

New Approaches to Assessing and Treating Early-Stage Colon and Rectal Cancer: Summary Statement from 2007 Santa Monica Conference

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Abstract The 2007 Santa Monica Conference on Assessing and Treating Early-Stage Colon and Rectal Cancer, a multidisciplinary meeting of leaders in surgery, medical and radiation oncology, and pathology, was convened on January 12 to 13, 2007. The purpose of the meeting was to assess current data and issues in the field and to develop recommendations for advancing patient care and clinical research. Topics included pathologic assessment and staging, transanal versus laparoscopic versus open resection, adjuvant therapy, genetic testing and counseling, cooperative group strategies, and the use of biological therapies and novel agents. A review of the key issues discussed, as well as conclusions and recommendations considered significant to the field, is summarized below and presented at greater length in the individual manuscripts and accompanying discussion that comprise the full conference proceedings. Although the management of early-stage colon and rectal cancers remains a challenge for all of us, the development and use of new technologies and methods of assessment and treatment over the past several decades is yielding encouraging results. A variety of opportunities to further improve outcomes were addressed in this forum, including recommendations that specific protocols be adopted regarding surgical and pathologic dissection and reporting, particularly for stage II disease; the corollary need to increase active multidisciplinary collaboration; and the development of comprehensive consensus guidelines and recommendations to standardize care in early-stage colorectal cancer.

Optimal Pathologic Staging: Defining Stage II Disease

Tumor stage is the most important indicator of prognosis, influencing most patient management decisions. Identifying stage II disease (i.e., transmural localized tumor without regional nodal metastasis) is critical in deciding whether adjuvant therapy should be administered. Yet, defining stage II

colorectal carcinoma by pathologic examination is not always straightforward, standardized, or adequate. Several key issues must be addressed, including involvement of the regional lymph nodes, total number of nodes assessed, extent of deepest tumor penetration, and circumferential margin status. Furthermore, additional pathologic features that may aid in the substratification of stage II tumors into different risk categories must also be assessed and reported in a standardized manner.

Conference participants agreed that lymph node status is the most important prognostic indicator described in a pathology report, especially if we are defining stage II disease. Numerous recent studies support the conclusion that the minimum number of lymph nodes for assignment of pN₀ should be between 12 and 18. However, it is widely recognized that fewer nodes are often available, harvested, or analyzed for patient staging in many medical centers today. There was general agreement that this is a very important issue that is best addressed by increased communication among surgeons, pathologists, and oncologists.

Participants recommended that protocols be adopted if <12 lymph nodes are found on initial examination; in such cases, the pathologist should reexamine the specimen, possibly including microscopic examination of extramural soft tissues. If ≥12 lymph nodes are not found on reexamination, the pathologist should document this in the pathology report and

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Received 7/3/07; accepted 7/9/07.

Grant support: The symposium and educational proceedings publications were supported by educational grants provided by Sanofi-Aventis, Hoffmann-La Roche, Amgen, Inc., Bristol-Myers Squibb/ImClone, and Genentech.

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doi:10.1158/1078-0432.CCR-07-1629

document the type and extent of reexamination undertaken to confirm this. It was also agreed that, although the pathologist should do a gatekeeper function, the surgeon bears responsibility for submitting both sufficient tissue for examination and a meticulous description of the surgical resection.

Staging Rectal Tumors

Several modalities are useful for the preoperative staging of rectal cancer, including digital rectal exam; computed tomography (CT); magnetic resonance imaging with traditional body, endorectal, or phased-array coils; endorectal ultrasonography (EUS) with rigid or flexible probes; and positron emission tomography with and without CT fusion. A combination of these modalities, usually influenced by availability and local expertise, is most often used to provide complete staging information. Increasing use of neoadjuvant therapy requires consistent expert application of these technologies, particularly CT/magnetic resonance imaging and EUS.

The clinical staging of rectal cancer involves extent of tumor involvement of the rectal wall and adjacent structures, presence or absence of adjacent lymphadenopathy, and determination of distant metastasis. CT imaging allows visualization of the entire abdomen and pelvis and is routinely used in staging, primarily for the evaluation of distant metastasis. Over the past 2 decades, magnetic resonance imaging is gradually replacing CT for locoregional rectal cancer staging. The development of endorectal coils has made detailed imaging of the rectal wall possible and improved T and N staging accuracy over that of body coil magnetic resonance imaging; phased-array magnetic resonance imaging holds further promise. EUS is considered the current gold standard for rectal cancer staging. Flexible EUS probes make nodal sampling possible; in the future, three-dimensional EUS may provide even greater accuracy than conventional two-dimensional EUS. Positron emission tomography has been used primarily in detecting recurrent disease and is increasingly being used in combination with CT to aid in the detection of nodal and distant metastasis.

Future Trends in Histopathologic Staging

The phenotypic characteristics identified on histopathologic examination should continue to be key in defining the primary tumor in colorectal cancer; yet, recent research suggests that new approaches could potentially strengthen the initial pathologic analysis. Approaches that are not yet standard practice, but that may improve prognosis in colorectal cancer, include primary carcinoma genotypic and phenotypic studies, analysis of additional histopathologic factors, and advanced lymph node staging.

Genotypic studies are well developed in two areas: microsatellite instability and chromosome 18q deletion/loss of heterozygosity. Immunophenotypic studies are available with regard to tumor suppressor gene/oncogene expression, proliferation/apoptosis, angiogenesis, and cell adhesion and signaling. Several specific prognostic markers (e.g., epidermal growth factor receptor, thymidylate synthase, and vascular endothelial growth factor receptor) have been identified. Controversy still surrounds the utility of ultrastaging of mesenteric lymph nodes for micrometastases using immunohistochemistry or reverse transcription-PCR.

Management of Early Rectal Cancer (T₁ and T₂)

Surgical procedures used in the treatment of rectal cancer have evolved dramatically over the past century. Abdominoperineal resection and anterior resection, the current mainstay of rectal cancer therapy, both allow for removal of the primary tumor and the draining lymph nodes. The latter may lead to decreased local and distant recurrence. Both operations, however, are associated with significant site-specific complications and the usual risks of major abdominal surgery, which has prompted the search for less invasive and safer alternatives that produce similar results.

Over the past 30 years, transanal excision has become a popular treatment option for T₁ and selected T₂ rectal adenocarcinomas. Optimal patient selection should be based on expert preoperative staging and achieving clear excision margins. Data from prospective and retrospective clinical trials are conflicting as to whether transanal excision of early-stage rectal cancer offers the same benefit as more radical surgery. Results of two prospective trials from the Cancer and Leukemia Group B and the Radiation Therapy Oncology Group suggest that if strict criteria (i.e., clear margins, well-differentiated/moderately well-differentiated tumor, and no lymphovascular invasion) are met, transanal excision seems to be a reasonable alternative. Recurrence rates with transanal excision are higher than those with radical surgery. Higher recurrence rates with local excision may be considered acceptable if balanced against rates of complications from standard resection and if survival is not compromised. Patients with unfavorable characteristics should be treated with additional therapy (i.e., standard resection or chemoradiation).

Options for Locally Advanced Rectal Cancer

The surgical management of T₃ and T₄ rectal cancer is becoming increasingly sophisticated, with the availability of numerous diagnostic and therapeutic alternatives. At present, total mesorectal excision is usually favored over less aggressive approaches in locally advanced rectal cancer because the risk of lymph node involvement is substantial. Total mesorectal excision can be achieved without compromising the anal sphincters, and continence can be preserved. If surgical margins are close, radiation therapy may be useful in minimizing local recurrence, but positive surgical margins are a poor prognostic indicator and cannot be adequately treated by radiation therapy. With good surgical technique, local recurrence may be quite low, thereby potentially obviating the need for adjuvant therapy in some patients. Neoadjuvant therapy is an increasingly used treatment for mid and low rectal cancers to enhance sphincter preservation and local control rates. For patients with high rectal cancer (stage T₁₋₂N₁ or T₃N₀ disease with minimal mesorectal invasion), surgery without neoadjuvant therapy may be an option.

Colonic stents may be useful as initial treatment in patients who present with large obstructing tumors. Large T₄ tumors that involve other pelvic structures may be most effectively treated with pelvic exenteration; however, this procedure is associated with significant complications and should not be undertaken lightly. In preoperatively treated patients who have tumors that are very close to the anus, 1-cm distal clearance may be a preferred alternative to the standard 2-cm rule. If the

anus is not directly involved and an adequate margin is feasible, doing an abdominal perineal resection is not advantageous.

Colon Cancer: Laparoscopy versus Open Resection?

Early clinical experience with laparoscopic colectomy was concerning due to anecdotal reports of wound recurrences, but preliminary data from four international randomized controlled trials—Barcelona, Clinical Outcomes of Surgical Therapy Study Group, Colon Cancer Laparoscopic or Open Resection, and Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer—suggest that the procedure is an acceptable alternative to open colectomy in patients with curable colon cancer. All four of the trials have shown that laparoscopic colectomy in patients with colon cancer results in a significant reduction in the use of narcotics and oral analgesics, length of hospital stay, and a more speedy return of bowel function and diet. Barcelona and Clinical Outcomes of Surgical Therapy Study Group have already reported recurrence and survival data, and laparoscopic resection has not been shown to be associated with a survival disadvantage. In a subset of patients with stage III colon cancer in the Barcelona trial, laparoscopic colectomy was associated with a cancer-related survival advantage; however, this result was not confirmed in Clinical Outcomes of Surgical Therapy Study Group.

Laparoscopic colectomy in colon cancer is gaining acceptance among clinicians, but its use in rectal cancer remains controversial and the investigational experience is incomplete. Results of multiple case-series and case-matched studies evaluating this procedure seem optimistic, but level 1 evidence to support its practice in rectal cancer is lacking. In fact, only one of the above-mentioned randomized controlled laparoscopy trials included a subset of patients with rectal cancer. A prospective randomized phase II trial has been developed by members of the American College of Surgery Oncology Group to test the hypothesis that laparoscopic surgery is a technically and oncologically safe and viable approach to the resection of rectal cancer.

Quality of Care Issues in Colorectal Cancer

In the presentation on quality of care, the idea was put forth that colorectal cancer, which is common, detectable, and treatable, is an ideal disease in which to address quality of care issues. Such a discussion requires a working vocabulary, and numerous definitions of quality of care can be found in the literature. A definition was proposed based on the three components of care in the Donabedian model—structure, process, and outcome—to provide a practical framework for discussion, as it suggests that providers would be compared with evidence-based quality measures. Structural components of care are features of the service provider or hospital, whereas process components include interactions between the service provider and patient; outcome components of care deal with the success or failure of the service or treatment (e.g., local tumor recurrence rate).

A question that is commonly asked is whether increased provider volume improves outcome. Numerous studies of

complex surgical procedures investigating this relationship have found a positive correlation between volume and outcome, more often in rectal cancer than colon cancer. Although multiple studies of colorectal cancer surgery have also supported surgeon and hospital volume as a predictor of outcome, the volume-to-outcome relationship generally seems to be smaller in magnitude than that in other surgical procedures. Additionally, a recent investigation using Medicare claims data could not identify differences in care between low- and high-volume providers that correlated with observed differences in outcome. One might reasonably ask whether regionalization of colorectal cancer care, particularly for non-rectal cancers, is an appropriate avenue for quality improvement or whether attention should instead be focused on process-based quality measures that could possibly improve care throughout the system.

The evaluation of health-related quality of life in colorectal cancer survivors is an important area being targeted for quality improvement. The National Quality Forum/American College of Surgeons/Commission on Cancer and National Comprehensive Cancer Network/American Society of Clinical Oncology have identified four colorectal cancer care-specific quality measures: postoperative chemotherapy for stages II to III rectal cancer; preoperative or postoperative radiation for stages II to III rectal cancer; adjuvant chemotherapy for stage III colon cancer; and assessing ≥ 12 lymph nodes after curative stage II to III colorectal cancer surgery in patients who have not received preoperative adjuvant therapy. Data collection and feedback programs are now available that will allow providers to monitor and improve their performance (e.g., American Society of Clinical Oncology's Quality Oncology Practice Initiative and American College of Surgeons' Electronic Quality Improvement Packets).

Neoadjuvant and Adjuvant Radiation in Locally Advanced Rectal Cancer

The goal of neoadjuvant or adjuvant radiation therapy in patients with locally advanced rectal cancer is to prevent local recurrence and its associated morbidity and mortality. Chemotherapeutic agents added to pelvic radiation therapy have been shown to result in improved local control and survival. In general, surgery alone has resulted in a 25% local failure rate in high-risk patients, whereas the use of preoperative or postoperative chemoradiotherapy has yielded rates of 10% to 15%. Similarly, long-term survival with surgery alone for T₃/T₄ or node-positive disease is 40% to 50% compared with 50% to 60% in those treated with combined radiation and chemotherapy.

One advantage of postoperative therapy is the ability to selectively treat patients at high risk of local failure based on pathologic stage. Several disadvantages have also been identified: the potential of a hypoxic postsurgical bed, larger radiation treatment volume, and the possibility that radiation therapy will be less effective, with potentially higher complication rates due to an increased risk of small bowel in the radiation field.

Several clinical trials have evaluated postoperative radiation therapy with or without chemotherapy. In a 9-year update of the Gastrointestinal Study Group trial, overall survival with postoperative chemotherapy plus radiation therapy was 54%

compared with 27% with surgery alone. The Mayo-North Central Cancer Treatment Group study showed that local control and survival were higher in patients who received combined modality treatment than in those who received postoperative radiation alone. In the National Surgical Adjuvant Breast and Bowel Project R-01 trial, postoperative chemotherapy improved disease-free and overall survival compared with observation and postoperative radiation treatment only; of note, improved overall survival was limited to males in a subset analysis. A trend toward improved local control, but not overall survival, was seen in patients receiving postoperative radiation therapy. Similarly, in National Surgical Adjuvant Breast and Bowel Project R-02, postoperative radiation did not seem to improve overall survival but did improve local control.

The CAO/ARO/AIO trial compared neoadjuvant chemoradiation to adjuvant chemoradiation. This landmark study showed that, simply by altering the sequence of chemoradiotherapy to surgery, improved rates of compliance, local control, sphincter preservation, and acute/late toxicity could be achieved, validating the advantages of preoperative therapy. These findings have led to a new standard of care in the United States in the treatment of rectal cancer.

Targeted Biological Agents in Early-Stage Colon Cancer

At present, standard adjuvant chemotherapy in patients with stage III and high-risk stage II colon cancer consists of an infusional 5-fluorouracil/leucovorin/oxaliplatin combination regimen (FOLFOX). Targeted biological agents, which have proven efficacy in advanced colorectal cancer, are currently being evaluated and hold promise in the adjuvant setting. The anti-vascular endothelial growth factor agent bevacizumab is under investigation in three large phase III adjuvant trials in colon cancer and one phase III adjuvant trial in rectal cancer. The anti-epidermal growth factor receptor agent cetuximab in combination with FOLFOX is under investigation in two phase III adjuvant trials in colon cancer. Definitive results of some of these trials are expected in the next 2 to 3 years.

In patients with stage II disease, there is controversy over which patients should be treated. Although stage II patients experience the same relative risk reduction in recurrence and mortality as stage III patients, the higher baseline cure rate with surgery alone means that the absolute improvement in survival for unselected stage II patients is approximately 4% to 6%. Therefore, adjuvant therapy for all stage II patients is neither mandated nor routine. Some patients with stage II disease may

have poor risk factors, such as poorly differentiated histology, perforation, and low number of assessed lymph nodes; these patients may be more likely to be offered adjuvant treatment. The decision to treat stage II colon or rectal cancer is not an easy one, and nuances in many variables must be taken into account, including choice of treatment, patient input, and the potential for significant short- and long-term toxicity. It is important to avoid the use of unproven drugs in the adjuvant setting and to encourage clinical trial participation.

Cooperative Group Strategies for Assessing Approaches in Early-Stage Disease

Clinical trial design has become increasingly complex due to the variety of options in the integration of multidrug combinations, schedules, and sequences. In that regard, the U.S. Gastrointestinal Intergroup recently developed a portfolio of adjuvant colon and rectal cancer trials that incorporates the therapeutic strategies of advanced disease trials. The National Cancer Institute and Centers for Medicare and Medicaid Services have deemed these studies to be of the utmost importance such that reimbursement is guaranteed by Centers for Medicare and Medicaid Services for Medicare patients who participate. Additionally, the Gastrointestinal Intergroup has consistently supported an environment that allows for innovative opportunities in translational research and has fostered the development of tumor banks, which could potentially enhance efficacy data and further the goal of individualized treatment.

Genetic Testing and Counseling

There are numerous logistical and informational challenges in the delivery of effective genetic counseling and testing, including how and where to obtain such services and uncertain reimbursement. Participants stressed the need to develop more cost-effective genetic tests with more rapid turnaround times and to educate insurers that genetic testing is a valuable form of preventive medicine that could have a sizable effect on the healthcare budget. Participants confirmed the importance of supporting public education programs that explain why genetic counseling should not be problematic for patient confidentiality and also supporting clinical trials that will improve understanding of the relationship between genetic test results and subsequent treatment.

Acknowledgments

We thank InforMEDical Communications, Inc. (Carlisle, MA) for editorial assistance and Continuing Medical Education Sponsorship.