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Perspectives on the treatment of colorectal carcinoma

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Abstract

Colorectal cancer includes cancerous growths in the colon, rectum and appendix. With 655000 deaths worldwide per year, it is the third most common form of cancer and the second leading cause of cancer-related death in the Western world. Advances in imaging, genetics, molecular diagnostics, surgical techniques and chemotherapy are now making significant gains in our ability to prevent, diagnose, and treat this serious disease. This article reviews some of these recent successes and shares a vision of future care based on current research.

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INTRODUCTION

Colorectal cancer includes cancerous growths in the colon, rectum and appendix. With 655000 deaths worldwide per year, it is the third most common form of cancer and the second leading cause of cancer-related death in the Western world. Advances in imaging, genetics, molecular diagnostics, surgical techniques and chemotherapy are now making significant gains in our ability to prevent, diagnose, and treat this serious disease. This article reviews some of these recent successes and shares a vision of future care based on current research.

CHEMOPREVENTION

Although colorectal cancer (CRC) is one of the most preventable forms of cancer, it remains a major cause of morbidity and mortality, and is the second leading cause of cancer death, representing a major public health concern in all developed countries. Most CRCs can be treated successfully if detected early by screening programs. Our improved understanding of colorectal carcinogenesis has facilitated the development of interventions designed to interrupt the progression of normal epithelium to cancer. Chemoprevention refers to use of synthetic or naturally occurring compounds to prevent the development of precancerous lesions (i.e. adenomatous polyps) or to reverse or delay their progression to invasive cancers. CRCs are thought to arise as a result of a series of molecular, biochemical, and histopathologic changes that transform normal colonic epithelial cells into a neoplasm, with an adenomatous polyp as an intermediate step in this process. This is a long, chronic process, therefore the window for intervention is long, possibly even decades^[1]. Molecular analyses of colorectal adenomas and carcinomas have led to a genetic model of colon carcinogenesis in which the development of cancer results not from any single genetic event but from the accumulation of a number of genetic alterations. Primary prevention strategies seek to prevent the formation of CRC in an otherwise healthy

population. Those individuals targeted may have not only predisposing genetic or environmental features, but also certain lifestyle risk factors, such as a lack of physical exercise, smoking, or alcohol intake. Secondary prevention involves patient populations who have presented with a known pre-malignant lesion or lesions, and subsequent prevention of the progression of these precancerous lesions into CRC. Finally, tertiary prevention focuses on the prophylaxis of secondary primary tumors in patients cured of their initial CRC. Chemoprevention trials have focused on these populations and include dietary or pharmacologic interventions as well as the use of nutrients in order to suppress or reverse the carcinogenic process. The best candidates for chemo-prevention include those individuals at high risk for development of CRC, such as those with a previous history of colorectal adenomas or carcinomas, those with familial adenomatous polyposis (FAP), and those with metabolic syndromes, especially with abdominal obesity and insulin resistance^[2]. New issues regarding the theoretical and clinical basis of chemo-prevention, however, have emerged, and questions regarding cardiovascular safety and other therapeutic indices have recently come up as barriers to the use of, for example, selective cyclooxygenase-2 inhibitors^[3]. Substantial evidence has shown that several drugs could have chemopreventive benefit. Chemoprevention clinical trials have shown no benefit with fiber or antioxidant interventions. Current data are insufficient to support the use of HRT to reduce the risk of CRC. Use of 5-ASA, UDCA, statins, calcium, vitamin D, folate, and selenium as chemopreventive agents seems to be promising, and further clinical trials will help to elucidate their chemopreventive potential^[4], and it is important that bacteria microflora modulates gut environment and mucosal immunity, and immune regulation (both at local and systemic level) in cancer development^[5]. Any protective benefit must be balanced against the potential side effects of the long-term ingestion of any putative chemopreventive agent. The risk (i.e. gastrointestinal complications) of regular use of ASA or conventional NSAIDs may outweigh the potential benefits in preventing CRC in populations at low risk. Chemoprevention cannot yet be accepted as standard medical practice. Chemoprevention should not replace a periodic fecal occult blood test (FOBT) and colonoscopic surveillance, as well as lifestyle modifications in view of known risk factors, such as reduction in the intake of red meat, appropriate physical exercise, smoking cessation, or weight control. Future studies will have to clarify the role of chemopreventive agents in CRC^[6].

NEW CRC SCREENING TECHNOLOGIES

There are now multiple CRC screening tests that vary in their ability to detect the different stages in the adenoma to carcinoma sequence. The original guaiac-based CRC test (Hemoccult II) was used to detect CRC at an early stage. Most of the newer tests have at least some capacity to

detect the larger adenomas and thus reduce CRC incidence as well as mortality. The different types of CRC screening tests are used according to the requirements of different stages of intervention, degree of invasiveness, frequency of repeat testing, and level of acceptance by patients. FOBT is the only CRC screening approach demonstrated to be effective in randomized controlled trials^[7]. Depending on whether the tests were done biennially or annually, and whether they were rehydrated or not, FOBT was associated with a 15%-33% reduction in CRC mortality, and a 17%-20% reduction in CRC incidence. The guaiac tests use the peroxidase activity of heme or hemoglobin as an indicator of occult blood. The FIT is based on detection of human globin. These tests were developed as a quantitative test for occult blood in the stool that did not require the 3 d dietary restrictions of the Hemoccult II test. FOBT, although not as sensitive for colorectal adenomas as colonoscopy, CT colonography or flexible sigmoidoscopy, offers the advantage of being noninvasive, and convenient for individuals. Colonoscopy was first introduced in the 1970s as a method to visualize the entire colon^[8]. In 1973, Wolff *et al*^[9] demonstrated the feasibility of colonoscopic polypectomy that initiated the use of colonoscopy as both a diagnostic and therapeutic tool. Fiberoptic colonoscopes were replaced by digital video-endoscopy that enhanced visual detection of polyps and provided a record of the reach to the cecum, postpolypectomy site, and cleanliness of the bowel. Technical improvements have facilitated polyp removal and maneuverability within the colon and rectum. Colonoscopy can be used as the primary screening tool or as the diagnostic and therapeutic tool after a positive FOBT, flexible sigmoidoscopy, or CTC test. The key conceptual basis for CTC—also called “Virtual Colonoscopy” or VC—arose over a decade ago, when it was recognized that thin-slice contiguous abdominal CT images could be reconstructed in software to simulate visualization of the lumen of the colon and create a “fly-through” display presenting polyps as prominent irregularities. It took a dozen years for this approach, combined with other improvements, to reach maturity. Between 2000 and 2002, commercial multirow detector CT scanners advanced from 4-row detector devices to 64-row assemblies, enabling high-speed imaging of the total abdomen within a single breath-hold, thus nearly eliminating motion artifacts that had bedeviled earlier efforts. Hardware and software innovations also made multiplanar displays visually-compelling 3D dynamic simulations possible. Magnetic resonance (MR) imaging is an accurate method of predicting the possibility of achieving a surgically clear circumferential resection margin (CRM), preventing incomplete surgical resection of the tumor, which will eventually increase the risk of local recurrence and allow a better chosen selection of patients for neo-adjuvant treatment. In addition, the diffusion-weighted MR imaging yields better diagnostic accuracy than the use of conventional MR imaging alone in the evaluation of patients with locally advanced rectal cancer^[10].

Fecal DNA testing represents a new noninvasive approach to CRC screening. The approach has been made

possible by elucidation, over the last 2 decades, of the molecular “pathway” or changes that occur as colon mucosa progresses from normal tissue to adenoma and to CRC. These changes provide “targets” that an assay can be designed to detect. Simultaneous technological advances have allowed human DNA to be separated and purified from stool and to be amplified and analyzed. An approach that measures DNA in stool has at least a theoretical advantage over an approach that measures bleeding, like FOBT. The possible theoretical advantage of stool DNA testing is that, because cancer is a disease of multiple mutations, a stool DNA assay might be made “sensitive enough” if the right markers can be discovered and measured. The first-generation DNA assay that was tested included multiple mutations of the *APC*, *K-ras*, and *P53* genes that are in the “pathway” described by Vogelstein *et al*^[11] along with BAT-26, a marker of mismatch-repair pathway tumors^[12]. In the future, the potential usefulness of stool DNA testing may be affected by different factors such as sensitivity, specificity, and commercial cost.

CHEMOTHERAPY

Despite many recent therapeutic advances CRC remains a major problem throughout the world, affecting close to 1000000 people worldwide, with half of them dying within 10 years of surgery. Significant management advances in the adjuvant and advanced settings have been presented, thus improving our understanding of the biology of the disease, and allowing better individualization of patient treatment.

Among the most interesting advances are the findings of a study showing that K-RAS mutations were associated with shorter progression-free survival (PFS), and that patients with colon cancer expressing a wild-type form of the KRAS gene respond better to epidermal growth factor receptor (EGFR) inhibitors than those in whom KRAS is mutated^[13]. Most notably, and with immediate effect, the European Medicines Agency has restricted the use of cetuximab as a first-line treatment for patients with colon cancer to those whose tumors have the wild-type KRAS gene.

Adjuvant treatment

Two important abstracts from the National Surgical Adjuvant Breast and Bowel Project (NSABP), focused on adjuvant chemotherapy. NSABP C-07^[14] enrolled over 2400 patients after radical surgery. They received either a weekly schedule of 5-fluorouracil (5-FU; 500 mg/m² bolus) followed by folinic acid (FA; 500 mg/m²) weekly for 6 wk repeated three times, or the same combination given with intravenous oxaliplatin, 85 mg/m², on days 1, 15 and 28 (the FLOX regimen). In the NSABP C-08 trial, 2700 patients with CRC were assigned randomly to bevacizumab or a placebo, in addition to oxaliplatin-based chemotherapy. This trial reported the safety of bevacizumab administered with chemotherapy after radical surgery. The CPT-GMA-301^[15] study evaluated postoperative irinotecan combined with 5-FU (the FOLFIRI regimen) versus 5-FU in patients

with radically resected liver metastasis and no evidence of extrahepatic spread, who had not received preoperative chemotherapy. This latest negative trial shows that irinotecan-based regimens are not effective in the adjuvant setting. After potentially curative surgery, irinotecan does not yet have a proven role.

Advanced disease

Using Oxaliplatin and cetuximab in first-line therapy treatment of metastatic colorectal cancer (OPUS)^[16], a first-line randomized phase II trial enrolled 340 patients who received either FOLFOX alone or with cetuximab. The primary endpoint response rate was higher in those patients receiving the combination treatment, although this did not reach statistical significance, and did not impact on PFS. The development of EGFR inhibitors has influenced the field of targeted therapeutics significantly. Unfortunately, the benefits of EGFR inhibitors are limited by several drug resistance mechanisms, which include KRAS mutations^[17]. Analyses of KRAS status in relation to efficacy showed that patients with KRAS wild-type tumors had significantly better outcomes with FOLFOX and cetuximab than with FOLFOX alone. In contrast, those with KRAS-mutated tumors did significantly worse when cetuximab was added to chemotherapy.

In the EVEREST trial, patients were treated with first-line irinotecan and cetuximab then randomized either to continue standard dose cetuximab or to receive dose-escalated cetuximab, in the absence of clinically significant skin toxicity, after 3 wk of treatment^[18]. Several key findings came out of this. Firstly, patients with wild-type KRAS had better outcomes in terms of response rate and PFS, than those with KRAS-mutated tumors had. Secondly, escalating the dose of cetuximab appeared to enhance efficacy only in patients with KRAS wild-type tumors. In conclusion, skin toxicity and KRAS wild-type status were independent predictors of better outcomes in patients receiving cetuximab. Dose escalation did not overcome the adverse impact of having a KRAS-mutated tumor.

Taken as a whole, these data represent a major milestone in our ability to personalize therapy and increase the cost-effectiveness of treating patients with advanced CRC using anti-EGFR antibodies. KRAS testing represents the first predictive biomarker that differentiates those patients who are likely to respond to EGFR inhibitors from those who are not.

Although the mechanism of action of VEGF antibodies is still a subject of investigation and study, the anti-VEGF antibody bevacizumab has been approved for the treatment of various solid cancers, including colorectal cancer. As bevacizumab has been integrated into the treatment of many different types of cancers, the development of bevacizumab-resistant tumors has become more common. Recent studies show that targeting other angiogenesis-signaling pathways such as platelet-derived growth factor-C, Bombina variegata peptide 8 and VEGFR-3 may lead to enhanced response in anti-VEGF resistant tumors^[19]. In the future, tailored treatments

consisting of combinations of chemotherapy, other targeted therapies and anti-angiogenesis agents will hopefully result in better patient outcomes.

Prolonged administration of oxaliplatin is associated with cumulative peripheral neurosensory impairment, and the best strategy to counteract this dose-limiting toxicity remains unclear. Two trials' abstracts addressed the question and tested the putative neuroprotective role of calcium/magnesium supplementation. Unfortunately, both trials closed prematurely and definitive conclusions are hard to draw. These data do not show any deleterious effect of calcium/magnesium supplementation in patients receiving oxaliplatin-based chemotherapy. Indeed, such supplementation may reduce neurotoxicity. Nevertheless, in the authors' opinion, with data from fewer than 300 patients, calcium/magnesium supplementation cannot be recommended.

RESECTION MARGINS IN MODERN RECTAL CANCER SURGERY

At present, the preferred treatment for rectal cancer is low anterior resection with total mesorectal excision and sphincter preservation. Complete removal of the tumor's lymphatic and vascular pad with free resection margins has led to a reduction in rates of local recurrence and improved disease-specific survival. In addition to considering the distal and proximal margins from the tumor edge, for an optimal outcome, it is essential to consider distal mesorectal spread and the circumferential mesorectal margin.

Distal resection margin

The removal of lower rectal tumors with sphincter preservation was made possible by the introduction of surgical staplers, and revision of the traditional 5-cm resection margin. Reports in the 1990s that intramural submucosal spread, noted in 40% of patients, extended for more than 1 cm distally in only 4%-6% of cases, led to the general acceptance of a 2-cm distal margin as adequate. Others showed that distal margins even smaller than 2 cm did not increase local recurrence rates or compromise 5-year survival^[20]. To preserve the sphincter in patients with ultra-low rectal cancer, Schiessel *et al*^[21] introduced the technique of transanal resection of part or the entire internal anal sphincter, whereby bowel continuity could be restored with proper distal margins. Using intersphincteric resection in 92 patients with a tumor at 1.5-4.5 cm (mean 3 cm) from the anal verge, Rullier *et al*^[22] achieved negative margins in 98% of cases; local recurrence was found in 2%. Factors associated with distal tumor spread beyond 1 cm consist of advanced stage at diagnosis and histologically aggressive disease, namely, poorly differentiated cancer and lymphovascular and perineural invasion. These factors also predicted poor prognosis, regardless of the length of the distal margin. A National Cancer Institute (NCI) Expert Panel Guidelines series published in 2000, recommended a distal margin length of 2 cm as ideal, with margins of 1 cm being acceptable in low rectal tumors^[23].

Distal mesorectal margin

Heald *et al*^[24] pioneered the use of TME, and reported distal mesorectal spread of 4 cm from the distal tumor edge. Hida *et al*^[25] noted that in patients with pT3 and pT4 rectal cancer, the extent of distal mesorectal spread was related to tumor location. The longest distance to a metastatic node was 2 cm. in carcinoma of the rectosigma, 4 cm. in carcinoma of the upper rectum, and 3 cm. in carcinoma of the lower rectum. They therefore concluded that a mesorectal margin of at least 5 cm. is required in the surgical treatment of locally advanced rectal cancer. They postulated that blockage of the upward lymphatic flow by the locally advanced cancer produced a downward spread in the mesorectum. They also suggested a 4-cm. mesorectal margin for adequate oncologic resection.

CRM

The CRM, also termed the radial resection margin, corresponds to the non-peritonealized surface of the resection specimen created by dissection of the subperitoneal aspect at surgery. The term CRM is specific to rectal tumors (and does not apply to large intestinal cancers in general). The posterior CRM is triangular, and runs up towards the sigmoid mesocolon; the anterior CRM is located in the most distal aspect of the specimen. The preoperative identification of patients at high risk of a positive CRM prior to surgery has improved with advances in magnetic resonance imaging (MRI) techniques. Recent data from the prospective, multicenter MRI and rectal cancer european equivalence study confirmed the accurate prediction of both T stage and CRM clearance of 1 mm. of the resection margin using MRI. The accurate determination of the CRM status is essential, because it is the single most important factor for predicting the risk of local recurrence in patients with rectal cancer. A positive CRM is defined as continuous or discontinuous tumor extension, or the presence of a positive lymph node < 1 mm. from the radial, nonperitonealized soft tissue edge. A positive CRM is associated with higher disease stage, higher histology grade, and tumor infiltration^[26]. A radial margin of less than 1 mm. was predictive of an increased risk of distant metastases (37% *vs* 15%) and shorter survival (70% *vs* 90%). Other factors directly related to a positive CRM are the surgical technique used, and the tumor location. The CRM was found to be positive in 7.3% of 1113 patients after TME or PME compared to 17% of 2450 patients after conventional blunt rectal dissection. Others reported that lower and anterior rectal tumors are at greater risk of a positive CRM, with a correspondingly dismal prognosis. This finding might be explained by the thinner mesorectum in these locations. Bernstein *et al*^[27] studied 3194 patients with known CRM status, and made the conclusion that a CRM of 2 mm. or less had an impact on the prognosis of T2 and T3 tumors located 6-15 cm above the anal verge, but not on lower tumors. A CRM of 2 mm. or less confers a poorer prognosis, and patients should be considered for neoadjuvant treatment.

ENDOSCOPIC SUBMUCOSAL DISSECTION

Endoscopic submucosal dissection allows en-bloc resection of a lesion, irrespective of the size of the lesion^[28]. Endoscopic submucosal dissection (ESD) has been established as a standard method for the endoscopic ablation of malignant tumors in the upper gastrointestinal (GI) tract in Japan^[29].

Although the use of ESD for colorectal lesions has been studied *via* clinical research, ESD is not yet established as a standard therapeutic method for colorectal lesions because colorectal carcinoma has unique pathological, organ-specific characteristics that differ radically from those of the esophagus and stomach, and scope handling and control is more difficult in the colorectum than in the upper GI tract. Depending on the efficacy of endoscopic mucosal resection (EMR) and the clinico-pathological characteristics of the colorectal tumor, the proposed indications for colorectal ESD are as follows: (1) lesions difficult to remove en bloc with a snare EMR, such as nongranular laterally spreading tumors (particularly the pseudo depressed type), lesions showing a type VI pit pattern, and large lesions of the protruded type suspected to be carcinogenic; (2) lesions with fibrosis due to biopsy or peristalsis; (3) sporadic localized lesions in chronic inflammation such as ulcerative colitis; and (4) local residual carcinoma after EMR. Saito *et al*^[30] treated a total of 400 patients for 405 lesions with ESD. The en-bloc resection rate was 87% and the curative resection rate was 86%, and the perforation rate was 3.5%. ESD is a feasible technique for treating large superficial colorectal tumors because it provides a higher en-bloc resection rate and is less invasive than surgical resection. It also provides precise histologic information^[31]. Colorectal ESD is currently in the development stage, and a standard protocol will be available in the near future^[32].

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