ABSTRACT

Staging of colorectal cancer (CRC) is based on the degree of tumor invasion into tissues of the colon, the number of lymph node metastases, and the presence or absence of distant metastasis. It is particularly important to distinguish between stage II and stage III CRC because patients in stage III most certainly will benefit from chemotherapy, whereas there is considerable debate as to whether it is worth the resources to similarly treat patients in stage II. Several clinical trials have established that only perhaps 5% of patients with stage II CRC benefit from chemotherapy, either because the cancer has been totally removed by resection or the patient is unresponsive to the therapy. Several advances are likely to increase the accuracy of staging. Identification of lymph node metastases is of primary importance. If resources are available to examine all lymph nodes recovered after resection, studies have shown that this will increase the likelihood of finding one or more positive lymph nodes. Current guidelines recommend a minimum of 12 lymph nodes to be assessed per resected specimen in order to have the cancer adequately staged. Identification of sentinel lymph nodes may decrease this workload, allowing for microsectioning of only a few nodes per resection. Genetic screening is becoming increasingly important. At present, loss of chromosome 18q and microsatellite stability are among the most useful markers of patients with higher risk in stage II. Work is continuing on other genetic markers, which, in the future, may further improve our ability to stage these patients.

DIAGNOSTIC TOOLS

Early stage colorectal cancer (CRC) can be curable by surgical resection. Unfortunately, at this stage the cancer is often asymptomatic. The right side of the colon is especially large, allowing tumors to reach an appreciable mass before any obstruction results in noticeable symptoms. As lesions in the ascending colon ulcerate, blood loss in the stool causes patients to present with symptoms of anemia, such as fatigue and palpitations. This has led clinicians to consider a CRC workup for any adult presenting with an iron deficiency anemia, with the exception of menstruating women. There exists a certain inconsistency, however, in preoperative workups in some areas of the United States, suggesting a need to discuss an appropriate staging strategy. There is general agreement among clinicians that a complete colonoscopy is an important preoperative procedure. A complete examination of the colon from the anus to the cecum is possible in 95% of patients with less than a 0.5% complication rate resulting in the detection of 90% to 95% of polyploid lesions. In addition, endoscopic ultrasound (EUS) has increasingly been incorporated into procedures for patients with rectal cancer. Although somewhat operator dependent, EUS is capable of determining the extent to which a tumor has penetrated through the bowel wall, thus contributing to the ability of the clinician to accurately stage the tumor. Lymph node assessment is less accurate by EUS.

Abdominal and pelvic imaging, such as computed tomography (CT), have become common, but their ability to accurately identify early stages of CRC is poor. These studies are most useful for determining the presence or absence of metastatic disease. Whereas chest X rays are often performed, seldom does one see a preoperative chest CT ordered. Positron emission tomography (PET) scans may occasionally be useful for diagnostic purposes; however, in most cases, PET scans do not contribute to the diagnosis. The measure of carcinoembryonic antigen (CEA) protein is useful...
as a baseline study for subsequent surveillance. CEA protein is expressed by over 90% of CRC tumors and presence of CEA in the serum is useful as a marker for metastatic disease. Genetic screening is also underutilized. Hereditary nonpolyposis colorectal cancer (HNPCC) accounts for 3% to 4% of all CRC and can easily be detected as mutations in certain DNA mismatch repair genes. The surgical strategy can change depending on whether the patient has HNPCC.

WHO SHOULD RECEIVE ADJUVANT CHEMOTHERAPY?

Staging clearly plays a critical role in assessing treatment. Patients with stage III CRC, for example, are routinely given adjuvant chemotherapy, whereas patients in stage II are not. The American Joint Committee on Cancer/TNM staging scale is shown in the Table. The T-scale refers to the extent of tumor invasion through the colon wall and clearly correlates with the possibility of metastasis. Lymph node involvement also serves as an important measure of prognosis. Categories include no nodal involvement (N0), 1 to 3 nodes (N1), and 4 or more nodes (N2). The M-scale denotes absence (M0) or presence (M1) of distant metastatic disease. Together the T, N, and M are used to establish the stage of the cancer as shown in the Table.

Lymphovascular invasion (LVI) is another important parameter. Indeed, a recent study presented at the 2006 American Society of Clinical Oncology annual meeting showed LVI to be predictive of metastasis. Perforation and obstruction of the colon are also associated with a poor prognosis. All these factors play into the decision as to whether adjuvant chemotherapy should be given postoperatively.

It is important to note that although a large number of patients are exposed to chemotherapy, only a relatively small number of those patients will benefit from this treatment. In part, this is because of the complete removal of the cancer by the surgeon. Obviously, this group will never benefit from chemotherapy because their cancer has already been cured. The second group will experience a return of the cancer unless it is eradicated by the chemotherapy. As improved efficacy equates to an increased number of cures, this is the highest priority task facing us at this time. At present we cannot distinguish between patients who are cured by surgery and who will benefit from chemotherapy. Additionally, we do not yet know who is more likely to respond to chemotherapy assuming that they still have remnants of the cancer remaining. Another issue is toxicity. Adjuvant chemotherapy for CRC is relatively mild in terms of side effects. Few patients lose much of their hair or experience a debilitating side effect that keeps them from pursuing their daily activities. However, for a few patients chemotherapy has significantly decreased quality of life; thus, we need to address the toxicity issue. Certainly, a great deal of effort has gone into the development of more efficacious chemotherapeutic regimens. There are now several available regimens, and work is under way to develop screening methods to assess which population will most benefit from a specific regimen.

<table>
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<th>Table. Staging of Colorectal Cancer by the American Joint Committee on Cancer (TNM classification)*</th>
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†T-scale measures the extent of tumor spread through the layers of the wall of the colon. T1 = extends into the submucosa; T2 = the muscularis propria; T3 = the subserosa; T4 = spread to nearby tissues.
‡M-scale measures metastasis. M0 = absence of metastasis; M1 = metastasis observed.
For the patient with stage II CRC, one might predict that 3% to 6% will actually benefit (ie, achieve a cure) from chemotherapy. From a population health-care perspective, one might ask if it is a waste of resources to treat this population. Consider the Multicenter International Study of Oxaliplatin/5-Fluorouracil (5-FU)/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial. This study involved approximately 2200 patients of which 40% were stage II and 60% were stage III. The overall benefit for patients in stage II was approximately 3%, whereas the benefit for patients in stage III was approximately 7% as shown in Figure 1. The results of this study have led to the combination of FOLFOX (5-FU, leucovorin, and oxaliplatin) as the standard of care for stage III CRC. Its use in patients with stage II CRC continues to be debated; these patients are still being followed. The relative benefits appear to be holding at 5 years with 3.5% for patients with stage II CRC and 8.6% for patients with stage III CRC (Figure 2). If one considers markers of poor prognosis (defined as T4, and/or bowel obstruction, and/or tumor perforation, and/or poorly differentiated tumor, and/or venous invasion, and/or <12 examined lymph nodes), the numbers for patients with stage II CRC improves somewhat to 5.4% (Figure 2). These small differences indicate the necessity of a large trial to establish their significance. It is estimated that 3000 to 4000 patients would need to be assessed to power a study to establish a significant difference of 3%. This was accomplished with the Quick and Simple and Reliable (QUASAR-1) trial. A total of 3289 patients with stage II CRC were randomized to receive weekly bolus 5-FU/leucovorin or observation only. Five-year recurrence rates in the treatment versus observation arms were 22.2% and 26.2%, respectively (relative risk, 0.78; 95% confidence interval, 0.67–0.91; \( P = .001 \)).

Another ongoing study that is considering patients with stage II CRC is the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial. Here 2709 patients with stage II and stage III CRC were randomized to receive 5-FU/leucovorin or FLOX (5-
FU/leucovorin and oxaliplatin). The complete results have not yet been published; however several interesting findings have emerged. The 5-FU/leucovorin was administered as a bolus and surprisingly, the same benefit was observed as in the MOSAIC trial. The 3-year interim results from this study are a disease-free survival of 71.6% for the Roswell Park arm and 76.5% for the FLOX arm with less neurotoxicity because of the reduced number of oxaliplatin doses.

**Nodal Sampling**

If we could refine the staging process we could better identify the patients with stage II CRC who are high risk. Perhaps the most important criteria currently to be considered is nodal assessment. In a study of 2427 resected T3 tumor specimens, the number of lymph nodes evaluated was compared to the number of positive lymph nodes found and the 5-year survival statistics for the patient population. As the number of recovered lymph nodes increased, the probability of finding a positive lymph node also increased. Given that adjuvant therapy is usually only offered to patients with nodal metastasis, it is of paramount importance to find those metastases if they exist. Figure 3 shows the relationship between the number of lymph nodes recovered and the number of specimens in which metastatic lymph nodes were found. However, the evaluation of so many lymph nodes requires tremendous resources. One new concept that may save much work is that of the sentinel lymph node. The sentinel lymph node is defined as that lymph node to which the primary tumor drains. If any lymph nodes were to become metastatic, one would predict that this would be the first. The technique developed to identify the sentinel lymph node involves the injection of isosulfan blue dye or fluorescein around the tumor. The draining lymph nodes are then stained and can be identified, removed, and carefully sectioned to look for micrometastases. In a retrospective study, Saha et al found that only 7% of the patients who underwent sentinel lymph node mapping had disease recurrence after resection as compared with 25% of the patients who had standard node staging performed. The results are intriguing and warrant further study.

**Molecular Staging Tools**

There exist several potential molecular markers for increased risk. Chromosome 18q is often mutated in CRC and contains the tumor suppressor gene DCC. A study from 1994 performed a retrospective examination of the relationship between loss of chromosome 18q and 5-year survival in patients with stage II and stage III resected CRC. If TNM staging alone was considered, 5-year survival was 74% for patients in stage II and 42% for patients in stage III. However, when the status of chromosome 18q was considered, the numbers changed markedly. The survival rate for patients in stage II with an intact chromosome 18q was 93% and 54% for the group of patients in stage II with a mutated chromosome 18q. Stage III statistics did not change appreciably.

Because HNPCC has been associated with mutations in DNA mismatch repair genes, screening for these mutant alleles will be informative. Additionally, as DNA mismatch repair genes serve as a sort of "spell check" for DNA during replication, loss of this function results in microsatellite DNA instability, which also can be assessed. In some ways, this may be more efficient because there are several potential mismatch repair genes that must be assessed for mutation, any one of which can result in microsatellite instability. Other markers such as p53, k-ras, and thymidylate synthase have been examined in retrospective studies;
at present, only microsatellite instability is associated with better survival, but perhaps less responsive to chemotherapy, in retrospective studies.\textsuperscript{16} Another molecular marker that is receiving attention currently is guanylyl cyclase C (GCC). This gastrointestinal tract-specific enzyme is normally expressed in apical membranes of intestinal epithelial cells and also is overexpressed in colorectal tumors but not in other tissues or tumors.\textsuperscript{17} Polymerase chain reaction detection of GCC has recently been clinically validated as a reproducible measure of lymph node micrometastases and is being used in a prospective clinical trial.\textsuperscript{18}

**APPLICATION OF BIOLOGICAL AGENTS IN STAGE II CRC**

Currently, several clinical trials are in progress focusing on the use of the new biological agents in stage II and stage III CRC. Eastern Cooperative Oncology Group 5202 is a phase III trial comparing FOLFOX4 to FOLFOX4 plus bevacizumab in patients with stage II CRC with loss of chromosome 18q and microsatellite stability. N0147 is a phase III randomized study of a different variant of the FOLFOX regimen (FOLFOX6) with or without the addition of cetuximab. This study is focused on stage III CRC. This will be a fairly large study with approximately 2300 patients accrued. The NSABP C-08 study is comparing FOLFOX6 with or without bevacizumab and will consider patients with both stage II and stage III CRC. Each arm of the study will enroll 1316 patients for a total of 2632. The AVANT study is examining bevacizumab in combination with FOLFOX6 or XELOX (also known as CAPOX [capecitabine and oxaliplatin]) regimens in the treatment of stage III CRC. The 3 arms of the study are FOLFOX6, FOLFOX6 plus bevacizumab, and XELOX plus bevacizumab. Each arm will recruit 1150 patients. Results from this trial will further help us define the role of adjuvant chemotherapy in stage II CRC.

**CONCLUSIONS**

Staging of CRC is of paramount importance because it will determine the course of treatment. Currently, the primary challenge is to determine which patients with stage II CRC are high risk and should be treated with chemotherapy in addition to resection and which patients with stage II CRC can be treated with resection alone followed by observation. This is compounded by the problem that only 3% to 6% of patients with stage II CRC will benefit from chemotherapy as demonstrated by several studies, such as the MOSAIC and QUASAR-1 clinical trials. LVI, perforation, and obstruction all have been shown to correlate with decreased survival and thus, are useful risk factors for the patient with stage II CRC. Improving nodal assessment will improve staging, however, it can be technically challenging and resource consuming. Molecular tumor evaluation is another strategy that may identify patients with high-risk stage II CRC. Loss of chromosome 18q and microsatellite stability have been shown to mark a higher risk population. Molecular testing for GCC also shows promise as a means to identify metastasis and thus, direct the patient with stage II CRC to adjuvant chemotherapy. Currently, the most attractive adjuvant regimen is one combining 5-FU and oxaliplatin, such as FOLFOX. However, several clinical trials are currently examining the role of the newer biological agents, bevacizumab and cetuximab, in adjuvant chemotherapy.

**REFERENCES**


