofiling and tumor gene expression array analysis.

Given the rapid rate of progress in this field, one can envision that the number of clinically useful pathologic markers will rise dramatically in coming years. Combined with advances in pharmacogenetics, this increased armamentarium of tumor biomarkers will enable those who care for CRC patients to assess prognosis and to optimize available therapies in a highly accurate and personalized manner.

References

7 Prognostic and Predictive Markers

22. Li C, Gardy R, Seon BK, et al: Both high intratumoral microvessel density determined using CD105 antibody and elevated plasma levels of CD105 in colorectal cancer patients correlate with
Prognostic and Predictive Markers


Colorectal cancer (CRC) is diagnosed in approximately 147,000 patients per year in the United States. Among these patients, 37% present with stage III disease and 28% with stage II disease. Although surgery remains the mainstay of treatment for early-stage colon cancer, a substantial fraction of patients are still not cured by surgery alone. Their survival depends on pathologic stage and specific clinical features, and varies from 30% to 60% for stage III to 60% to 80% for stage II. To date, tumor stage at the time of resection remains the most important prognostic factor: in tumors with full-thickness penetration of the bowel wall and/or locoregional lymph node involvement, the risk of microscopic residual and/or distant metastatic disease is significantly higher than in limited stage I tumors.

For nearly 15 years, adjuvant therapy with the fluoropyrimidine fluorouracil (5-FU) was viewed as standard treatment. In the United States, bolus schedules of 5-FU in combination with the reduced folate leucovorin (LV) were widely used, while in Europe, infusional schedules of 5-FU/LV were preferred. Since the MOSAIC trial was reported in 2003, oxaliplatin (Eloxatin)-based chemotherapy has become a new standard treatment option for the adjuvant setting.

Currently, there is great interest in incorporating the targeted biologic agents bevacizumab (Avastin) and cetuximab (Erbitux) into the various cytotoxic chemotherapy regimens in an attempt to improve clinical efficacy in the adjuvant-therapy setting. The potential role of biologic agents in adjuvant treatment will be reviewed in Chapter 7, “Biologic Agents in the Adjuvant Treatment of Colon Cancer.” The clinical benefit of adjuvant chemotherapy for localized node-negative (stage II) disease is definite albeit small. Further identification of key prognostic and predictive biomarkers may allow future adjuvant therapy to be individualized for patients with stage II and perhaps even stage III disease.
Evolution of Adjuvant Treatment of Colon Cancer

See Table 1 below for a timeline summarizing the development of regimens for the adjuvant treatment of colon cancer.

Although clinical trials were initiated in the 1960s, no definite survival advantage was seen with adjuvant therapy compared with surgery alone until 1988 when the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01 trial showed that treatment with fluorouracil and levamisole for 1 year following surgical resection conferred significant clinical benefit with respect to disease-free survival (DFS) and overall survival (OS) compared to surgery alone.[5] The Intergroup 0035 study using 5-FU and levamisole for 1 year, the North Central Cancer Treatment Group (NCCTG) study using 6 months of 5-FU and leucovorin (LV), and the IMPACT study using 5-FU/LV for 6 months demonstrated similar improvements in DFS and OS rates.[6-10]

These encouraging results led to a direct comparison of these regimens in the Intergroup study INT-0089, which randomized 3,759 patients (20% with high-risk Dukes stage B2 disease) to receive standard 5-FU + levamisole for 12 months, 5-FU + high-dose LV, 5-FU + low-dose LV, or 5-FU + low-dose LV + levamisole.[11] The latter three regimens were administered for 6 months. This pivotal study affirmed that 6 months of therapy with

| TABLE 1. Development of regimens for the adjuvant treatment of colon cancer |
|-----------------------------|-------------------------|
| 1990                        | 5-FU/levamisole better than surgery alone |
| 1994                        | 5-FU/LV better than surgery alone |
| 1998                        | 5-FU/LV better than 5-FU/levamisole |
| 1998                        | 6 months = 12 months |
| 1998                        | Leucovorin of no benefit |
| 1998                        | HDLV = LDLV |
| 1998                        | Weekly = monthly schedule of 5-FU/LV |
| 2002                        | Infusional LVSFU2 = monthly bolus |
| 2004                        | FOLFOX better than LVSFU2 |
| 2005                        | Capecitabine = 5-FU/LV |
| 2005                        | FLOX better than 5-FU/LV |

FLOX = 5-FU, leucovorin, oxaliplatin; FOLFOX = leucovorin, 5-FU, oxaliplatin; HDLV = high-dose leucovorin; LDLV = low-dose leucovorin; LV = leucovorin.
5-FU + LV resulted in virtually identical clinical benefit when compared to the other three treatment arms, with prolonged follow-up (median of 10 years). This study also provided an opportunity to further understand the natural history of patients with high-risk colon cancer. At 5 and 10 years after completion of adjuvant therapy, approximately 10% of patients will experience another cancer-related event (an absolute decrease of 10% in DFS) and nearly 14% of patients will die (an absolute decrease of 14% in OS).

The findings from the NSABP C-04 study were similar.[6] Between July 1989 and December 1990, a total of 2,151 patients were randomly assigned to receive 5-FU + LV (weekly regimen), 5-FU + LEV, or the combination of 5-FU + LV + levamisole. A pairwise comparison between patients treated with 5-FU + LV or 5-FU + levamisole revealed a prolongation in DFS in favor of the 5-FU + LV group (65% vs 60%; \( P = .04 \)); there was a small prolongation in OS that was of borderline significance (74% vs 70%; \( P = .07 \)). However, no differences in the pairwise comparison were observed between patients who received 5-FU + LV or 5-FU + LV + levamisole for either DFS (65% vs 64%; \( P = .67 \)) or OS (74% vs 73%; \( P = .99 \)). Of note, no significant differences in safety profile were observed between these two treatment regimens. The presence of levamisole did not appear to provide any further clinical benefit, and as a result, levamisole was subsequently dropped from future adjuvant chemotherapy regimens.

Based on the clinical data from these trials, adjuvant chemotherapy using 6 months of 5-FU + LV became the standard of care in the United States. Moreover, 5-FU/LV has served as the backbone for various combination regimens that have incorporated oxaliplatin (Eloxatin) and/or irinotecan (Camptosar). Oxaliplatin-based chemotherapy is now accepted as the new standard of care in the adjuvant treatment of stage III colon cancer, when combination chemotherapy is selected. The oral fluoropyrimidine capecitabine (Xeloda) was shown to be as effective as and safer than intravenous 5-FU/LV in patients with stage III colon cancer, and it can be considered an effective alternative to 5-FU/LV in the adjuvant therapy of stage III colon cancer when monotherapy is desired.

**Candidates for Adjuvant Therapy**

Adjuvant chemotherapy for patients with node-positive (stage III) colon cancer and high-risk stage II disease is now widely accepted. In patients with normal risk stage II disease, however, the role of adjuvant therapy remains a subject of ongoing debate.

**Options for Adjuvant Therapy**

**Bolus 5-FU**

Studies from the NSABP and other US cooperative groups have demonstrated that 5-FU–based adjuvant chemotherapy is associated with improvements in DFS and OS.
These studies led to the widespread use of 5-FU/LV for 6 months as standard adjuvant chemotherapy in the United States. In the United States, the two most commonly used bolus 5-FU/LV dose schedules are the Mayo Clinic regimen (5-FU 425 mg/m² and LV 20 mg/m² days 1–5 every 4 weeks for six cycles) and the Roswell Park/NSABP regimen (5-FU 500 mg/m² and LV 500 mg/m² weekly for 6 weeks given on an every-8-week schedule for 4 cycles) (Table 2).
Infusional vs Bolus 5-FU

Infusional regimens of 5-FU/LV are associated with improved response rates and a trend toward a small survival benefit over bolus regimens in advanced CRC. They are characterized by an improved safety profile, with reduced hematologic toxicity in the form of myelosuppression. These data provided the rationale to investigate continuous infusion 5-FU in the adjuvant setting. In three randomized clinical studies (GERCOR, Intergroup 0153, SAFFA) that compared continuous infusion 5-FU with bolus 5-FU as adjuvant therapy in colon cancer, no statistically significant differences were observed in either DFS or OS. However, the safety profile favored the regimens using continuous infusion 5-FU with decreased myelosuppression (Table 3). As a result of these studies, infusional regimens of 5-FU/LV have been favored in Europe. These results led to the incorporation of LV5FU2 (Table 2), a continuous infusion 5-FU/LV regimen developed by de Gramont and colleagues in France, as the backbone for combination regimens using oxaliplatin or irinotecan in subsequent phase III adjuvant studies.

Oral Fluoropyrimidines

Oral fluoropyrimidines were initially developed with the rationale that they might more closely mimic infusional schedules of 5-FU. In fact, on a pharmacologic basis, the pharmacokinetics of capecitabine are more similar to continuous infusion 5-FU than is observed with intermittent infusion schedules, as developed by de Gramont and colleagues in France and by the German AIO cooperative group. With the documented benefit from 5-FU infusion schedules, capecitabine was developed to offer a safe, effective, and more convenient treatment option for patients. The Xeloda Adjuvant Chemotherapy Trial (X-ACT) was designed to test the equivalence of capecitabine and bolus 5-FU/LV in the adjuvant setting. Patients with stage III colon cancer were randomized to receive 24 weeks of treatment with either oral capecitabine 1,250 mg/m² twice daily, days 1–14 every 21 days, or the Mayo Clinic regimen of bolus 5-FU/LV. In terms of clinical efficacy, patient treated on the capecitabine arm had at least equivalent DFS bordering on superiority when compared to the 5-FU/LV arm. However, the capecitabine arm had an improved safety profile as patients experienced significantly (P < .001) less diarrhea, stomatitis, nausea/vomiting, alopecia and neutropenia, but more hand-foot syndrome (HFS) than those receiving 5-FU/LV. Fewer patients receiving capecitabine experienced grade 3/4 neutropenia and febrile neutropenia/sepsis (P < .001). Of note, capecitabine had a similar, favorable safety profile in patients aged < 65 years and in those > 65 years old. Based on these results, capecitabine was approved for use as adjuvant therapy for stage III colon cancer when fluoropyrimidine monotherapy is being considered (Table 3).

Building on the results of the X-ACT trial, a follow-up study investigated the com-
Adjuvant Chemotherapy of Colon Cancer

A randomized phase III trial comparing XELOX (capecitabine, 2 weeks on, 1 week off and oxaliplatin once every 3 weeks) regimen and 5-FU/LV (Mayo Clinic or Roswell Park regimen) was subsequently conducted. The results of a planned safety analysis have now been reported. The overall rate of treatment-related adverse events was similar in both arms. However, patients receiving XELOX experienced less all-grade diarrhea and alopecia, and more peripheral neuropathy, vomiting, and HFS than those patients receiving 5-FU/LV. When compared with the Mayo Clinic regimen, XELOX resulted in fewer grade 3/4 hematologic but more grade 3/4 gastrointestinal toxicities. In contrast, when compared with the Roswell Park regimen, patients treated with XELOX experienced fewer grade 3/4 gastrointestinal yet more grade 3/4 hematologic toxicities. As expected, grade 3/4 peripheral neuropathy and grade 3 HFS were higher with XELOX. Treatment-related mortality within 28 days from the last study dose was low in both arms, 0.6% in the XELOX group and 0.6% in the 5-FU/LV group. The clinical efficacy data are expected sometime in early 2008.

**Oxaliplatin**

The superior clinical efficacy of the FOLFOX regimens in the treatment of advanced colon cancer provided the rationale for clinical trials assessing oxaliplatin-based chemotherapy in the adjuvant setting. The MOSAIC trial was a pivotal randomized phase

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**TABLE 3. Comparison of toxicities with bolus and infusional 5-FU**

<table>
<thead>
<tr>
<th></th>
<th>GERCOR</th>
<th>Intergroup 0153</th>
<th>SAFFA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus CI</td>
<td>Bolus CI</td>
<td>Bolus CI</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9% 4%</td>
<td>19% 7%</td>
<td>15% 5%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>7% 2%</td>
<td>18% 8%</td>
<td>18% 4%</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>3% 1%</td>
<td>13% 3%</td>
<td>2% 1.5%</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>0% 0%</td>
<td>0.4% 4%</td>
<td>3% 7.1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>16% 7%</td>
<td>51% 0.7%</td>
<td>55% 1%</td>
</tr>
<tr>
<td>All toxicities</td>
<td>26% 11%</td>
<td>71% 35%</td>
<td>68% 21%</td>
</tr>
</tbody>
</table>

CI = continuous infusion.
III clinical trial conducted in Europe as adjuvant therapy for stage II and III colon cancer. This study randomized 2,246 patients with stage II/III colon cancer to receive 6 months of LV5FU2 (bolus plus infusional 5-FU/LV) or FOLFOX4 (Table 2). In terms of clinical efficacy, FOLFOX4 was found to be superior to LV5FU2 in terms of 3-year disease-free survival, which was the primary endpoint of this trial. A combined analysis for stage II and stage III patients revealed a 23% risk reduction for 3-year recurrence (hazard ratio [HR] 0.77, \( P = .002 \)). Disease-free survival after 3 years was 78.2% in the FOLFOX4 arm and 72.9% in the LV5FU2 arm. An updated disease-free survival analysis at 4 years showed that FOLFOX4 was associated with a 24% reduction in relapse (\( P = .0008 \)).

At the 2007 American Society of Clinical Oncology meeting, the 6-year final analysis of overall survival was presented. The DFS benefit observed in all patients at 3 and 4 years, respectively, continued, at 5 years (HR: 0.80, \( P = .005 \)), and the patients that derived the true benefit from FOLFOX chemotherapy were those with stage III and high-risk stage II disease (HR: 0.78, \( P = .005 \)). In terms of overall survival (OS), there was a trend towards improved OS in the entire patient cohort (HR: 0.85, \( P = .057 \)). However, stage III and high-risk stage II patients experienced a significant improvement in OS with FOLFOX while those with low-risk stage II disease derived no benefit in OS. With respect to long-term safety, there was no increased risk of developing a secondary cancer, which was approximately 5% in both arms, and the rate of peripheral sensory neuropathy continued to decrease over time.

The main side effect of FOLFOX4 was peripheral sensory neuropathy, which is secondary to oxaliplatin therapy. Grade 3 neurotoxicity was observed in 12.4% of patients overall and in 18% of patients who received the entire planned cumulative dose of oxaliplatin (1,020 mg/m²). However, the peripheral neuropathy proved reversible in the vast majority of patients such that 12 and 18 months after discontinuation of therapy only 1.1% and 0.5% of patients, respectively, experienced residual grade 3 neurotoxicity. Of note, in the 6-year final analysis, the rate of peripheral sensory neuropathy continued to decrease over time.

A study conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP C-07) provides further support for the importance of oxaliplatin in the adjuvant setting. In this study, 2,407 patients were randomized to the control arm, which was the Roswell Park schedule 5-FU/LV (500 mg/m² of both given weekly for 6 weeks followed by 2 weeks rest for 3 cycles) or to the experimental arm, which was the same weekly 5-FU/LV regimen plus oxaliplatin (FLOX; Table 2). Oxaliplatin was administered at 85 mg/m² every 2 weeks on weeks 1, 3, and 5 of the 8-week cycle (cumulative dose, 765 mg/m²). Seventy-three percent of patients received the planned oxaliplatin treatment. The primary endpoint of this study was 3-year disease-free survival, which favored the...
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FLOX arm (76.1 vs 71.8%; \(P = .004\)) with a hazard ratio of 0.80 (95% CI = 0.69 to 0.93), a 20% risk reduction in favor of FLOX \((P < .004)\). The 4-year disease-free survival rates were 67.0% for 5-FU/LV and 73.2% for FLOX, respectively, which confirmed that the DFS benefit is maintained.

The FLOX regimen was relatively well-tolerated, although the overall incidence of grade 3/4 toxicities was slightly higher in the FLOX arm compared to 5-FU/LV (60% vs 50%). The incidence of GI toxicity in the form of enteritis leading to diarrhea and dehydration was higher in patients treated with FLOX when compared to 5-FU/LV (4.5% vs 2.7%). Only 8% of patients experienced grade 3 neurotoxicity, and after 12 months, this number decreased to 0.5% of patients. While additional efficacy data are awaited to fully define whether FLOX is as effective as FOLFOX4, the results reported to date would suggest that the improvement in DFS is equivalent between these two oxaliplatin-based regimens. Perhaps of greater importance is the suggestion that lower cumulative doses of oxaliplatin, as administered in the NSABP C-07 trial, may be as effective as the higher cumulative doses administered in the MOSAIC trial.

Irinotecan

To date, irinotecan-based regimens have not shown any clinical benefit when used in the adjuvant setting. In the Cancer and Leukemia Group B (CALGB) C89803 study, accrual was terminated prematurely after an interim analysis identified a higher than expected 60-day all cause mortality rate in patients treated with the weekly schedule of irinotecan, 5-FU, LV (IFL) (2.2% in IFL vs 0.8% in control arms).[22] This increased mortality was attributed to two syndromes associated with irinotecan: a gastrointestinal syndrome characterized by diarrhea, nausea and vomiting, dehydration coupled with febrile neutropenia and electrolyte imbalances and a vascular syndrome characterized by acute, fatal myocardial infarction, cerebrovascular accident, and pulmonary embolism. The nearly 3-fold increase in early mortality in this study may be responsible for the lack of survival benefit over bolus 5-FU/LV in the C89803 trial.

Recently, irinotecan was combined with the LV5FU2 infusion regimen in the PETACC-3 and ACCORD-2 randomized controlled studies in the adjuvant setting. In contrast to the bolus, weekly schedule of IFL, the 60-day all-cause mortality rate was significantly lower, 0.9% in the PETACC-3 and 0.5% in the ACCORD-2 studies, rates similar to those observed with continuous infusion 5-FU alone.[23,24] However, neither of these studies, which used an infusional 5-FU/LV regimen combined with irinotecan, was able to show clinical benefit. Based on the negative findings of these three clinical trials, irinotecan-based chemotherapy cannot be recommended for use as adjuvant therapy. Moreover, these results highlight the critical principle of not extrapolating
clinical efficacy data from the advanced disease setting into the adjuvant setting without conducting the key randomized clinical studies.

Optimal Time to Initiate Adjuvant Therapy After Surgery

In most cases, adjuvant treatment is generally started within 6 to 7 weeks after surgery. However, delays in commencing adjuvant therapy are not uncommon in everyday clinical practice. The effect of treatment delay with respect to patient outcome has not been well-established. In a Swedish adjuvant therapy study, 2,224 patients with stage II/III colon cancer were randomized to surgery alone or to adjuvant chemotherapy.[25] With respect to adjuvant chemotherapy, the different regimens that were used included 5-FU/levamisole for 12 months (n = 444), 5-FU/LV for 4 to 5 months according to either a modified Mayo Clinic schedule (n = 262), or the Nordic schedule with 5-FU 500 mg/m² IV push and LV 60 mg/m² 30 minutes later days 1 and 2 every 14 days for 10 (n = 397).[24] Randomization was performed after a median of about 30 days, and patients who received adjuvant chemotherapy did so after a median of 49 days. Of note, overall survival was significantly inferior for patients who started adjuvant therapy beyond 8 weeks after surgery.

In all of the randomized clinical trials showing survival benefit, adjuvant therapy was generally initiated within 35 days, and the maximum permissible number of days was 56. In NSABP C-03, patients who did not start treatment within the stipulated 42 days were excluded from analysis.[26] There are relatively limited data on the relevance of a delay in starting adjuvant therapy, although intuitively, this would seem to be a potentially important factor that determines eventual outcome. In most of the subsequent adjuvant trials, comparing different schedules (type of drugs, doses and treatment duration) and failing to detect any differences between schedules, longer times to randomization and treatment initiation were allowed. Thus, there is a danger that the conclusion drawn from these trials, namely that the treatments are equally effective may be inappropriate.

Optimal Duration of Adjuvant Chemotherapy

The Intergroup-0035 study led to the adoption of 5-FU/levamisole as standard adjuvant therapy to be administered for a 12-month period. However, 30% of the patients had to discontinue treatment prematurely secondary to toxicity, with the median duration on therapy being 5 months.[7,8,10] A series of randomized phase III trials were subsequently performed, including the INT0089 and INT0089-46-51, and these studies established 6 months as the standard treatment duration.[11,27] In addition, a randomized phase III conducted by the GERCOR group in France randomized patients with stage II and III colon cancer between a semimonthly (LVFU2) with a monthly (5-FU/LV) regimen, and a
second randomization was performed between 24 and 36 weeks (12). Disease-free survival was similar between the LVFU2 and 5-FU/LV groups (hazard ratio [HR] = 1.04; \( P = .74 \)) and between 24 and 36 weeks of therapy (HR = 0.94; \( P = .63 \)). Analysis of overall survival showed a slight excess in the number of deaths in LVFU2 compared with 5-FU/LV, but this difference was not statistically significant (HR = 1.26; \( P = .18 \)). The most commonly observed grade 3/4 toxicities were neutropenia, diarrhea, and mucositis. Toxicities were significantly lower in the LVFU2 group (all toxicities, \( P < .001 \)).

A randomized phase III study was conducted by Chau et al, which compared 6 months of treatment with Mayo Clinic regimen to a 12-week course of PVI 5-FU (300 mg/m²/d). No differences in OS were observed, although PVI 5-FU was associated with a trend towards improved RFS and OS compared with bolus 5-FU/LV as well as significantly reduced toxicity.[14] These data are clinically relevant as patient quality of life would be maintained and/or improved earlier if the duration of chemotherapy was shorter. This issue becomes even more important when the adjuvant treatments include oxaliplatin-based chemotherapy, given that oxaliplatin is associated with a cumulative dose-dependent neurotoxicity. As such, a shorter duration of treatment would result in a potentially reduced incidence of peripheral neuropathy.

Role of Adjuvant Radiation Therapy in Colon Cancer

After a potentially curative surgical resection for colon cancer, the risk of local-regional recurrence is rather significant. In several series, the risk of local-regional recurrence ranges from 30% to 70% in patients with tumor adherence to surrounding structures, tumor penetration through the bowel wall, and/or involvement of regional lymph nodes. A number of retrospective and nonrandomized studies have suggested that postoperative adjuvant radiation therapy (XRT) might result in decreased local recurrence.

The GI Intergroup conducted a randomized phase III study, Intergroup Protocol 0130, to determine whether XRT added to adjuvant chemotherapy could improve outcome in high-risk patients with tumor adherence or invasion of surrounding structures or with T3N1 or T3N2 tumors. Patients were randomized to receive adjuvant chemotherapy with 5-FU/levamisole with or without radiation therapy. Overall survival and disease-free survival were virtually identical between the two treatment arms, and a significantly higher rate of toxicity, mainly in the form of hematologic toxicity was observed in patients treated with chemotherapy plus XRT.[28] While this study did not show any benefit with the use of adjuvant XRT, the results should be viewed with caution as patient enrollment was terminated due to slow accrual. As only 222 patients were enrolled onto this study, with an original target of 700 patients, this study had limited power to detect potential differences in treatment effect.
Rationale for Targeted Agents in the Adjuvant Therapy of CRC

The biologic targeted agents have shown significant clinical activity when used in combination with cytotoxic chemotherapy for the treatment of advanced CRC. With this as rationale, a series of clinical studies have been initiated to evaluate the respective roles of bevacizumab and cetuximab in the adjuvant therapy setting. These trials are reviewed in greater detail in Chapter 7.

The clinical benefit of oxaliplatin-containing regimens as adjuvant therapy for CRC,[19] and the data showing significant survival benefit when bevacizumab is used as first-line therapy in patients with metastatic CRC,[29] provide the rational basis for combining bevacizumab with oxaliplatin-containing regimens as adjuvant therapy in patients with early-stage colon cancer. The combination of FOLFOX chemotherapy plus bevacizumab is being investigated in two large randomized phase III trials: NSABP C-08 and AVANT.

The clinical activity of cetuximab in patients with advanced CRC was initially investigated in the second and third-line setting, and this anti-EGFR antibody was shown to have promising clinical activity and an acceptable safety profile.[30] More recently, phase II and phase III studies have confirmed the efficacy of cetuximab in combination with either FOLFIRI or FOLFOX chemotherapy in the first-line treatment of advanced CRC. This success in the advanced disease setting fueled significant interest in developing cetuximab in the adjuvant setting of colon cancer. Currently, in the United States, cetuximab is being evaluated in the adjuvant setting in the NO147 study, which is a randomized phase III trial of FOLFOX chemotherapy with or without cetuximab after curative resection for patients with stage III colon cancer.

Role of Adjuvant Therapy in Stage II Colon Cancer

Stage II colon cancer accounts for approximately 25% of all patients who present with CRC. Patients who present with stage II disease have a relatively good prognosis after definitive surgical resection, with a 72% to 85% OS rate (stage IIA: T3, N0, M0, 85%; stage IIB: T4, N0, M0, 72%). In contrast to the well-established survival benefit of adjuvant chemotherapy for node-positive stage III disease, its role in low-risk stage II colon cancer remains somewhat controversial. Only a statistically insignificant 2% to 4% improvement in OS rate with adjuvant therapy has been demonstrated. For this reason, careful selection of patients, who would derive greatest benefit from adjuvant therapy, is of critical importance.

In general, the clinical data coming from several randomized phase III trials have been inconclusive with respect to the potential clinical benefit of adjuvant chemotherapy in stage II colon cancer. This is mainly due to the fact that these studies have been rela-
tively underpowered to show real differences in clinical efficacy. In general, the number of stage II patients enrolled onto these various studies have ranged from 300 to 1,000. The Quasar (Quick and Simple and Reliable) Study from the United Kingdom is the largest trial done to date having enrolled over 3,000 patients. While 91% of the patients enrolled onto this study had stage II disease, 8% of patients had stage III disease and another 29% of patients presented with rectal cancer.[31] In addition, patients were offered different fluoropyrimidine-based regimens and different schedules of administration, including every 4 weeks or weekly regimens. Although a small survival difference on the order of 3% at 5 years ($P = .02$) was observed for all patients treated with chemotherapy, the difficulty in properly evaluating this study is that 29% of patients had rectal cancer, a disease with a higher disease recurrence rate when compared to colon cancer. Thus, inclusion of these high-risk patients in the control arm could have skewed the results of the trial in favor of the adjuvant therapy arm.

One strategy to overcome the limitations of small randomized trials has been to pool data from several clinical trials and/or to analyze data from registries. Three such attempts have been undertaken, as described below:

(1) NSABP Trials (pooled analysis of NSABP C-01, C-02, C-03, C-04): NSABP C-01 and C-02 randomized stage II and III patients to surgery alone vs combination chemotherapy using semustine (methyl-CCNU), vincristine (Oncovin), and 5-FU (MOF) and with perioperative 5-FU portal vein infusion, respectively.[5,32] C-03 and C-04 compared 5-FU/LV vs MOF plus 5-FU/levamisole, respectively.[6,26] The 1,565 stage II patients comprised 41% of the total of 3,820 patients. A 30% reduction in overall mortality was observed for stage II patients (odds of death, 0.70), compared with an 18% risk reduction for stage III patients (odds of death, 0.82). No difference was observed in mortality risk reduction for stage II patients with or without high-risk features (obstruction, perforation, or T4), with an absolute survival improvement of 5%. Based on this analysis, the NSABP recommended adjuvant chemotherapy for stage II and III colon cancer. However, these recommendations are somewhat limited given that trials C-03 and C-04 did not have a surgery-alone arm, and the MOF regimen, levamisole, and portal vein 5-FU infusions are no longer used in clinical practice.

(2) Pooled Intergroup Meta-Analysis: A total of 3,302 stage II and stage III patients with colon cancer were enrolled onto seven randomized trials, which compared adjuvant 5-FU/LV or 5-FU/levamisole vs observation.[27] A multivariate analysis adjusted for T stage, histologic grade, nodal status, and adjuvant 5-FU–based chemotherapy. Disease-free survival of 67% vs 55% (HR 0.70) and 5-year OS of 71% vs 64% (HR 0.74), respectively, were significantly improved with adjuvant chemotherapy. The advantage of chemotherapy was observed in all subsets, although patients with node-negative disease
(stage II) did not demonstrate a survival advantage (81% vs 80%, \( P = .113 \)).

(3) Cancer Care Ontario Practice Guideline Initiative Gastrointestinal Cancer Disease Site Group Analysis: This was a systematic review of 37 trials and 11 meta-analyses published after 1987. A separate meta-analysis sanctioned by the American Society of Clinical Oncology (ASCO) was performed on a subset of 12 trials (4,187 patients) with an observation arm and at least one 5-FU–based adjuvant chemotherapy arm for stage II colon cancer patients.[33] The mortality risk ratio did not reach statistical significance (HR 0.87; 95% CI = 0.75 to 1.10, \( P = .07 \)).

To better define the potential group of patients with stage II disease who would benefit from adjuvant chemotherapy, the subset of high-risk stage II disease was developed. This distinction has mainly been based on several clinical features, including T4 lesions with tumor perforation, bowel obstruction, poorly differentiated tumors, lymphatic and/or venous invasion, and perineural invasion experience, each of which predict poor clinical outcome.[34,35] Patients with these adverse risk factors have only a 5-year survival of 60%, which is similar to patients who present with stage III disease. Node-negative

<table>
<thead>
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<th>TABLE 4. American Society of Clinical Oncology recommendations for stage II disease</th>
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<tr>
<td>• No reason to routinely recommend adjuvant therapy</td>
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<tr>
<td>• If there is any benefit in overall survival, it is on the order of 2% to 4%</td>
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<td>• To detect a 2% benefit, a randomized controlled trial would have to enroll &gt; 9,000 patients</td>
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<td>• High-risk subsets exist</td>
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<td>Inadequate lymph node sampling</td>
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<td>T4 lesions</td>
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<td>Perforation/obstruction</td>
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<td>Poorly differentiated histology</td>
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<td>Lymphovascular invasion</td>
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(34, 35)
disease can be diagnosed if at least 12 regional lymph nodes are inspected and found to be free of disease. The survival of patients with node-negative disease is therefore highly dependent on the skills of the surgeon and pathologist. Thus, if a stage II patient has fewer than 12 negative nodes examined, the general recommendation is to treat this individual with adjuvant chemotherapy, as it is conceivable that the extent of disease may have been underestimated.

The American Society of Clinical Oncology[36] and the National Comprehensive Cancer Network (NCCN)[37] recently published recommendations as to how to treat patients with stage II colon cancer (Table 4). Based on the available clinical data, there was firm evidence to routinely recommend adjuvant therapy. If any benefit in OS is to be derived from adjuvant therapy, it is relatively small, on the order of 2% to 4%. In fact, to detect a 2% benefit, a randomized clinical trial would require > 9,000 patients. The ASCO panel also acknowledged the subset of high-risk patients, and identified this group to include patients with inadequate lymph node sampling, T4 lesions, perforation/obstruction at the time of presentation, and poorly differentiated histology. In the case of high-risk stage II colon cancer, the recommendation was to offer adjuvant chemotherapy, as these individuals are at increased risk for disease recurrence.

As an additional guide for physicians to determine the risk for disease recurrence and the potential benefit from adjuvant chemotherapy for patients with stage II disease, evidence-based calculators are available on the Internet. The two models that have been most widely used can be found at www.mayoclinic.com/calcs or at www.adjuvantonline.com.

Role of Molecular Markers in Adjuvant Therapy of Stage II Colon Cancer

At this time, there are insufficient data to support the use of molecular biomarkers as part of the evaluation process in everyday clinical practice for patients with early-stage colon cancer (Table 5). The most promising markers that have been developed thus far include loss of heterozygosity (LOH) on chromosome 18q21 (DCC) and microsatellite instability (MSI). LOH of 18q occurs in approximately 70% of colon cancer and is associated with loss of the DCC gene, which has been shown to play a causal role in the development of CRC. Several trials have demonstrated that LOH of 18q is associated with worse prognosis.[38] MSI has been identified as a biomarker identifying good prognosis and chemosensitivity in stage III colon cancer. MSI arises from mutations and/or functional defects in mismatch repair enzymes, which is the abnormality typically observed in the HNPCC phenotype. The presence of MSI highlights the increased risk of genetic mutations and a higher risk for developing colon cancer.[39] Interestingly, the presence of MSI appears to confer a better prognosis in patients with early-stage colon cancer. Loss
of heterozygosity of 18q and MSI both predict prognosis. It is conceivable that MSI may predict for response to chemotherapy, and this molecular biomarker needs to be evaluated in future clinical trials. One such study is ECOG 5202, a randomized phase III trial in which stage II patients are stratified as low or high risk depending on the presence of a deletion in chromosome 18q and the presence of MSI or MSS. If the tumor is determined to be MSI or 18q normal, no adjuvant therapy will be administered, and patients will be simply observed. However, should the tumor be MSS and have a deletion in chromosome 18q, patients will then be randomized to receive FOLFOX plus or minus bevacizumab.

In addition to investigating individual molecular biomarkers to predict disease recurrence, especially in stage II colon cancer, significant efforts have been placed recently on developing gene expression profiling strategies. In particular, DNA microarray-based gene expression profiling technology offers a systematic combinatorial approach to identify new prognostic biomarkers. Two such studies have already been performed and have identified a 23- and 30-gene signature profile that may identify patients at high risk of disease relapse, who might then be appropriate candidates for more aggressive adjuvant therapy.[40,41] Further studies are needed to validate these gene expression profiles as true prognostic biomarkers independent from pathologic staging and other clinical parameters.

Endpoints of Efficacy of Adjuvant Therapy in CRC

Disease-free survival has been increasingly used as a surrogate endpoint for OS in the most recent series of randomized clinical trials for adjuvant therapy.[19,23,28] The
main reason for why OS is no longer viewed as an appropriate endpoint in trial design is that there are now a wide range of effective treatment options for first-, second-, and third-line therapy, which would then obscure the effect of the primary treatment. Moreover, using OS as the primary endpoint would require many years of follow-up, which would delay the introduction of more active agents and treatment regimens into routine clinical practice.

Sargent et al pooled data from 20,898 patients who were enrolled onto 18 randomized phase III colon cancer adjuvant clinical trials.[42] The primary hypothesis was that DFS, with 3 years of follow-up, is an appropriate primary endpoint to replace 5-year OS. Eighty percent of disease recurrences occur within the first 3 years; 91% of patients with recurrence by 3 years died before 5 years. The correlation between 3-year DFS and 5-year OS was 0.89 (Figure 1). These results suggest that DFS and OS are highly correlated in
patients treated on phase III adjuvant colon clinical trials, and that DFS after 3 years of median follow-up is an appropriate end point for adjuvant colon cancer clinical trials. Of note, Sargent and colleagues have recently suggested that 2-year DFS may be a reasonable endpoint in adjuvant therapy studies, although this potential surrogate endpoint needs to be further validated. The 3-year DFS has gone from 61% to 65% with fluoropyrimidine monotherapy to 72% with the most active oxaliplatin-based chemotherapy, whether it be the FOLFOX or FLOX combination regimens.

**Surveillance for Patients After Completion of Adjuvant Therapy**

The optimal posttreatment surveillance of patients who have undergone surgical resection and adjuvant therapy is another issue of much debate. A recent meta-analysis suggests some benefit with more aggressive screening. However, no information is provided as to which aspect of the intensive surveillance is most beneficial. For successfully treated patients with no known residual disease, the general recommendation is to perform a history and physical examination every 3 months for the first 2 years and then every 6 months for a total of 5 years. For ≥ T2 lesions, a CEA test is recommended at baseline and every 3 months for 2 years, then every 6 months for the next 2 to 5 years if the clinician determines that the patient is a potential candidate for aggressive curative surgery. Colonoscopy is indicated within 1 year of resection (or 3 to 6 months if not performed preoperatively due to obstruction) and is repeated annually if neoplastic polyps are noted. If the colon is free of polyps, colonoscopic surveillance should then be performed at least every 2 to 3 years. Chest, abdomen, and pelvic CT scans may be performed on an annual basis for 3 years for patients with high-risk stage II/III disease. Although there is great interest in using position-emission tomography (PET) scan, this diagnostic imaging modality is not routinely recommended.

**Managing an Increasing Carcinoembryonic Antigen Level**

There are no clear recommendations as to the proper evaluation of a patient with an increasing CEA level following curative resection and/or adjuvant therapy. NCCN guidelines recommend a careful history and physical examination and surveillance colonoscopy, chest, abdomen, and pelvic CT scans. If imaging study results are normal in the face of an increasing CEA, CT scans should then be repeated every 3 months if symptoms occur. PET scan may be useful in this situation, particularly to identify the presence of isolated metastases. These guidelines do not recommend a so-called “blind abdominal exploration” for patients whose workup for an increased CEA level is negative. In the case of local recurrence or resectable organ-confined metastasis such as in the case of liver- and/or lung-limited disease, curative surgery may be possible.
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Recurrence or Disease Progression After Adjuvant FOLFOX

Since oxaliplatin-based regimens are now the most commonly used adjuvant chemotherapy, an important issue pertains to the choice of first-line regimen for recurrent and/or metastatic disease after FOLFOX adjuvant therapy. If a patient does not have any residual neuropathy and there has been > 12 months of disease-free interval after adjuvant FOLFOX therapy, FOLFOX can be used in combination with the anti-VEGF antibody bevacizumab. If disease recurrence occurs within 12 months of having completed adjuvant chemotherapy, it is quite reasonable to consider an irinotecan-based chemotherapy regimen to be combined with bevacizumab. There is now a growing body of evidence to suggest that the anti-EGFR antibody may be effectively and safely used in combination with FOLFOX and/or FOLFIRI regimens in the first-line treatment of advanced CRC.

Conclusions

Oxaliplatin-based chemotherapy is now the standard of care as adjuvant chemotherapy for stage III colon cancer and for those with high-risk stage II disease. Based on the clinical studies conducted to date, irinotecan can not be recommended for use in the adjuvant setting. The oral fluoropyrimidine capecitabine has demonstrated equivalent efficacy to bolus 5-FU/LV as adjuvant treatment, and is a standard of care when fluoropyrimidine therapy is being considered. Currently, phase III randomized studies are ongoing to determine the role of capecitabine in combination with oxaliplatin and the biologic agents bevacizumab and cetuximab in the adjuvant setting. Disease-free survival has been increasingly used as a surrogate efficacy endpoint and its definition will require international agreement to interpret results from randomized clinical trials appropriately.

For stage II colon cancer, adjuvant therapy remains an area of ongoing discussion. In medically fit patients, chemotherapy with FOLFOX can be offered, especially in those with high risk characteristics such as intestinal perforation, T4 tumors, poorly differentiated tumors, inadequately pathologically examined (< 12) lymph node and extramural venous or lymphatic invasion. For average risk patients, a discussion of the small benefit of chemotherapy should be made, and the patient must play an active role in the decision-making process.

Six months of adjuvant treatment is the current standard duration, and treatment should generally start within 6 to 8 weeks after surgery. With the advent of the biologic targeted therapies in metastatic CRC, the next wave of adjuvant therapy trials is focusing on integrating these new targeted agents with cytotoxic chemotherapy regimens. However, aside from assessing the additional benefit of these novel agents to standard cytotoxic chemotherapy regimens, it will be important to address the optimal duration of these
agents, the short- and long-term consequences of these agents on patient quality of life, and the pharmacoeconomic costs associated with these treatments.

References
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28. Martenson JA, Jr, Willett CG, Sargent DJ, et al: Phase III study of adjuvant chemotherapy and


Adjuvant Chemotherapy of Colon Cancer


Colorectal cancer (CRC), the third leading cancer and the second leading cause of cancer-related mortality in the United States, accounts for nearly 150,000 new cancer cases and 60,000 deaths each year.[1] Despite curative surgery in patients with early-stage disease, the risk of recurrence after definitive local treatment and adjuvant chemotherapy remains high, especially within the first 3 years after initial diagnosis and treatment. Over the past 15 years, significant advances have been made in the adjuvant chemotherapy of colon cancer. In particular, the major breakthroughs have been with the development of infusional fluorouracil (5-FU) regimens, the development of the oral fluoropyrimidine capecitabine (Xeloda), and the introduction of oxaliplatin (Eloxatin)-based regimens.[2] Despite the clinical benefit of these cytotoxic agents and regimens, disease recurrence continues to be a major problem. It is clear that new therapeutic agents are necessary to effect further gains in long-term disease-free survival.

Since 2004, three new biologic agents have been approved for use in the management of metastatic colorectal cancer (mCRC). The activity of these agents in advanced disease provides a rationale for their incorporation into standard cytotoxic chemotherapy regimens in the adjuvant setting. The design of biologic agents to specifically target and disrupt aberrant molecular pathways in cancer cells is central for targeted-therapy approaches in combating cancer. When compared with traditional cytotoxic agents, these targeted biologics have distinct mechanisms of action, and thus are attractive in their potential to provide additive and/or synergistic efficacy to standard chemotherapy regimens.

Therapeutic monoclonal antibodies represent one of the most rapidly growing classes of targeted biologic agents in cancer treatment, and they are poised to make a major impact in the treatment of CRC as well as a broad range of other cancers. Several key signaling pathways have been implicated in the development and progression of CRC, and many are physiologically available for targeting with monoclonal antibodies. These novel targets include several growth factors, receptors, and tumor-specific/tumor-selective
Bovic agents. In particular, cetuximab (Erbitux) and panitumumab (Vectibix), which target the epidermal growth factor receptor (EGFR), and bevacizumab (Avastin), which targets the vascular endothelial growth factor (VEGF), have provided significant advances in the treatment of mCRC. These therapeutic monoclonal antibodies are typically administered in combination with cytotoxic chemotherapy regimens, for which enhanced clinical efficacy has already been well-documented in mCRC.

Bevacizumab

Bevacizumab is a humanized IgG1 murine antibody directed against all isoforms of VEGF-A.[3] To date, it is the most clinically advanced monoclonal antibody targeting the VEGF signaling pathway. Bevacizumab has been extensively studied in patients with mCRC in combination with 5-FU/leucovorin, irinotecan-based, and oxaliplatin-based chemotherapy, and has been shown to provide significant clinical benefit with respect to tumor response, progression-free survival (PFS), and overall survival (OS). Given its significant clinical activity, bevacizumab was approved by the US Food and Drug Administration (FDA) in 2004 for the first-line treatment of mCRC in combination with any intravenous fluoropyrimidine-containing regimen.

In the Eastern Cooperative Oncology Group (ECOG) E3200 study, bevacizumab was combined with FOLFOX4 (5-FU, leucovorin, oxaliplatin) chemotherapy in the second-line setting. A total of 829 patients with advanced CRC, previously treated with 5-FU–based therapy and irinotecan (Camptosar) for advanced disease or relapsed disease following adjuvant chemotherapy, were randomized to one of three treatment arms: FOLFOX4, FOLFOX4 plus bevacizumab, or bevacizumab alone.[4] The bevacizumab-alone arm was closed to accrual in 2003, when a predetermined analysis found that this arm showed significantly reduced clinical efficacy in comparison to the other two arms. With respect to toxicity, the addition of bevacizumab to FOLFOX4 did not increase the side effects typically associated with oxaliplatin.

Patients receiving bevacizumab in combination with FOLFOX4 had a significant improvement in response rate (RR, 9% vs 22%, \( P < .0001 \)) and median overall survival (OS, 12.5 vs 10.7 months, \( P < .0024 \)) when compared to patients treated with FOLFOX4 alone. This effect translated into an absolute 17% improvement in OS and a 26% relative risk reduction in death in the patients receiving the combination of bevacizumab plus FOLFOX4 compared with those receiving FOLFOX4 alone. This study was the first phase III study to demonstrate the ability of bevacizumab to enhance the efficacy of an oxaliplatin-based regimen.

The TREE 1 and TREE 2 studies evaluated the safety and efficacy of three different oxaliplatin-based combinations with or without bevacizumab in patients with previously
untreated mCRC (Figure 1).[5] In the TREE 1 study, modified FOLFOX (mFOLFOX \( n = 49 \)), bFOL (bolus 5-FU/oxaliplatin \( n = 50 \)), and CapOx (capecitabine/oxaliplatin \( n = 48 \)) were found to be similar in clinical activity, although the bFOL arm was inferior to the other regimens with respect to RR and time to progression (TTP). In general, mFOLFOX and bFOL were well tolerated, while treatment with CapOx was associated with increased gastrointestinal toxicity.

This study was subsequently amended to include the same three arms of the study in combination with the anti-VEGF antibody bevacizumab. Moreover, given the increased toxicities observed with the CapOx arm, the dose of capecitabine was subsequently reduced from 1,000 to 850 mg/m². In TREE 2, the addition of bevacizumab to each of the three arms—mFOLFOX \( n = 71 \), bFOL \( n = 70 \), and CapOx \( n = 72 \)—significantly improved confirmed RR \( (P = .011, \text{ pooled logical aggregation analysis}) \).[7] The median TTP and OS for patients treated with mFOLFOX plus bevacizumab were 9.9 and 26 months, respectively, nearly identical to the findings observed with the combination of CapOx plus bevacizumab (TTP 10.3 months; OS 27 months). When analyzed together, the median OS was significantly higher in the TREE 2 study when compared to TREE 1 (24.4 vs 18.2 months). The addition of bevacizumab to each of the three oxaliplatin-based regimens was well tolerated, and bevacizumab did not worsen the side effects normally associated with
any of the oxaliplatin-based therapies. Thus, the TREE 2 trial is important as it represents the first clinical study to document the clinical efficacy and safety profile of bevacizumab in combination with oxaliplatin-based chemotherapy in the first-line setting.

The NO16966 protocol is an international randomized phase III study evaluating the safety and efficacy of oxaliplatin-based combination chemotherapy with or without bevacizumab in patients with previously untreated mCRC.[6] The trial was initially opened in 2003 with the main objective to compare the clinical efficacy and safety profile of two oxaliplatin-based regimens: one using intravenous 5-FU/LV as the fluoropyrimidine backbone and the other using oral capecitabine as the fluoropyrimidine backbone. The two arms of this study included FOLFOX4 as the control arm and capecitabine/oxaliplatin (XELOX) as the experimental arm. As the study was ongoing, and it was clear that bevacizumab was to be approved in the United States for front-line therapy, the trial was amended to a 2 × 2 placebo-controlled design: FOLFOX4 with or without bevacizumab vs XELOX with or without bevacizumab.

In patients treated on the XELOX arm with (n = 350) or without (n = 350) bevacizumab, the addition of bevacizumab significantly increased PFS by nearly 2 months (7.4 vs 9.3 months, *P* = .0026). The side-effect profiles were similar to those previously reported with bevacizumab, and no safety signals were identified. This is the first randomized trial documenting the efficacy of bevacizumab when combined with oxaliplatin-based chemotherapy in the first-line setting.
Despite its significant clinical activity, bevacizumab therapy is associated with a number of safety signals. The incidence of gastrointestinal perforation in patients with mCRC receiving bevacizumab was 2.4% in comparison to 0.3% in patients with chemotherapy alone.\[8,9\] In some cases, this complication was fatal. An increased incidence of postoperative wound-healing complications has also been observed in patients with mCRC requiring surgery within 60 days of bevacizumab treatment. Bleeding events, most commonly in the form of epistaxis, have also been reported. The most common side effects are hypertension and the development of arterial thromboembolic events such as heart attack, stroke, transient ischemic attack, or unstable angina. These particular toxicities could become a significant issue when this agent is used for a prolonged time in the adjuvant setting. Because patients in the adjuvant setting are potentially curable, significantly greater attention must be placed on the short- and long-term consequences related to adjuvant therapy. For this reason, the risk-to-benefit ratio and the impact on overall quality of life of a particular treatment agent and/or regimen must be carefully evaluated.

There is now a growing body of evidence to support the concept that bevacizumab can be safely and effectively combined with 5-FU, capecitabine, irinotecan, and oxaliplatin chemotherapy in the advanced disease setting. These clinical data then provide the rationale for incorporating bevacizumab into standard chemotherapy regimens that are approved for adjuvant therapy. There are currently several ongoing phase III clinical trials that are investigating the role of bevacizumab in the adjuvant setting; these studies include AVANT (BO17920), NSABP C08, and QUASAR-2.

The AVANT Trial (BO17920)

AVANT is a phase III randomized trial that evaluates the role of bevacizumab in combination with oxaliplatin-based chemotherapy in patients with stage II or III colon cancer (Figure 2). Patients are randomized to one of three arms: FOLFOX4 alone vs FOLFOX4 plus bevacizumab vs XELOX plus bevacizumab. Patients treated on the FOLFOX4/bevacizumab arm receive bevacizumab 5 mg/kg every 2 weeks for 12 cycles, while those on the XELOX/bevacizumab arm receive bevacizumab 7.5 mg/kg every 3 weeks for 8 cycles. Patients randomized to the FOLFOX4/bevacizumab or XELOX/bevacizumab arms receive bevacizumab alone for an additional 24 weeks following completion of chemotherapy. Patients on the FOLFOX4 alone arm will not receive any bevacizumab during this same time period. The primary endpoint of this trial is disease-free survival, while the secondary endpoints are safety and overall survival. The target accrual goal for this study is 3,450 patients.

In February 2006, patient recruitment was temporarily halted following an interim safety analysis that identified a potentially higher rate of sudden death due to cardio-
vascular events on the XELOX/bevacizumab arm. After a more in-depth analysis of the data, the all-cause mortality, excluding deaths due to recurrent colon cancer, was 0.8% (six cases) in the FOLFOX4 alone arm, 0.5% (four cases) in the FOLFOX4/bevacizumab arm, and 1.05% (eight cases) in the XELOX/bevacizumab arm. This analysis concluded that these all-cause mortality rates are consistent with those previously reported in other adjuvant studies in colon cancer, and as such, recruitment was subsequently resumed in May 2006. Enrollment onto this trial continues, and more than two-thirds of the trial’s target enrollment of 3,450 patients has been accrued.

The NSABP C08 Trial

The National Surgical Adjuvant Breast and Bowel Project (NSABP) C08 protocol is a randomized phase III trial, the main goal of which is to determine the role of bevacizumab in combination with oxaliplatin-based chemotherapy in patients with stage II or III colon cancer (Figure 3). Patients with stage II or III colon cancer were randomized to either mFOLFOX6 (oxaliplatin 85 mg/m² IV on day 1, leucovorin 400 mg/m² on day 1, 5-FU 400 mg/m² IV bolus on day 1, and 5-FU 2,400 mg/m² IV continuous infusion over 46 hours on days 1–2) alone for 12 cycles or mFOLFOX6 in combination with bevacizumab for 12 cycles followed by bevacizumab monotherapy for an additional 6 months. Patients on the mFOLFOX6/bevacizumab arm received bevacizumab 5 mg/kg IV every 2 weeks in addition to mFOLFOX6. Patients were stratified by number of positive lymph nodes (0 vs 1–3 vs > 3). The primary endpoint of this trial is disease-free survival, and the secondary
endpoint is overall survival. Enrollment onto this study has been completed (N = 2,600), and clinical efficacy data are expected within the next 3 years.

The QUASAR-2 Trial

The QUASAR-2 protocol is a phase III trial to evaluate the role of bevacizumab in combination with capecitabine in patients with stage II/III colon cancer (Figure 4). When originally designed and opened to accrual in April 2005, this study planned to test the clinical efficacy of irinotecan-based chemotherapy in the adjuvant setting. However, given the disappointing results of the PETACC-3 and ACCORD-2 adjuvant studies, which showed no clinical benefit with irinotecan as adjuvant therapy, this trial was suspended.[10,11] At about this same time, the X-ACT trial highlighted the clinical efficacy of capecitabine monotherapy in adjuvant treatment of stage III colon cancer.[12] As such, the QUASAR-2 trial was then redesigned as a two-arm trial with capecitabine with or without bevacizumab.

This study was reopened to accrual in September 2005, and eligible patients for this trial include stage III colon cancer and stage II colon cancer with high-risk features, as defined by T4 primary tumor, lymphatic invasion, vascular invasion, peritoneal involvement, or poor differentiation. Patients are randomized to capecitabine alone or capecitabine plus bevacizumab. The capecitabine dose is 1,250 mg/m² twice a day on days 1–14 every 3 weeks for 8 cycles (24 weeks), and the dose of bevacizumab is 7.5 mg/kg administered on day 1 every 3 weeks for 8 cycles (24 weeks), followed by bevacizumab monotherapy.

7.5 mg/kg every 3 weeks for an additional 8 cycles (24 weeks). The primary endpoint of this trial is disease-free survival, with the secondary endpoints being safety profile and overall survival. The target accrual for this study is 3,500 patients.

This clinical trial, as well as the NSABP C-08 and AVANT trials, incorporates treatment with bevacizumab monotherapy for an additional 24 weeks once the standard 6 months of standard cytotoxic chemotherapy with or without bevacizumab has been completed. The rational basis for this additional 6-month treatment remains unclear, and this approach raises concerns as to whether this may exacerbate the known safety signals commonly seen with bevacizumab as well as identify new ones.

The E5202 Trial

Approximately 20% to 25% of patients with stage II colon cancer will present with recurrent disease after definitive surgical resection; these patients would benefit from
adjuvant chemotherapy. However, one of the remaining challenges is to identify which stage II patients would derive real benefit from adjuvant chemotherapy.

Watanabe et al analyzed tumor tissues from 460 patients with stage III and high-risk stage II colon cancer who received adjuvant chemotherapy with a fluorouracil-based regimen in the ECOG trial, and reported that both loss of heterozygosity at chromosome 18q (18q LOH) and the level of microsatellite instability (MSI) are related with 5-year survival after adjuvant chemotherapy. Loss of heterozygosity at 18q was present in 49% of cancers, and MSI-H was present in 21% of cancers. The 5-year OS for patients with microsatellite-stable stage III colon cancer after fluorouracil-based adjuvant chemotherapy was 74% in those with retained 18q alleles and 50% in those with 18q LOH (relative risk of death with 18q LOH is 2.75, \( P = .006 \)).

Based on these prior translational studies, the goal of E5202 trial is to use molecular biomarkers to stratify patients with stage II disease into low and high risk, which would then determine subsequent treatment decisions (Figure 5). Patients at high risk for disease recurrence are identified based on their molecular profiles; this study is evaluating the feasibility of genetic profiling using the DCC gene and the MSI gene. The DCC gene is also known as 18q LOH. The criterion for the low-risk group is MSS or MSI-L with retention of 18q alleles or MSI-H, and that for the high-risk group is MSS with 18q LOH or MSI-L with 18q LOH. Patients in the high-risk group are randomized to either FOLFOX6 (oxaliplatin 85 mg/m\(^2\) IV on day 1, 5-FU 400 mg/m\(^2\) on day 1, leucovorin 400 mg/m\(^2\) on day 1, and 5-FU 2,400 mg/m\(^2\) IV infusion over 46 hours on days 1–2, repeated every 2 weeks) alone for 12 cycles or FOLFOX6 plus bevacizumab (5 mg/kg on day 1, repeated every 2 weeks) for 12 cycles followed by bevacizumab monotherapy for additional 6 months. Patients with low-risk features will be assigned to observation alone. This trial is actively enrolling patients, and the accrual goal for this study is 3,610.

Cetuximab

Cetuximab is an IgG1 chimeric monoclonal antibody that binds with high affinity to EGFR. This molecule competitively inhibits binding of the natural ligands to EGFR, thereby blocking receptor phosphorylation and downstream growth signaling, inducing receptor internalization, and reducing the level of EGFR expression on the cell surface. Cetuximab has been shown to exert antitumor effects through inhibition of cell proliferation by inducing cell-cycle arrest and apoptosis, inhibiting tumor angiogenesis, and possibly activating immune-mediated mechanisms such as antibody-dependent cellular cytotoxicity and/or complement-dependent cellular cytotoxicity.

The role of cetuximab in first-line combination therapy for mCRC is currently undergoing intense investigation. A large multicenter phase II study was conducted in
Europe (ACROBAT) to evaluate the efficacy of cetuximab combined with FOLFOX4 in the first-line setting.[22] An overall RR of 74% and a TTP of 12.3 months were reported in the initial 42 patients available for analysis.[22] The regimen was well tolerated, and the impressive results of this pilot study provide strong rationale for further clinical investigation.

The CRYSTAL study is a randomized phase III trial to evaluate the efficacy of cetuximab in combination with FOLFIRI (5-FU, leucovorin, irinotecan) in previously untreated patients with mCRC. Patients (N = 1,217) were randomized to receive cetuximab plus FOLFIRI or FOLFIRI alone. The combination of cetuximab plus FOLFIRI was associated with a significantly higher median PFS of 8.9 vs 8.0 months with FOLFIRI treatment (hazard ratio = 0.85; log-rank P value = .0479), and the 1-year PFS rate was in favor of the combination arm (34% vs 23%). Of note, there was a correlation between the median PFS and grade of skin toxicity observed such that patients with grade 0/1 skin toxicity had a PFS of 5.4 months, grade 2 skin toxicity had a PFS of 9.4 months, and grade 3 skin toxicity had a PFS of 11.3 months, respectively. Moreover, the addition of cetuximab to FOLFIRI significantly improved the overall response rate (38.7% vs 46.9%, P = .0038).

The combination treatment was well tolerated. Neutropenia, diarrhea, and skin rash were the most common grade 3/4 toxicities in the combination arm. The incidence of grade 3/4 neutropenia (23.3% vs 26.7%) and diarrhea (10.5% vs 15.2%) was similar.
in both arms. As expected, severe skin rash was more frequent in the combination arm (0.2% vs 18.7%). This is the first randomized phase III trial documenting the efficacy of cetuximab when combined with FOLFIRI in the first-line setting.\cite{23}

The Cancer and Leukemia Group B (CALGB) 80203 protocol is a randomized phase III study that provides further evidence that cetuximab can significantly improve overall response rates when added to first-line chemotherapy (FOLFOX or FOLFIRI) regimens (52% RR with cetuximab vs 38% RR without cetuximab, \(P = .029\)).\cite{24} At the time of the ASCO 2006 meeting, the median follow-up was relatively short, and additional time is needed for the clinical data on TTP and OS to properly mature. In follow-up to this study, CALGB 80405 is an important phase III study in the first-line treatment of metastatic CRC, in which physicians can select either FOLFOX or FOLFIRI as the cytotoxic chemotherapy regimen to be then combined with cetuximab, bevacizumab, or the combination of cetuximab plus bevacizumab. The goal for this study is to accrue 2,289 patients, and enrollment onto this study is presently ongoing.\cite{24}

**Panitumumab**

Panitumumab is a fully human IgG2 antibody that binds with high affinity to EGFR and inhibits EGFR downstream signaling. Preclinical studies have documented its activity as a single agent and in combination with chemotherapy in the treatment of colorectal cancer.

The pivotal phase III trial compared panitumumab with best supportive care in 463 patients with mCRC for whom standard chemotherapy had failed. In this trial, the dosing schedule of panitumumab was 6 mg/kg given on an every-2-week schedule. This trial showed that panitumumab significantly increased PFS compared with best supportive care (BSC) alone (hazard ratio = 0.54; \(P < .000000001\)).\cite{25} The overall RR was 8% for patients treated on the panitumumab arm. The time to response was 8 weeks, while the duration of response was 17 weeks. Panitumumab therapy did not result in improvement in overall survival. Based on the positive findings from this study, panitumumab was approved by the FDA at the end of September 2006 in the disease refractory setting after treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

The use of panitumumab in combination with cytotoxic chemotherapy is being further investigated as first-line therapy in mCRC in the Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial. In this randomized phase III trial, patients were randomized to receive either FOLFOX or FOLFIRI as their cytotoxic chemotherapy regimen and then randomized to receive either bevacizumab or the combination of bevacizumab plus panitumumab. The primary endpoint of this study is PFS. In January 2007, a planned interim study analysis revealed an increased incidence of grade 3 diarrhea, dehydration,
and infections in the panitumumab-treated patients. At the time of a preplanned interim efficacy analysis in March 2007, significant differences in PFS and OS were observed in favor of the control arm, which then led to the discontinuation of panitumumab treatment in this trial. Further details of this clinical trial are expected in mid-to late 2007.

**Anti-EGFR Antibodies in the Adjuvant Setting: Future Directions**

**The PETACC-8 Study**

The PETACC-8 protocol is a randomized, multinational/multicenter European phase III study to evaluate the efficacy of cetuximab in combination with FOLFOX4 in the adjuvant treatment of patients with stage III colon cancer (Figure 6). Patients are randomized to cetuximab (400 mg/m² loading dose followed by 250 mg/m² weekly) plus FOLFOX4 or FOLFOX4 alone. Patients receive treatment every 2 weeks for a total of 12 cycles (24 weeks). The primary endpoint of this trial is recurrence-free survival at 3 years. The secondary endpoints are overall survival, treatment compliance, safety, and biologic study for evaluation of markers predictive for relapse and/or treatment efficacy. Randomization will be stratified by no obstruction and no perforation vs obstruction and/or perforation, T1–3 vs T4, N1 vs N2. The accrual goal for this study is 2,000 patients.
The Intergroup N0147 Trial

The Intergroup N0147 trial is a multicenter phase III trial that evaluates the efficacy of cetuximab in combination with mFOLFOX6 in the adjuvant treatment of patients with stage III colon cancer (Figure 7). This study was originally designed to include irinotecan-based chemotherapy. However, based on the negative results of the PETACC-3 and ACCORD-2 trials, the irinotecan-containing arms were closed in June 2005. In the revised trial design, patients are randomized to either 12 cycles of mFOLFOX6 (oxaliplatin 85 mg/m² IV on day 1, leucovorin 400 mg/m² IV on day 1, and 5-FU 400 mg/m² bolus followed by 2,400 mg/m² continuous IV infusion over 46 hours beginning on day 1, every 2 weeks) or mFOLFOX6 plus cetuximab (400 mg/m² loading dose, followed by 250 mg/m² weekly). The primary endpoint of this trial is recurrence-free survival at 3 years, and the accrual goal is 2,400 patients.

Conclusion

Significant advances have been made in the management of mCRC with the targeted, biologic agents bevacizumab, cetuximab, and panitumumab. Their efficacy in the advanced disease setting provides rationale for using them in adjuvant setting in combination with the active cytotoxic chemotherapy for stage II and III colon cancer. At present, there are several adjuvant phase III trials using bevacizumab and/or cetuximab in combination with oxaliplatin-based chemotherapy to evaluate the role of these respective biologic agents in the adjuvant treatment of colon cancer. While the results from these clinical trials are not expected for at least another 3 years, it is clear that positive results from any of these trials may well translate into a paradigm shift in what is considered as standard of care for adjuvant therapy.

While significant focus has been placed on identifying more active adjuvant treatment regimens, great efforts continue to be placed on developing molecular biomarkers which may help predict clinical response and/or identify patients at increased risk for developing drug-specific toxicities. To date, no such biomarkers currently exist. However, in the adjuvant setting, identification of these key biomarkers may be more critical for the use and development of these novel biologic agents to avoid their potential short- and long-term side effects.

References


Chapter 8: Combined-Modality Chemoradiotherapy Approaches for Locally Advanced Rectal Cancer

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The management of locally advanced rectal cancer continues to be the focus of much attention. Since the early 1990s, postoperative adjuvant chemoradiotherapy has been widely used to treat patients with stage II and III rectal cancer. However, over the past few years, significant efforts have shifted toward developing neoadjuvant approaches that combine chemotherapy with radiotherapy prior to surgical resection. Based on the pivotal randomized study performed in Germany comparing neoadjuvant with postoperative adjuvant chemoradiotherapy, the neoadjuvant chemoradiotherapy approach has now become the standard of care in the United States for patients with locally advanced rectal cancer.

This chapter reviews the development and evolution of the key clinical trials that have been conducted over the past 20 years, as well as provides an overview of the newer cytotoxic chemotherapy and biologic agents that are being incorporated into the various chemoradiotherapy regimens.

Adjuvant Chemoradiation

The role of chemotherapy with concurrent radiation in the management of locally advanced rectal cancer was initially evaluated in the adjuvant setting. Several randomized phase III trials have shown that chemotherapy, when administered with concurrent radiation therapy after curative resection of locally advanced rectal cancer, decreases locoregional recurrence and improves survival.

The Gastrointestinal Study Group 7175 trial was a pivotal study showing that adjuvant concurrent chemoradiation improves both local control and overall survival for patients with locally advanced rectal cancer, when compared with surgery alone or radiotherapy alone. [1] After curative surgical resection of rectal cancer, patients (N = 202) were randomized to one of four treatment arms: (1) no postoperative therapy, (2) postoperative radiotherapy alone, (3) postoperative chemotherapy alone with fluorouracil (5-FU) and
methyl-CCNU, and (4) concurrent chemoradiation with 5-FU and methyl-CCNU.

With a median follow-up of 80 months, the recurrence rate was low in patients treated with concurrent chemoradiation (33%) when compared to those who did not receive postoperative therapy (55%). Time to tumor recurrence was also significantly prolonged in the concurrent chemoradiation arm when compared to the no postoperative therapy arm ($P < .009$). Overall survival (OS) did not differ significantly among the treatment groups. This study supported the incorporation of adjuvant chemoradiation as the standard of care for patients with locally advanced rectal cancer (Dukes stage B2 and C).

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial, the potential role of adjuvant therapy in the management of Dukes B and C rectal cancer after curative surgical resection was investigated. After surgical resection of the primary rectal cancer, patients were randomized to one of three arms: (1) no further treatment ($n = 184$), (2) adjuvant MOF (5-FU/methyl-CCNU/vincristine [Oncovin]) chemotherapy ($n = 187$), or (3) adjuvant radiation therapy alone ($n = 184$). Patients treated with adjuvant chemotherapy experienced a significant increase in disease-free survival (DFS) ($P = .006$) and OS ($P = .05$) when compared to surgery alone. Patients treated with adjuvant radiation therapy experienced an overall reduction in locoregional recurrence in comparison to surgery alone (25% vs 16%, $P = .6$). However, no significant difference in DFS and OS was observed between the radiation therapy and surgery alone arms.

The North Central Cancer Treatment Group 79-47-51 trial evaluated the role of adjuvant chemoradiation in the management of high-risk rectal cancer by comparing concurrent chemoradiation with radiation alone in the adjuvant setting. A total of 2,004 patients were randomized to either adjuvant radiation alone or adjuvant radiation with concurrent 5-FU/methyl-CCNU combination chemotherapy. With a median follow-up of 7 years, patients on the concurrent chemoradiation arm experienced a significant reduction in disease recurrence by 34% ($P = .0016$), cancer-related deaths by 36% ($P = .0071$), and overall deaths by 29% ($P = .025$). This trial is important as it clearly demonstrated that the combined modality of concurrent chemoradiation was superior to radiation alone in the adjuvant therapy of rectal cancer with significant survival benefit.

The NSABP protocol R-02 evaluated the role of radiation in addition to chemotherapy in the adjuvant setting. In this phase III randomized trial, 741 patients with Dukes B and C rectal cancer were randomized to either adjuvant chemotherapy alone or adjuvant chemoradiation. Patients were stratified according to sex, number of positive lymph nodes, age, and institution. Male patients were randomized to one of four treatment arms: (1) 5-FU/leucovorin (LV) weekly for 6 weeks followed by a 2-week rest period given on an every-8-week cycle, (2) infusional 5-FU/LV plus radiotherapy, (3) MOF (methyl-CCNU, vincristine [Oncovin], and 5-FU: 325 mg/m²) on a 10-week cycle, or (4) MOF plus radio-
therapy given on a 10-week cycle. Female patients were randomized to 5-FU/LV alone or 5-FU/LV plus radiotherapy.

Patients treated with chemoradiation experienced a significant reduction in the cumulative incidence of locoregional relapse from 13% to 8% at 5-year follow-up ($P = .02$). With respect to the role of systemic chemotherapy, no differences in 5-year OS were observed between the MOF and 5-FU/LV chemotherapy arms in male patients (62% vs 65%, $P = .17$). This study suggests that radiation therapy, when combined with chemotherapy in the adjuvant setting, plays an important role in reducing the incidence of locoregional recurrence.

5-FU–based chemotherapy has been the foundation of chemotherapy regimens in the adjuvant therapy of rectal cancer. In the early trials, 5-FU was administered via bolus schedules of administration. However, significant interest was directed toward developing infusional schedules of 5-FU, based on preclinical observations that infusional 5-FU therapy was able to prolong the exposure of noncycling tumor cells to 5-FU, thereby enhancing antitumor activity and reducing overall toxicity.

O'Connell et al investigated the role of protracted venous infusion (PVI) 5-FU in combination with radiation in adjuvant therapy rectal cancer in 660 patients who had undergone potentially curative resection for stage II or III rectal cancer.[5] Patients were randomized to one of four arms: (1) bolus 5-FU (350 mg/m² on days 1–5, 400 mg/m² on days 36–40, 300 mg/m² on days 134–138, and 350 mg/m² on days 169–173) with methyl-CCNU (130 mg/m² on day 1 and 100 mg/m² on day 134) plus radiation therapy with concurrent bolus 5-FU, (2) 5-FU/methyl-CCNU plus radiation therapy with concurrent PVI 5-FU (225 mg/m²/d for the entire radiation period), (3) 5-FU (500 mg/m² on days 1–5 and days 36–40, 450 mg/m² on days 134–138 and days 169–173) plus radiation therapy with concurrent bolus 5-FU, and (4) bolus 5-FU plus radiation therapy with concurrent PVI 5-FU.

Patients who received PVI 5-FU experienced a significant decrease in the overall rate of tumor relapse (47% vs 37%) and distant metastasis (40% vs 31%) when compared to patients treated with bolus 5-FU/LV combined with radiation therapy. In the cohort of patients who did not receive methyl-CCNU but received PVI 5-FU, there was a significant decrease in the overall rate of tumor relapse and distant metastasis. Although administration of PVI 5-FU was not associated with a significant decrease in local recurrence, a significant improvement in time to relapse and survival was observed when compared to bolus 5-FU treatment; their tumor relapse and death rates were decreased by 27% and 31%, respectively.

In terms of safety profile, the incidence of severe diarrhea was significantly higher among patients who received PVI 5-FU, while severe neutropenia was significantly higher
among those who received the bolus 5-FU. PVI 5-FU appeared to be more effective than bolus 5-FU. This was a pivotal study, as it showed for the first time that infusional 5-FU was superior to bolus 5-FU in the adjuvant chemoradiation treatment of early-stage rectal cancer. Moreover, this study provided the rationale for using PVI 5-FU in the neoadjuvant setting to be combined with radiation therapy.

The Intergroup 0144 protocol evaluated the role of infusional vs bolus schedules of 5-FU chemotherapy combined with radiation therapy in the adjuvant treatment of rectal cancer. After curative resection, patients (n = 1,917) were randomized to one of three treatment arms: (1) bolus 5-FU in two 5-day cycles every 28 days before and after radiation in combination with PVI 5-FU 225 mg/m²/d during radiation, (2) PVI 5-FU for 42 days before and 56 days after radiation in combination with PVI 5-FU during radiation, and (3) bolus 5-FU/LV in two 5-day cycles before and after radiation in combination with bolus 5-FU/LV. After a median follow-up of 5.7 years, no significant differences in clinical efficacy were observed in terms of locoregional failure, DFS, and OS between bolus vs PVI 5-FU. However, PVI 5-FU was associated with an improved safety profile, as the incidence of severe hematologic toxicity was markedly reduced (4% vs 49% to 55%) when compared with the bolus 5-FU arm.

Neoadjuvant Chemoradiotherapy

A key issue surrounding the management of locally advanced rectal cancer relates to the optimal sequence of chemoradiation and surgery. More specifically, the question that has been the subject of much debate revolves around whether combined-modality chemoradiotherapy should be given prior to or following surgical resection. There are several potential advantages for administering chemoradiotherapy in the preoperative neoadjuvant setting. They include the following: (1) theoretic advantage of irradiating tissue that has not been rendered hypoxic by prior surgery, (2) reduced risk of radiation-induced toxicity to small bowel that has been trapped in the pelvis by surgical adhesions, (3) increased ability to more effectively deliver chemotherapy to the primary tumor site as the vasculature has not been compromised following surgery, (4) enhanced potential to excise the irradiated segment of large bowel and perform an anastomosis with viable colon to achieve improved postoperative bowel function, (5) increased accuracy of preoperative staging evaluation, and (6) increased opportunity to perform sphincter-sparing surgery of low-lying tumors.

Prospective, randomized trials initiated in the United States compared the clinical efficacy of preoperative chemoradiotherapy with that of standard, postoperative chemoradiotherapy for patients with stage II and III rectal cancer. Unfortunately, Radiation Therapy Oncology Group (RTOG) 94-01 and NSABP R-03[7] were closed prematurely as a result of poor patient enrollment.
The CAO/ARO/AIO-94 trial is a landmark German study designed to define optimal timing for chemoradiation in patients with resectable rectal cancer.[8] A total of 823 patients with clinical stage T3/4 or node-positive disease were randomized to receive neoadjuvant chemoradiotherapy or adjuvant chemoradiotherapy. Patients on the neoadjuvant chemoradiation arm (n = 415) received protracted venous infusion of 5-FU (1,000 mg/m²/d via over 120 hours) during the first and fifth weeks of radiotherapy (5,040 cGy delivered in 28 fractions of 180 cGy, 5 days per week). After total mesorectal excision (TME), patients then received 5-FU (500 mg/m²/d, 5 days per week, every 4 weeks) for an additional month (four cycles). Patients randomized to the adjuvant chemoradiation arm (n = 384) received the identical 5-FU and radiation treatments as listed above after TME, and the same four cycles of bolus 5-FU was started 1 month after the completion of chemoradiation. There was no significant difference in inpatient mortality, postoperative complication rates, anastomosis leakage rates, delayed sacral wound healing, postoperative bleeding, and ileus. Severe diarrhea, hematologic effects, and local perineal skin toxicity were generally greater in the adjuvant arm compared to neoadjuvant arm. Patients treated with neoadjuvant therapy experienced lower rates of grade 3/4 acute toxicities (27% vs 40%, \( P = .001 \)). A higher incidence of chronic severe toxic effects was observed in patients treated on the adjuvant arm (24% vs 14%, \( P = .01 \)); gastrointestinal effects (15% vs 9%; \( P = .07 \)) and strictures at the anastomotic site (12% vs 4%, \( P = .003 \)).

In terms of clinical outcome, the rate of sphincter-sparing surgery was higher in the neoadjuvant arm when compared to the adjuvant arm. Of the 194 patients determined before randomization to require abdominoperineal resection (APR), 39% on the neoadjuvant arm and 19% on the adjuvant arm were able to undergo sphincter preservation surgery (\( P = .004 \)). The cumulative incidence of local recurrences at 5 years was significantly lower in patients treated with neoadjuvant chemoradiotherapy when compared to those receiving adjuvant treatment (6% vs 13%, \( P = .0006 \)). No differences were observed in the cumulative incidence of distant recurrences at 5 years (36% vs 38%, \( P = .85 \)), 5-year OS (76% vs 74%, \( P = .80 \)), and the 5-year DFS (68% vs 65%, \( P = .32 \)). This study is important as it was the first to clearly demonstrate that neoadjuvant chemoradiotherapy was superior to adjuvant combined-modality therapy in terms of improved local control and safety profile in the treatment of locally advanced stage II/III rectal cancer.

The European Organisation for Research and Treatment of Cancer 22921 protocol was a randomized trial to evaluate the role of concurrent chemoradiation in the neoadjuvant setting along with the role of adjuvant chemotherapy in patients with resectable stage T3/4 rectal cancer.[9] Patients (n = 1,011) were randomized to one of four treatment arms: (1) preoperative radiation (45 Gy over 5 weeks) alone, (2) preoperative radiation plus two 5-day courses of chemotherapy (5-FU 350 mg/m²/d and LV 20 mg/m²/d in the first and fifth weeks of radiation therapy), (3) preoperative radiotherapy plus four post-
operative courses of chemotherapy, and (4) preoperative radiotherapy and chemotherapy plus postoperative chemotherapy. Randomization was well balanced, with approximately 250 patients allocated to each treatment arm.

Patients treated with preoperative chemotherapy and radiotherapy experienced a higher pathologic complete response (pCR) rate of 13.7% vs 5.3% in patients treated with only preoperative radiotherapy. A lower pathologic stage of disease was observed in the combined chemoradiotherapy arm, as reflected by tumor and nodal substage. In addition, significant histologic changes were noted in the combined-modality arm, such that the number of tumors with venous, perineural, and lymphatic invasions was markedly reduced in the preoperative combined treatment group compared with the preoperative radiotherapy group. Finally, patients treated with neoadjuvant chemoradiotherapy experienced a significantly reduced local failure rate when compared to the radiotherapy-alone group (8% vs 17%, \(P = .002\)). This study provides further evidence that the addition of chemotherapy to preoperative radiotherapy confers clinical benefit by significantly enhancing local control.

The Fédération Francophone de Cancérologie Digestive trial FFCD9203 evaluated the potential survival benefit of concurrent chemoradiation in the neoadjuvant setting by randomizing patients to preoperative radiotherapy alone (n = 363) or concurrent neoadjuvant chemoradiation (n = 370).[10] Patients treated on the concurrent chemoradiation arm received bolus 5-FU 350 mg/m² and LV 20 mg/m² IV on days 1–5 on weeks 1 and 5 with concurrent radiation. In both arms, patients received four cycles of adjuvant 5-FU/LV following surgical resection. The pCR was significantly improved with the addition of chemotherapy from 3.7% to 11.7% (\(P < .05\)), although the sphincter-sparing rate was similar in the two arms (53% vs 52%). With a median follow-up of 69.3 months, patients treated with neoadjuvant concurrent chemoradiation experienced an improved 5-year local failure rate (8% vs 16.5%). However, no improvements in DFS or OS have been observed to date, although longer follow-up is needed to directly assess the impact on survival.

**Advances in Chemotherapy for Neoadjuvant Chemoradiation**

**Capecitabine**

Capecitabine (Xeloda) is an oral prodrug of 5-FU that has been shown to be as effective as bolus 5-FU/LV in the adjuvant therapy of early-stage colon cancer and in the treatment of metastatic colorectal cancer.[11] This oral fluoropyrimidine has a more favorable safety profile than bolus 5-FU with respect to myelosuppression, stomatitis, alopecia, nausea, and vomiting.[12,13] Currently, capecitabine is approved in the United States for the first-line therapy of metastatic colorectal cancer when fluoropyrimidine
monotherapy alone is being considered, and as monotherapy for the adjuvant treatment of stage III colon cancer.

Preclinical in vivo animal studies have documented the synergistic interaction between capecitabine and radiotherapy when given concurrently.[14] Of note, treatment with radiation results in an upregulated expression of thymidine phosphorylase, one of the key enzymes required for the conversion of capecitabine to its active metabolite 5-FU. Sawada and colleagues determined that a single dose of local radiotherapy (5 Gy) increased thymidine phosphorylase levels by up to 13-fold at 9 days after radiotherapy. Moreover, this radiation-induced upregulation of thymidine phosphorylase appeared to be selective for tumor tissue, as it was not observed in normal host tissues.

Dunst et al[15] were the first group to evaluate the concurrent combination of radiotherapy and capecitabine in rectal cancer. To exploit the potential synergistic effect of radiotherapy and capecitabine, the oral fluoropyrimidine was administered continuously for the duration of the radiation treatments. Capecitabine was administered at escalating doses from 250 to 1,250 mg/m² bid. In terms of safety profile, this combined-modality therapy was well tolerated, and dose-limiting grade 3 hand-foot syndrome was observed in two of six patients treated at the 1,000 mg/m² bid dose. Nine partial remissions were observed in 10 patients treated. Based on this phase I study, the combination of capecitabine and radiotherapy is safe and effective for the neoadjuvant treatment of rectal cancer. The recommended dose of capecitabine, when administered concurrently with radiotherapy for a period of about 6 weeks, is 825 mg/m² bid.

In follow-up, Krishnan et al[16] conducted a phase II study in patients with locally advanced rectal cancer (T3/4, N+) using the combination of radiotherapy and capecitabine, which was administered at a dose of 825 mg/m² bid during the entire course of radiotherapy. A total of 54 patients were enrolled onto the study. Of the 51 patients evaluable for pathologic response, pCR was observed in 18% of patients, while 24% of patients had microscopic residual disease. Of the 27 patients whose primary tumors were located within 5 cm from the anal verge, 67% were able to undergo sphincter-preserving surgery. This combined-modality therapy was well tolerated and grade 3/4 toxicities were rare.

To evaluate the tolerance and efficacy of neoadjuvant capecitabine-based chemoradiation, DePaoli et al[17] treated 53 patients with locally advanced resectable rectal cancer with capecitabine (825 mg/m² bid) with concurrent radiotherapy (50.4 Gy delivered in 28 fractions). All patients underwent surgery followed by a 4-month course of adjuvant single-agent capecitabine chemotherapy. No grade 4 toxicities were reported, and grade 3 toxicities were reported in 11% of patients (leukopenia 4%, hand-foot syndrome 4%). Fifty-seven percent of patients were downstaged and the pCR rate was 24%. Among those with low-lying tumors (≤ 5 cm from anal verge; n = 34), 59% were able to undergo
sphincter-preserving resection.

Taken together, these various studies provide evidence that capecitabine-based neo-adjuvant chemoradiation is an effective and tolerable regimen for patients with locally advanced resectable rectal cancer. Moreover, the use of capecitabine provides a more convenient treatment option than protracted infusional schedules of 5-FU.

An alternative strategy is to administer capecitabine twice daily from Monday to Friday throughout the course of radiotherapy. Ngan et al.[18] conducted a phase I trial of preoperative radiotherapy (50.4 Gy given in 28 fractions in 5 weeks and 3 days) combined with oral capecitabine in patients with T3/4, N0–2 rectal cancer. This combination regimen was active as 19% of patients experienced a pCR. This treatment regimen was very well tolerated, and no patient treated at the 900 mg/m² bid dose level experienced a dose-limiting toxicity. Although no direct comparative studies have been performed, to date, comparing continuous dosing of capecitabine with a Monday to Friday dosing schedule, it appears that either treatment approach can be safely and effectively combined with radiotherapy. If the Monday to Friday dosing regimen is to be given, the dose of capecitabine should be 900 mg/m² bid.

**Oxaliplatin**

Oxaliplatin (Eloxatin) is a third-generation platinum analog with broad-spectrum activity against gastrointestinal malignancies, including colorectal, pancreas, and gastric cancer. It is presently approved in the United States for the first- and second-line therapy of metastatic colorectal cancer when used in combination with 5-FU plus leucovorin (FOLFOX4). In addition, oxaliplatin has also been approved for adjuvant therapy in stage III or high-risk stage II colon cancer when used in combination with 5-FU and leucovorin (FOLFOX4).

In a phase I/II study designed to evaluate the role of oxaliplatin in neoadjuvant combined-modality therapy, patients with locally advanced rectal cancer were treated with oxaliplatin (30 mg/m² on day 1 weekly), PVI 5-FU (200 mg/m² daily for 6 weeks), and radiotherapy (50.4 Gy delivered in 1.8-Gy fractions) over a 6-week period.[19] In the phase II portion of this study, weekly oxaliplatin was escalated to a dose of 60 mg/m². Eighteen patients were enrolled onto the phase I portion, while 26 patients were enrolled onto the phase II part of this study. The maximum tolerated dose for weekly oxaliplatin was determined to be 60 mg/m². Fifty-six percent of patients entered at the maximum tolerated dose completed all 6 weeks of oxaliplatin. Eight of 32 patients (25%) enrolled at the phase II dose experienced a pCR. This study concluded that the addition of oxaliplatin to infusional 5-FU–based combined-modality therapy for patients with locally advanced...
rectal cancer was associated with a high pCR rate but at the expense of increased toxicity when compared to infusional 5-FU.

In a phase II French study designed to determine the efficacy and tolerability of oxaliplatin-based chemoradiotherapy, 40 patients with resectable rectal cancer were given radiotherapy (50 Gy over 5 weeks with a concomitant boost), two cycles of oxaliplatin 130 mg/m² on day 1, followed by 5-day PVI 5-FU 350 mg/m²/d plus LV 100 mg/m².[20] Concurrent chemoradiation was given in weeks 1 and 5. An objective clinical response was seen in 30 patients (75%) and a pathologic CR was achieved in 15% of surgical specimens. Sphincter-sparing surgery was possible in 26 patients.

STAR-01 is a randomized phase III trial evaluating the role of oxaliplatin in 5-FU–based chemoradiation for neoadjuvant therapy of resectable rectal cancer. The safety profile of this trial was reported recently.[21] A total of 410 patients are randomized to either infusional 5-FU (225 mg/m²/d) with concurrent radiotherapy or infusional 5-FU (225 mg/m²/d) plus oxaliplatin 60 mg/m² weekly × 6 with concurrent radiation. In terms of safety profile, an increased incidence of grade 3/4 diarrhea was observed in the oxaliplatin arm when compared to infusional 5-FU alone (17% vs 7%). At this time, the clinical efficacy data are not yet available.

Irinotecan

Irinotecan (Camptosar) is a topoisomerase I inhibitor with broad-spectrum activity in colorectal cancer and other gastrointestinal malignancies as well as in non–small-cell and small-cell lung cancer. This cytotoxic agent is approved by the US Food and Drug Administration as monotherapy for the second-line treatment of patients with metastatic colorectal cancer and as first-line therapy for metastatic colorectal cancer when used in combination with 5-FU plus LV. As outlined in Chapter 6, “Adjuvant Chemotherapy of Colon Cancer,” there is, at present, no role for irinotecan in the adjuvant therapy of early-stage colon cancer.

A phase II trial was performed to evaluate the role of irinotecan in 5-FU–based neoadjuvant chemoradiation of rectal cancer.[22] Patients (n = 39) with locally advanced rectal cancer received infusional 5-FU 200 mg/m²/d on days 1–5 and irinotecan 50 mg/m² weekly with concurrent radiation. After TME, patients received four cycles of 5-FU/folinic acid chemotherapy. Tumor downstaging was observed in 84% of patients with a pCR rate of 20%.

The RTOG 0012 study was a randomized phase II study that investigated the clinical activity and toxicity of neoadjuvant irinotecan plus infusional 5-FU–based chemoradiation for advanced T3/T4 distal rectal cancers.[25] Patients were randomized to one of two
arms: PVI 5-FU (225 mg/m² per day, 7 days per week) plus radiation or 5-FU/irinotecan (5-FU 225 mg/m² per day, 5 days per week, and irinotecan 50 mg/m² once weekly for 4 weeks) plus radiation. Of note, patients randomized to the infusional 5-FU-alone arm received a boost of 9.6 Gy for T3 and 14.4 Gy for T4 cancers, while a lower boost of 5.4 Gy for T3 and 9 Gy for T4 tumors was given to patients randomized to arm 2 (infusional 5-FU plus irinotecan).

Clinical efficacy, as determined by the extent of tumor downstaging and pCR rates, was equivalent in the two arms. Tumor downstaging was observed in 78% of patients in both arms, and the pCR rate was also the same (28%) for both treatment regimens. The incidence of acute and late toxicities was also similar, although the incidence of grade 3/4 nonhematologic toxicity mainly in the form of gastrointestinal toxicity was slightly higher in patients treated with the combination of infusional 5-FU and irinotecan vs infusional 5-FU alone (45% vs 38%). This study showed that neoadjuvant chemoradiation is safe and effective with either dose intensification of radiation therapy or with combination chemotherapy. Unfortunately, no precise conclusions can be made as to the true additive benefit of irinotecan to infusional 5-FU chemotherapy given the imbalance in radiation treatments.

**Combination of Capecitabine and Irinotecan**

Capecitabine-based chemoradiation given in combination with other cytotoxic agents has been of particular interest in the treatment of locally advanced rectal cancer. In a phase II trial designed to investigate capecitabine/irinotecan (CAPIRI)-based neoadjuvant chemoradiation, patients (n = 36) were given CAPIRI concurrently with radiotherapy.[24] Irinotecan was given at a weekly dose of 50 mg/m² and capecitabine was given twice a day on days 1–38 at a dose of 500 mg/m². Radiotherapy (50.4 Gy) was administered concurrently with CAPIRI. CAPIRI-based chemoradiation was well tolerated. The main grade 3/4 toxicities observed were leukopenia (25%, n = 9), diarrhea (11%, n = 4), nausea/vomiting (5%, n = 2), and elevation of serum transaminases (< 1%, n = 1). A pCR was achieved in 15% of patients (5 of 34) and 3-year OS for all patients with surgery was 80%.

**Combination of Capecitabine and Oxaliplatin**

Infusional 5-FU with oxaliplatin is considered to be one of the standard regimens for advanced colorectal cancer. Capecitabine appears to be comparable in efficacy to PVI 5-FU. To evaluate the activity and safety of capecitabine/oxaliplatin (CAPOX)-based neoadjuvant chemoradiation, 110 patients with locally advanced rectal cancer were given capecitabine (1,650 mg/m² on days 1–14 and 22–35) plus oxaliplatin (50 mg/m² on days
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1, 8, 22, and 29) with concurrent radiotherapy (50.4 Gy delivered in 28 fractions).[25] Four cycles of adjuvant CAPOX (capecitabine 1,000 mg/m² twice daily on days 1–14 and oxaliplatin 130 mg/m² on day 1 every 3 weeks) were administered. Pathologic CR was achieved in 16% of patients (n = 17). Full-dose preoperative CAPOX-based chemoradia-
tion was administered in 96% of patients. The main grade 3/4 chemoradiation-associated
toxicity was diarrhea, which was observed in 12% of patients (n = 13).

To evaluate the merits of administering CAPOX prior to neoadjuvant capecitabine-
based chemoradiation and resection, 77 patients with newly diagnosed high-risk rectal
cancer were enrolled in a study with neoadjuvant CAPOX followed by capecitabine-based
chemoradiation, TME, and then adjuvant single-agent capecitabine.[26] Neoadjuvant
CAPOX was given for a total of 3 months: capecitabine 1,000 mg/m² twice daily on days
1–14 and oxaliplatin 130 mg/m² on day 1 every 3 weeks. For capecitabine-based chemo-
radiation, capecitabine (1,650 mg/m²/d 7 days per week) was given concurrently with
radiation. Of the 70 patients who received neoadjuvant CAPOX, the overall response
rate was 88%. After capecitabine-based chemoradiation, the tumor response rate was
97%. Pathologic CR was observed in 24% of patients. This study showed that neoadjuvant
CAPOX prior to capecitabine-based neoadjuvant chemoradiation and TME resulted in
substantial tumor regression, rapid symptomatic response, and achievement of R0 surgi-
cal resection.

RTOG-0247 is a randomized phase II trial evaluating the role of CAPOX and CAPIRI
in the neoadjuvant chemoradiation of rectal cancer. Patients are randomized to one of
two arms: CAPOX (capecitabine bid 5 days/wk and oxaliplatin weekly) plus radiation or
CAPIRI (capecitabine bid 5 days/wk and irinotecan weekly) plus radiation. After surgical
resection, patients in each arm receive nine cycles of FOLFOX chemotherapy as adjuvant
therapy. This trial is currently accruing patients.

PETACC-6 is a randomized trial that is investigating the role of CAPOX chemotherapy
in the neoadjuvant chemoradiation treatment of early-stage rectal cancer. Patients
with high-risk features are randomized to either capecitabine alone (capecitabine 825
mg/m² bid on days 1–38) plus radiation, or CAPOX (capecitabine 825 mg/m² bid on
days 1–38 and oxaliplatin 50 mg/m² weekly × 4) plus radiation. After TME, patients
receive adjuvant chemotherapy. Patients randomized to the capecitabine-alone arm
receive capecitabine 1,000 mg/m² bid days 1–14 every 3 weeks for 6 cycles, while those
randomized to the CAPOX arm receive capecitabine 1,000 mg/m² bid days 1–14 and
oxaliplatin 130 mg/m² on day 1 every 3 weeks for six cycles. The target accrual goal for
this study is 1,090 patients.

Finally, NSABP R-04 is a four-arm randomized phase III trial comparing preoperative
radiotherapy and continuous infusion 5-FU with or without oxaliplatin with preoperative
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radiotherapy and capecitabine with or without oxaliplatin. This is an interesting study that addresses two clinically relevant issues: the potential for capecitabine to replace continuous infusion 5-FU, and the potential clinical benefit of combining fluoropyrimidine therapy, whether it be infusional 5-FU or oral capecitabine, with oxaliplatin. Following neoadjuvant chemoradiotherapy, surgical resection will be performed, and the subsequent use of postoperative adjuvant therapy is left open to investigators.

Cetuximab

Cetuximab (Erbitux) is an IgG1 chimeric monoclonal antibody targeting the epidermal growth factor receptor (EGFR). This biologic agent is currently approved in combination with irinotecan for the treatment of metastatic colon cancer for patients who had progress on prior irinotecan-based chemotherapy or as monotherapy in patients who are deemed to be intolerant of irinotecan chemotherapy.[27] To assess the safety and preliminary efficacy of neoadjuvant capecitabine plus cetuximab-based chemoradiation, 40 patients with locally advanced rectal cancer received cetuximab (400 mg/m² given intravenously as a loading dose on the week prior to initiation of radiotherapy, then 250 mg/m² weekly for 5 weeks) and capecitabine (dose level I: 650 mg/m² orally twice daily; dose level II: 825 mg/m² twice daily) with concurrent radiotherapy (1.8 Gy per day, 5 days per week for 5 weeks).[28]

No dose-limiting toxicity was observed in this study. Severe diarrhea was experienced in 15% of patients. Three grade 4 adverse events were observed, including one myocardial infarction, one pulmonary embolism, and one pulmonary infection with sepsis. Two patients (5%) achieved pCR. This study showed that preoperative radiotherapy in combination with capecitabine and cetuximab was feasible and worthy of further investigation.

To establish the feasibility and efficacy of capecitabine, irinotecan, and cetuximab–based neoadjuvant chemoradiation, 20 patients with locally advanced rectal cancer received cetuximab (one time loading dose of 400 mg/m² on day 1 followed by 250 mg/m² on days 8, 15, 22, and 29), irinotecan (dose level I: 40 mg/m² on days 1, 8, 15, 22 and 29; dose level II: 40 mg/m²; and dose level III: 50 mg/m²), and capecitabine (800 mg/m² on days 1–58; dose level II: 1,000 mg/m², and dose level III: 1,000 mg/m²) given concurrently with radiotherapy.[29] Dose level II was determined to be the recommended dose for future studies. A total of 10 patients were treated on dose level II. Five patients were found to have a pCR. Thus, neoadjuvant cetuximab, capecitabine, and irinotecan–based chemoradiation appears to be a feasible and well-tolerated treatment regimen.

The Southwest Oncology Group study SWOG0713 is a phase II trial evaluating the role of cetuximab in combination with CAPOX in neoadjuvant chemoradiation of rectal cancer. Patients receive CAPOX (capecitabine 825 mg/m² bid on days 1–14 every 3
weeks for two cycles, and oxaliplatin 50 mg/m² weekly × 5) and weekly cetuximab plus concurrent radiation. This study is currently open to accrual, with an enrollment goal of 80 patients.

The EXPERT-C trial is a phase II study in high-risk rectal cancer that investigates the role of cetuximab in combination with XELOX. Patients are randomized to one of two arms: XELOX plus weekly cetuximab for 12 weeks followed by capecitabine plus cetuximab with concurrent radiation for 6 weeks, or XELOX for 12 weeks followed by capecitabine with concurrent radiation for 6 weeks. After TME surgery, patients on the XELOX/cetuximab arm receive XELOX plus cetuximab for 12 weeks, while those randomized to the XELOX arm receive XELOX alone for 12 weeks. The accrual goal is 162 patients, and the primary endpoint of this trial is pCR rate.

Bevacizumab

Bevacizumab is an IgG1 humanized monoclonal antibody targeting the vascular endothelial growth factor (VEGF). This biologic agent is approved for the first-line treatment of metastatic colorectal cancer in combination with any intravenous 5-FU–based chemotherapy and also approved for use in the second-line setting in combination with FOLFOX4 chemotherapy. At present, there are several randomized phase III clinical trials evaluating the role of bevacizumab in combination with cytotoxic chemotherapy in the adjuvant treatment of colon cancer, as outlined in Chapter 7, “Biologic Agents in the Adjuvant Treatment of Colon Cancer.” With respect to rectal cancer, the role of bevacizumab in the preoperative combined-modality treatment of locally advanced rectal cancer is being actively investigated.

In an innovative phase I trial, Willett et al.[30] studied bevacizumab in combination with infusional 5-FU along with concurrent radiotherapy. They evaluated two different doses of bevacizumab and observed that the 5 mg/kg dose level was better tolerated than the 10 mg/kg dose. A series of pharmacodynamic studies were performed as part of this clinical trial. This translational component of the phase I trial revealed that a single infusion of bevacizumab was able to decrease tumor perfusion, vascular volume, microvascular density, interstitial fluid pressure and the number of viable, circulating endothelial and progenitor cells, and increase the fraction of vessels with pericyte coverage. Of 11 evaluable patients, 10 had a complete clinical response, with two showing a pCR. This study showed that bevacizumab could be safely and effectively combined with cytotoxic chemotherapy and radiotherapy. Several studies of neoadjuvant therapy with concurrent bevacizumab, 5-FU–based chemotherapy, and radiotherapy are presently ongoing.

The E3204 trial is a phase II study to evaluate the role of bevacizumab in neoadjuvant chemoradiation. Patients receive CAPOX (capecitabine 825 mg/m² twice daily 5 days per
week and oxaliplatin 50 mg/m² weekly × 5) and bevacizumab 5 mg/kg on days 1, 15, and 29 with concurrent radiation. After surgery, patients receive eight cycles of FOLFOX plus bevacizumab (5 mg/kg every 2 weeks) as adjuvant therapy. This study is presently open to accrual, with an enrollment target of 39 patients.

**Conclusion**

Significant advances have been made in the treatment of patients with locally advanced rectal cancer. In 1990, the National Institutes of Health convened a consensus conference to review the optimal treatment approaches for patients with colorectal cancer. Based on that meeting, the recommendation was to administer postoperative adjuvant chemoradiotherapy for patients with stage II and III rectal cancer; for nearly 15 years, that particular approach was viewed as the standard of care. However, in 2004, the German Rectal Cancer Study Group showed for the first time that neoadjuvant chemoradiotherapy was superior to postoperative adjuvant chemoradiotherapy in terms of improved local control, enhanced sphincter preservation, and reduced acute and chronic toxicities. Subsequent to that pivotal study, two other randomized clinical trials from Europe provided further evidence supporting the use of concurrent chemoradiotherapy in the neoadjuvant setting. Taken together, these studies have created a major paradigm shift in the way in which stage II and III rectal cancer is managed, such that for the past 3 years, the standard of care has moved away from adjuvant combined-modality therapy toward a preoperative neoadjuvant combined-modality approach for patients with locally advanced rectal cancer.

Currently, much attention is being placed on developing more active and potentially more convenient radiosensitizers to be combined with preoperative radiotherapy. When combined with radiotherapy, the oral fluoropyrimidine capecitabine has been shown to provide greater convenience for patients as well as confer clinical benefit and a potentially improved safety profile when compared to infusional 5-FU regimens. Given their activity in the metastatic disease setting, oxaliplatin and irinotecan are being tested in combination with either 5-FU or the oral fluoropyrimidine capecitabine, with the hope that they will provide greater local control and perhaps an enhanced systemic control of distant metastatic disease.

Clinical trials are also directed toward investigating the potential role of the biologic agents, which target the EGFR and/or VEGF signaling pathways. Cetuximab and bevacizumab are the two targeted therapies that are being most actively investigated in combination with conventional chemoradiotherapy regimens, and we eagerly await the results of these clinical trials.
Finally, the optimal adjuvant therapy to be administered once neoadjuvant chemoradiotherapy and surgical resection have been performed remains a subject of ongoing clinical investigation.

References


1. The assessment of at least ____ lymph nodes is a quality measure being targeted by the National Cancer Institute-sponsored National Quality Forum on colorectal cancer care?
   (a) 6
   (b) 12
   (c) 15
   (d) 24

2. Which of the following statements concerning pathologic examination of colorectal cancer lesions is true?
   (a) Routine immunohistochemistry is recommended to test all harvested lymph nodes.
   (b) Patients with node-negative, micrometastatic disease detected by immunohistochemistry always have a significantly poorer outcome.
   (c) Currently, the clinical significance of micrometastatic disease not detectable by conventional means is unclear.
   (d) All of the above.

3. Laparotomy results in smaller postoperative increases in serum levels of the interleukin-6 and -1, tumor necrosis factor-α, C-reactive protein, and vascular endothelial growth factor than does laparoscopy.
   (a) True
   (b) False

4. Which of the following initially was used as a palliative measure for patients with disseminated rectal cancer or those believed to be at high surgical risk but then was proven to successfully treat early, curable tumors, with survival rates varying from 58% to 82%?
   (a) Electrocoagulation
   (b) Endocavitary contact radiotherapy
   (c) Transanal endoscopic microsurgery
   (d) Local excision

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5. Which of the following statements is true?
(a) Genuine micrometastases within regional lymph nodes, even though classified as N1, are of unproven prognostic significance.
(b) Immunohistochemistry allows for the detection of isolated tumor cells, also known as micrometastases.
(c) Stage II colorectal cancer patients with and without occult residual disease have the same likelihood of having undetected metastases in the lymph nodes of their primary resection specimens.
(d) Reverse transcriptase–polymerase chain reaction is a validated method for distinguishing nodal micrometastases from single isolated tumor cells in lymph nodes.

6. According to evidence-based guidelines recently published for the use of tumor markers in colorectal cancer decision-making, which of the following must not be used as an independent prognostic test to guide treatment?
(a) Elevation of preoperative carcinoembryonic antigen level
(b) Microsatellite instability status
(c) Status of surgical margins
(d) None of the above

7. Recent basic research suggests that the loss of which receptor may increase the invasiveness and apoptosis resistance of colorectal tumor cells?
(a) Netrin-1 receptor
(b) Transforming growth factor β receptor
(c) Epidermal growth factor receptor
(d) Vascular endothelial growth factor receptor type 1

8. What is the generally recommended surveillance for successfully treated colorectal cancer patients who have ≥ T2 lesions?
(a) A carcinoembryonic antigen test at baseline and every 3 months for 2 years, then every 6 months for the next 2 to 5 years if the patient may be a potential candidate for aggressive curative surgery
(b) Colonoscopy performed within 2 years of resection
(c) History taken and physical examination performed every 6 months for the first 3 years and then annually for a total of 5 years
(d) All of the above
9. The 6-year final overall survival analysis of the MOSAIC trial in stage II or III colon cancer patients given either bolus infusion 5-FU/LV (LV5FU2) or oxaliplatin plus 5-FU/LV (FOLFOX4) found
   (a) The disease-free survival benefit found at 3 and 4 years with FOLFOX continued at 5 years.
   (b) Patients with stage III disease derived true benefit from FOLFOX.
   (c) There was a trend toward improved overall survival in the entire patient cohort.
   (d) All of the above

10. Administration of neoadjuvant capecitabine/oxaliplatin (CAPOX) given for newly diagnosed high-risk rectal cancer before capecitabine-based neoadjuvant chemoradiation and total mesorectal excision resulted in substantial tumor regression, rapid symptomatic response, and achievement of R0 surgical resection.
   (a) True
   (b) False

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1. A patient who undergoes sigmoidoscopy and is diagnosed with a tumor in the sigmoid colon should undergo full colonoscopy only if the physician has evidence of lesions in other colonic areas.
   (a) True
   (b) False

2. Which of the following is associated with laparoscopic surgery performed in colon cancer patients?
   (a) The learning curve for laparoscopic proctectomy is shorter than for laparoscopic colectomy.
   (b) The learning curve to feel comfortable with laparoscopic colectomy is 10 to 20 cases.
   (c) Equal oncologic outcome has been found between laparoscopic and open colectomy.
   (d) Certain larger, bulker tumors are better suited to laparoscopic colectomy than to open surgery.

3. At least how many lymph nodes should be evaluated to establish whether colorectal cancer has metastasized?
   (a) At least 5 to 7
   (b) No more than 7 to 12
   (c) At least 15 to 20
   (d) The number of lymph nodes removed and analyzed is not important

4. Based on currently available information, colorectal cancer patients who receive which of the following apparently derive more benefit in terms of disease-free survival at 3 and 4 years?
   (a) Capecitabine monotherapy
   (b) Oxaliplatin plus a fluoropyrimidine
   (c) 5-FU/leucovorin
   (d) Bevacizumab monotherapy

5. What factors would be important when considering palliative surgical resection of a primary colon tumor in patients with documented, widespread metastatic colorectal cancer?
   (a) Patient age
   (b) Location of metastases
   (c) Patient performance status
   (d) Patient decision for treatment
   (e) All of the above
6. When contemplating surgery for a metastatic colorectal cancer patient, the best strategy is to delay systemic therapy while considering all possible surgical options.
   (a) True
   (b) False

7. A colorectal cancer patient presenting with a T4, N1 lesion received upfront combined modality chemoradiation and then underwent surgery. Subsequent analysis showed the lesion to be staged at T1, N0. The patient then should have received adjuvant chemotherapy.
   (a) True
   (b) False

8. A prototype of colorectal cancer that has practically no architecture, that initially appears to be aggressive, that has bundle lymphocytic infiltrate, that has high microsatellite instability, and that carries a favorable diagnosis is
   (a) Adenocarcinoma.
   (b) Medullary carcinoma.
   (c) Squamous cell carcinoma.
   (d) Small cell carcinoma.
   (e) Signet-ring carcinoma.

9. Which of the following is a true statement?
   (a) Colorectal tumors with high microsatellite instability offer a better prognosis than do microsatellite-stable tumors.
   (b) Four genes commonly involved in generating microsatellite instability and which are routinely the targets of testing are MLH1, MSH2, PMS3, and WNT1.
   (c) Immunohistochemical analysis of tumor tissue is crucial to the diagnosis of colorectal cancer.
   (d) All of the above

10. In patients with stage II or III colorectal cancer, the highest risk for disease recurrence occurs within the first 3 to 5 years.
   (a) True
   (b) False

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