Current Concepts in the Management of Colorectal Cancer

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INTRODUCTION

Colorectal cancer is the fourth commonest malignancy and the second leading cause of cancer-related deaths in the United States. In the year 2001, there were an estimated total of 135,400 new cases of colorectal cancer.\(^1\) In terms of cancer deaths, this disease was estimated to account for 56,700 deaths in the United States. The lifetime risk of developing colorectal cancer for the American population is 1 in 17 (6%). When age adjusted incidence and mortality of colorectal cancer is evaluated from the SEER data from 1973-1997, a very pertinent finding is a decrease in incidence and decrease in mortality from this disease beginning at approximately 1985. The most plausible explanation for the decrease in incidence in the past two decades has been the effect of appropriate screening for this disease, with colonoscopic removal of precancerous adenomas, and thus prevention of development of colorectal cancer. The explanation for decrease in mortality is also likely related to screening, with the identification of colorectal cancers at an earlier stage, which are more amenable to cure than more advanced lesions; and secondly, improved multimodality therapies including surgery, radiation therapy and chemotherapy. This corresponds with a progressively improved 5-year survival for colorectal cancer, as evidenced by SEER data from 1974-1996, which showed an overall 5-year survival of 50% for this disease in 1974-1976, with an improvement to over 60% in 1989-1996. Colorectal cancer is a preventable disease by appropriate screening and removal of precursor lesions. Ongoing emphasis for routine screening of both average-risk and high-risk patient populations must be encouraged.

COLORECTAL CANCER RISK GROUPS

Colorectal cancer can be stratified into varying risk groups. Seventy-five percent of all colorectal cancers are sporadic, whereas approximately 25% of patients are considered at increased risk for this disease. Two well-recognized syndromes for inherited colorectal cancer are Familial Adenomatous Polyposis, which accounts for 1% of colorectal cancers, and Hereditary Nonpolyposis Colon Cancer, which accounts for approximately 5% of colorectal cancers. Patients with a family history of colorectal cancer are recognized as having an increased risk for this disease. This risk group (Familial Colon Cancer) accounts for 15-20% of colorectal cancers. Inflammatory bowel disease patients are in a high-risk category for this disease, and account for approximately 1% of colorectal cancers.\(^2\) Data from the National Polyp Study\(^3\) has demonstrated that a family history of adenoma is associated with an increased incidence of colorectal cancer in family members and that the incidence is identical regardless of whether the family member had an adenoma or an actual cancer.

Familial Adenomatous Polyposis is an autosomal dominant disease, with over 90% penetrance. Colorectal adenomas, which are the precursor lesions for colorectal cancers, develop in and around puberty. If untreated, colorectal cancer will develop in these patients once they reach approximately age 30. Extra-colonic tumors are prevalent, and include upper GI neoplasms, desmoids, osteomas, thyroid tumors, brain tumors, and other lesions. Hereditary Nonpolyposis Colon Cancer is also an autosomal dominant inherited disease. It demonstrates 70% penetrance, and colorectal adenomas commonly develop once the patients reach 20 years of age, with colorectal cancers occurring commonly in their 40s. Extra-colonic cancers occur in the endometrium, ovary, stomach,
genitourinary tract, small bowel and biliary tract. The Amsterdam Criteria have been proposed to identify patients with Hereditary Nonpolyposis Colon Cancer. These criteria follow the 3-2-1 Rule, in which three or more relatives have HNPCC cancers, one of whom must be a first-degree relative of the other two; two or more generations are involved; and one cancer occurs under age 50. Germ line mutations have been identified in these inherited colorectal cancer syndromes. In Familial Adenomatous Polyposis, the mutations occur in the APC tumor suppressor gene on chromosome 5q. In HNPCC, the mutations are in the DNA mismatch repair genes (MMR) on chromosomes 2, 3, 7.

PATHOLOGY OF COLORECTAL CARCINOMA

The adenoma to carcinoma pathway is now well recognized and accepted as the explanation as to how colorectal cancers develop. The pathologic aspects of colorectal carcinoma have been well recognized with established molecular correlations, in which normal mucosa progresses to development of an adenomatous polyp, which in some cases can progress to an adenoma with low-grade dysplasia, which in turn progress to high-grade dysplasia and eventual invasive adenocarcinoma. These morphologic changes can be correlated with genetic abnormalities. An APC mutation causes normal mucosa to progress to an early adenoma with low-grade dysplasia. A subsequent K-ras mutation correlates with the progression of an early adenoma to an intermediate adenoma with low-grade dysplasia, with a subsequent DCC mutation which promotes progression to a late adenoma with high-grade dysplasia, and then finally a p53 mutation that results in an invasive adenocarcinoma. Much work is currently being undertaken to try to identify the steps in progression of a colorectal carcinoma, from an invasive adenocarcinoma confined to the bowel wall to one that develops lymph node metastasis and/or distant metastatic disease. In general, this is felt to be sequential, from the primary lesion to lymph nodes to distant organs and systemic disease. Various additional genetic abnormalities associated with this progression, such as 13q and 14q losses, and p16 gene abnormalities, have been identified. Other factors include growth factors and their receptors, collagenases and collagenase inhibitors, cell adhesion molecules, and angiogenesis mediators. There are significant prognostic implications of selected gene abnormalities, and clearly the goal is to identify predictors of recurrence in order to help target therapy. Genetic abnormalities that have been identified and are currently undergoing extensive research are transforming growth factor ß1 (TGF-ß1) expression, p53 abnormal expression, microsatellite instability (replication error phenotype), and DCC gene mutation (18q loss).

SURGICAL MANAGEMENT OF COLORECTAL CANCER

The extent of resection for colon cancer is based on the location and the lymphatic drainage of that section of colon. For cecal, ascending colon and hepatic flexure carcinomas, a right hemicolectomy is performed. For mid-transverse colon lesions, an extended right hemicolectomy is performed. For splenic flexure carcinomas, a left hemicolectomy is performed. For descending colon and sigmoid carcinomas, an anterior resection is performed. There has been recent interest in sentinel lymph node mapping, similar to that used for breast carcinoma and melanoma staging. Its applicability for colorectal cancers, however, is not yet justified, as there is no evidence that it actually changes current management. The technique involves injection of a blue dye in close proximity to the primary lesion, then waiting a short time to identify dye deposition in a sentinel lymph node. Studies have demonstrated that a sentinel node can be identified, and that micrometastatic disease can be identified by immunohistochemical staining. However, there has not been any definitive demonstration that patients with micrometastatic disease in the lymph nodes have a different outcome than those patients who do not have micrometastasis. A study by Bilchik et al reported that 1-3 sentinel nodes were
identified in each patient. No non-sentinel node was positive if all sentinel nodes in the same specimen were negative by histopathology. Immunohistochemistry identified occult metastases in 53% of patients whose sentinel nodes were negative by conventional staging techniques. However, the significance of lymph node micrometastasis in colorectal cancer remains debatable. The proponents of sentinel lymph node mapping for colon cancer maintain that a more limited resection might be feasible if the sentinel lymph node is found to be negative. At the present time this modality is experimental, and does not alter the surgical management of colon cancer.

Minimally invasive surgery for colorectal cancer is currently being extensively evaluated. Several retrospective and prospective cohort studies have demonstrated comparability of the extent of resection for colon cancer when comparing laparoscopic assisted techniques to standard open colectomy. Some studies suggest an earlier postoperative recovery and shorter hospital stay, despite a longer operating time. The results of several multicenter randomized prospective controlled trials are being awaited, to establish whether the long-term oncologic outcome is comparable. In the NIH multicenter randomized controlled trial being conducted here in the United States, an accrual of 900 patients has been completed, and it is anticipated that in two years the survival and the recurrence data will be available. A recent quality of life assessment of this NIH trial has been published showing only a very minimal short-term quality of life benefit with laparoscopic assisted colectomy, compared to standard colectomy, at two weeks postoperatively. The authors concluded that laparoscopic colon resection should not be offered to patients with colon cancer until the results of randomized controlled trials establish safety and efficacy.

Conventional surgery for rectal cancer has been evolving, based on the known extent of lymphatic spread from a primary rectal cancer. Total mesorectal excision has become the standard of care for mid- and distal rectal cancers, using a sharp dissection technique to preserve the visceral fascial envelope, thus incorporating all the regional areas of potential lymphatic spread within the mesorectum. Radial or circumferential margins have been demonstrated to be of utmost importance in minimizing local recurrence, as opposed to emphasis on distal rectal margins in years gone by. Furthermore, the surgeon has been documented to be an independent prognostic factor on multivariate analysis in several studies evaluating the outcome following rectal cancer surgery. Sphincter-saving procedures can be performed on the majority of patients with rectal cancer, with various techniques for rectal reconstruction. The simplest of the sphincter-saving procedures is a local excision, in which a full-thickness disk of the rectal wall is excised, incorporating the rectal cancer. This operation addresses only the primary lesion, and does not address the potential for lymph node metastasis. Therefore, preoperative staging is extremely important in order to accurately select patients who are best suited to local excision. Current data would suggest that the ideal candidates for local excision are T1, well-to-moderately differentiated rectal cancers within 8 cm of the anal verge, measuring less than 3 cm in diameter, in which there are no adverse histologic features. The adequacy of local excision for rectal cancer has been reexamined by two recent reports from the University of Minnesota. The recurrence rate analysis for T1 and T2 cancers resected locally with 54-month follow-up indicated that the local recurrence rate for T1 lesions was 18%, and 37% for T2 lesions. Survival rate for T1 lesions was 98%, and 89% for T2 lesions. A subsequent report compared recurrence and survival outcomes of patients treated with local excision and radical surgery. The 5-year local recurrence rate after local excision was 28%, compared to 4% after radical resection; and the estimated 5-year survival after local excision was 69%, compared to 82% after radical surgery. This was statistically significant for T2 lesions. These two reports raise significant concerns regarding the use of local excision as curative therapy for early rectal cancer, and the role of local excision is currently being reevaluated. A study from Memorial Sloan-Kettering Cancer Center shows a similar high local recurrence rate after
local excision, and documents that the addition of adjuvant chemoradiation does not prevent such local recurrence. Furthermore, only 25% of patients were salvaged by surgery for their recurrent disease.

Sphincter-saving radical procedures using a coloanal anastomosis have been demonstrated to be oncologically comparable to the gold standard of abdominoperineal resection. Autonomic nerve preservation surgery is inherent in the total mesorectal excision technique, and sexual function can be preserved in close to 90% of male patients under age 60.

Surgery for the hereditary forms of colorectal cancer differs in the extent of resection and the timing of surgery. For Familial Adenomatous Polyposis, the impact of surveillance and surgery on survival has been well documented. Recognized family members should undergo screening beginning at about age 10, and once the diagnosis of FAP is established in a given family member, prophylactic colectomy is recommended. Selected patients can be managed by a total colectomy with ileorectal anastomosis, followed by careful surveillance of the retained rectum. Other patients are best managed by a total proctocolectomy with ileoanal pouch reconstructive procedure. For Hereditary Nonpolyposis Colorectal Cancer, the overall risk of cancers of the colon and rectum approaches 80%. When an initial colorectal cancer is diagnosed in an HNPCC family member, a subtotal colectomy is the recommended procedure of choice. In female patients consideration should be given for a prophylactic hysterectomy, because of the high incidence of endometrial cancer.

ADJUVANT THERAPY FOR COLON CANCER

Adjuvant chemotherapy for Stage III colon cancer is well established, with evidence for an overall survival benefit in node-positive patients. There are several ongoing development strategies for adjuvant chemotherapy for colon cancer. In general, adjuvant treatment follows definitive surgery, and is given with curative intent. The first successful adjuvant regime that led to the use of postoperative chemotherapy in Stage III colon cancer patients was based on a study of 929 patients with Stage III colon cancer, randomized to postoperative chemotherapy vs. observation alone. The chemotherapy used was 5FU/levamisole. Five-year disease-free survival of 61% vs. 44% (p<.0001) was reported. Current development strategy is ongoing to identify new agents and to establish activity initially in Stage IV metastatic disease. Once it is established that a single agent has activity, then active combinations of drugs will be developed and validated in randomized trials, with the intent of moving active combinations into the adjuvant setting for Stage III disease in the hope of increasing cure rates. One example of this strategy has been the use of irinotecan (CPT-11) in colorectal cancer. This drug was found to have 17-32% response in previously untreated patients, and a 13-23% response in 5FU refractory patients. A Phase 3 randomized trial of metastatic colorectal cancer by Saltz et al studied patients randomized to CPT-11 alone vs. CPT-11 with 5FU/leucovorin vs. 5FU/leucovorin alone. The triple-drug combination demonstrated a significantly improved response: 39% vs. 21%, with a statistically significant increase in survival in the Stage IV patients.

Recent technological advances, along with the discovery of the role of growth factors in modulating cell proliferation and differentiation, have led to the development of new therapeutic agents for the treatment of cancer, targeting a patient population that may benefit from anti-receptor specific therapy. One such example is the development of C225 (cetuximab), which is a chimeric monoclonal antibody directed against the epidermal growth factor receptor (EGFr). This antibody has been demonstrated to have cytostatic activity in preclinical studies. In a study in CPT-11 refractory patients who are found to be EGFr-positive, a 17% major response rate was documented when C225 was added to CPT-11 therapy.
ADJUVANT THERAPY FOR RECTAL CANCER

Adjuvant therapy for rectal cancer is given to improve local control and overall survival, to enhance sphincter preservation and function, and to improve quality of life. There have been five randomized trials evaluating postoperative chemoradiation for T3N0 or node-positive rectal cancer, documenting an improvement in local recurrence and in overall survival compared to surgery alone. Whether adjuvant chemoradiation for rectal cancer should be given preoperatively or postoperatively remains somewhat controversial, although there is a trend towards using the therapy preoperatively, for a number of reasons. The potential advantages of using preoperative therapy are biological, with decreased potential for seeding and increased radiosensitivity. There is also evidence to substantiate that the use of preoperative therapy can enhance sphincter preservation surgery and increase resectability of locally advanced cancers. Furthermore, there appears to be a decreased potential for acute side effects with the use of preoperative adjuvant therapy, compared to using it postoperatively. Approximately 10% of patients who undergo preoperative chemoradiation will sustain a complete pathologic response. However, the data from Memorial Sloan-Kettering indicates that it is very difficult to determine this clinically prior to surgery, and that in patients who appeared to have a complete clinical response, some 70% still had microscopic residual disease. Hence, the recommendation for radical surgery following preoperative chemoradiation is still the therapy of choice. Future studies will determine the potential predictive ability of markers for the response to adjuvant chemoradiation for rectal cancer. These potential markers include thymidylate synthase, p53, Ki67, microsatellite instability, bcl-2, and DCC. Currently, results are conflicting as to the predictive capability of these markers. New chemotherapeutic agents in rectal cancer include CPT-11, oxaliplatin, UFT, tolmuex, capecitabine, and targeting agents including C225 and anti-VEGF, as well as antibodies such as 17-1a.

PREOPERATIVE STAGING OF RECTAL CANCER

The preoperative staging of rectal cancer with currently available modalities is very important in selecting optimal treatment. The rationale for preoperative staging is to maximize cure, to minimize mortality and morbidity by perhaps selecting less radical surgical procedures, and to allow participation in controlled trials where preoperative staging allows comparable comparison of treatment regimens for similarly staged tumors. The underlying assumption is that treatment will vary with stage of disease. Preoperative staging of rectal cancer is performed to try to identify the early confined lesion, for which local therapy may be appropriate; and, at the other extreme, to identify the locally advanced lesion, which may benefit from preoperative adjuvant chemoradiation. The modalities that we have available are clinical assessment, endorectal ultrasound, CT imaging and MRI imaging. CT scanning is useful for identification of distant metastatic disease, but it does not show the layers of the rectal wall, nor is it reliable for determining lymph node metastases. Conventional MRI is comparable to CT scanning; however, the endorectal MRI coil does allow visualization of the layers of the rectal wall, and is comparable to endorectal ultrasound in depth of wall staging. Endorectal ultrasound imaging is the simplest and most accurate modality for staging depth of wall invasion. It can be used in the clinic setting, and is of value as an extension of the physical examination. In a comparative systematic review of articles evaluating the efficacy of staging modalities for rectal cancer, identified endorectal ultrasound as the most accurate at detecting bowel wall penetration, with an overall accuracy of 87%, compared to 84% for MRI with endorectal coil, and 82% and 73% respectively for conventional MRI and CT scanning. However, for detecting lymph node status endorectal ultrasound accuracy was only 74%; whereas MRI with endorectal coil was the best at 82%.
Endorectal ultrasound imaging is the simplest and most accessible staging modality, and is the current procedure of choice for the preoperative staging of rectal cancer.

SCREENING AND PREVENTION

The prevention of colorectal cancer is an achievable goal. Screening for colorectal cancer and adenomatous polyps should be offered to all men and women without risk factors beginning at age 50. Furthermore, patients identified with increased risk for this disease should undergo appropriate screening on a regular basis. For patients with a family history of colorectal cancer or adenoma, screening is recommended beginning at age 40 or 10 years before the age of diagnosis of the family member with this disease. Currently recommended screening modalities include annual fecal occult blood testing with flexible sigmoidoscopy every five years, or colonoscopy every five years or double contrast barium enema with proctoscopy or flexible sigmoidoscopy every five years. Colonoscopy is the screening method of choice in many centers today and is the preferred method for patients at increased risk for this disease. Mortality reduction from various forms of colorectal screening is well established. Fecal occult blood testing on a yearly basis has been shown to reduce mortality from this disease by 33%. Flexible sigmoidoscopy on an every-five-year basis has been demonstrated to reduce mortality by 30%. The estimated combined mortality reduction with these two modalities is in the vicinity of 50%. The National Polyp Study demonstrated a significant decrease in the incidence of colorectal cancer following colonoscopic polypectomy. There is increasing data to suggest that, for patients in the average-risk category, an initial colonoscopy followed by no further surveillance results in a cumulative incidence of colorectal cancer identical to that of initial colonoscopy followed by regular surveillance colonoscopy. Both of these options show a significantly diminished incidence of colorectal cancer, compared to the non-screened population. This has led to a proposal for the average risk population of a once-in-a-lifetime screening colonoscopy, in which a colonoscopy negative for any adenoma results in no further screening for that individual. If a patient is found to have an adenoma, then surveillance colonoscopy after removal is recommended. Virtual colonoscopy is a new modality that uses CT scan colography to evaluate the colon for polyps or neoplasms. This modality shows considerable promise as a screening tool for colorectal neoplasms. The data to date suggests that the detection of colorectal polyps and cancer by helical CT with 3-dimensional reconstruction approaches that of conventional colonoscopy and exceeds that of double-contrast barium enema. In a prospective study in which 100 patients at high risk for colorectal neoplasm underwent virtual colonoscopy followed by immediate conventional colonoscopy, the authors concluded that both modalities had a similar efficacy in the detection of polyps 6 mm or more in diameter. The advantage of conventional colonoscopy is that this can be completed as a one-stage procedure, and polyps can be removed if they are found. However, the advantage of virtual colonoscopy is that it is a less invasive procedure, and in instances where a stenotic lesion precludes completion of conventional colonoscopy, or colonic anatomy limits a complete exam, virtual colonoscopy can be very efficacious.

The future approach to colorectal cancer prevention will be with the use of genetic testing to identify which patients are at risk of developing polyps and eventual cancers. Currently, patients identified as having a hereditary form of colorectal cancer are counseled with respect to the potential value of genetic testing to identify a mutation. If the mutation can be identified it has value in determining the risk of other family members for developing this disease.

Colorectal cancer is a preventable disease, and every effort should be made to encourage routine screening of the average-risk population, as well as those with an increased risk for this disease.
REFERENCES


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