Colon Cancer: What's New?

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ABSTRACT

Colorectal cancer is the third most common cancer. Standard colonoscopy is the first-tier screening method. However, other non-invasive tests have shown high cancer detection rates. The age when screening is started is controversial: the U.S. Preventive Service Task Force (USPSTF) and the American College of Physicians (ACP) recommend the starting age of 50 while the American Cancer Society (ACS) recommends 45. In 2021, the American College of Gastroenterology (ACG) revised the guideline of the first screening age from 45-years-old to 50-years-old. A recent study confirmed that the risk of colorectal cancer is lowered by a high fiber diet, low red meat intake, and consumption of yogurt. The detection of specific molecular and genetic characteristics of each patient's cancer cells is the utmost important component of precision medicine. Many biomarkers of cancer cells are discussed along with their inhibitors. A recent study showed that three-month adjuvant chemotherapy is not inferior to six-month chemotherapy.

INTRODUCTION

Colorectal cancer is the third most common and second lethal cancer in the U.S., and its incidence is gradually decreasing, although the incidence among younger age groups has increased recently, especially in the left side of the colon and rectum.^{1,2}

Colorectal cancer starts from adenomatous polyps, but hyperplastic polyps have no risk of cancer development. The adenomas have three histological subtypes: tubular, villous, and tubulovillous adenomas. About 80% of all colonic adenomas are tubular adenomas, 5–10% are villous, and about 10% are tubulovillous adenomas. Approximately 5% or less of all adenomas progress to cancer over 7–10 years. The risk is higher for adenomas with high-grade dysplasia, larger size (>10 mm), or villous components.³

COLORECTAL CANCER SCREENING

There is a controversy about when colorectal cancer screening should be started. The U.S. Preventive Service Task Force and American College of Physicians recommend colorectal cancer screening beginning at age 50,^{4,5} but the American Cancer Society urges that regular screening begins at age 45. In 2021, the American College of Gastroenterology (ACG) updated the guideline and now recommends the starting age of 45.⁵ ACG, considered the fact that the incidence of colorectal cancer in younger people (age ≤50) has been increasing.¹

Discontinuation of screening should be considered when persons up to date with screening (particularly colonoscopy) reach age 75 or have less than ten years of life expectancy. The American Cancer Society

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recommends that for people ages 76–85, the decision to be screened should be based on a person's preferences, life expectancy, overall health, and prior screening history.⁴

Screening for higher risk groups starts at earlier ages

African Americans: age 45; strong family history: age 45; patients with inflammatory bowel disease: eight years after the diagnosis; patients with adenomatous colon polyps: three–five years after diagnosis; Lynch Syndrome: age 25; familial polyposis syndrome: ages 10–15.

Screening methods

Colonoscopy (Figure 1) every ten years is the preferred screening test for average-risk people. An annual Fecal Immunochemical Testing (FIT) is recommended for patients unable or unwilling to have a colonoscopy. FIT has almost similar detection rates compared with colonoscopy: more than 73–88% sensitivity and over 90–98% specificity in detecting colorectal cancer.⁶ Because FIT detects human blood (globin) in the stool, dietary restriction to avoid red meat is unnecessary. The Stool Guaiac test can cause false-positive test results as it also detects animal blood. It is largely abandoned as a screening test because of its low sensitivity and specificity. Multitarget stool DNA testing (MT-sDNA: Cologuard®) combines fecal markers for hemoglobin and DNA mutation and methylation. Screening is done every three years, and when compared with FIT, it has a higher single-application sensitivity but a lower specificity because of more false-positive results.⁷ MT-sDNA (Cologuard®) is an expensive test costing \$500-600.

Computed tomography (C.T.) colonoscopy (virtual colonoscopy) (Figure 2) is a non-invasive screening test compatible with standard colonoscopy in detecting colorectal cancer. It is suitable for elderly patients with underlying morbidity and is done every five years. Patients require bowel preparation or swallowing to tag the stools in the bowel and digitally remove them for accurate testing.

Capsule colonoscopy (Figure 3) every five years is a third-tier screening option^{4,6} but is not approved by the FDA to screen for colorectal cancer. The FDA allowed capsule colonoscopy when standard colonoscopy was incomplete. The patient swallows a capsule containing a video camera. An antenna and recorder attached to the patient's body

FIGURE 1.

Standard Colonoscopy

record the images until the capsule passes through the bowel, typically taking 5–8 hours. The NHS England started a trial to have the capsule colonoscopy at home during the COVID-19 pandemic.⁸ If any of the above non-invasive screening tests showed abnormal findings, a standard colonoscopy must be done within three months.

RISK FACTORS AND PROTECTIVE FACTORS

Many clinical studies showed factors increasing the risk of colorectal cancer lack of regular physical activity, obesity, diabetes mellitus, certain diets such as red meat or low fiber diet, cigarette smoking, and alcohol.⁹ Also, patients with inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, a personal or family history of colorectal cancer or colorectal polyps, a genetic syndrome such as familial adenomatous polyposis or hereditary non-polyposis colorectal cancer (Lynch syndrome) have an increased risk. Vitamin D deficiency has also been shown to increase the risk and mortality of colorectal cancer.²²

Recently a large umbrella study reviewing 9,954 publications and 222 full-text articles found convincing evidence of an association between lower colorectal cancer risk and high intakes of dietary fiber, dietary calcium, and yogurt and lower intakes of alcohol and red meat. However, although suggestive, no convincing conclusion was drawn about the risk of colorectal cancer and other dairy products, whole grains, processed meat, and specific dietary patterns.¹⁰

SURGERY FOR COLON CANCER

Open colectomy has been a standard surgery for colon cancer. However, for experienced surgeons who have performed at least 20 laparoscopic resections, the laparoscopic group had a shorter hospital stay duration (five vs. six days) without any significant differences in perioperative complication and mortality rates as well as five-year-survival rates.¹¹ During the surgery, at least 12 regional lymph nodes must be harvested. Fewer than 12 lymph nodes are high risk and poor prognostic signs in Stage II and cause a high recurrence rate in stage IIIA colon cancer.¹² For management of malignant colonic polyp, endoscopic resection is sufficient if they are completely resected en bloc, and no high-risk features are present. For non-pedunculated polyps, deep submucosal invasion is a high-risk feature associated with lymph node metastasis. Because the entire submucosa is typically not removed with endoscopic resection, this high-risk feature could not be evaluated adequately in some patients. The U.S. Multi-Society Task Force on Colorectal Cancer (USMSTF) recommended that patients with the high-risk feature, defined by deep invasion (1mm or more) into the submucosa should be considered for colon resection.¹³ Other high-risk features requiring radical surgery include poorly differentiated adenocarcinoma, lymphovascular invasion, cancer or dysplasia on resection margins, or T1-T2 tumor.¹⁴

MOLECULAR GENOMIC TESTS OF COLORECTAL CANCER CELLS AND PRECISION MEDICINE

Precision medicine is an approach for disease treatment that takes into account individual variability in genes, environment, and lifestyle for each person. The detection of specific molecular and genetic characteristics of each patient's cancer cells is the utmost important component of precision medicine. About 15–20% of colorectal cancer cells have a mutation in DNA Mismatch Repair (MMR) genes, resulting in a deficiency of MMR enzyme (dMMR). The dMMR enzymes cause high rates of DNA errors causing repeated Micro-Satellite fragments of DNA, which is called Micro-Satellite Instability (MSI). When the PCR molecular test reveals a high rate of MSI, it is reported as MSI-H. When the specific gene mutation such as MMR gene mutation occurs only in cancer cells, it is 'somatic mutation,' while the MMR mutation is germline affecting all body cells, it causes Lynch Syndrome.

CLINICAL USE OF MMR AND MSI

Interestingly, patients having MSI-H cancer cells due to dMMR have a good prognosis, although these cancer cells are frequently poor-differentiated.¹⁵ Moreover, colorectal cancer cells with MSI-H/dMMR do not respond to the commonly used chemotherapeutic drug, fluorouracil (5-FU) or capecitadine (Xeloda®). Therefore, patients with MSI-H/dMMR should not receive fluorouracil (5-FU) alone but receive combination chemotherapy with other chemotherapy drugs such as oxaloplatin. Since stage II colon cancer patients with MSI-H/dMMR have a better prognosis, these patients can be spared adjuvant chemotherapy.¹⁵ Patients with MSI-H/dMMR frequently respond to immunotherapy with checkpoint inhibitors, such as pembrolizumab (Keytruda®) or nivolumab (Opdivo®).¹⁶

FIGURE 2.

C.T. (Virtual) Colonoscopy showing a polyp (green arrows)

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BIOMARKERS OF COLORECTAL CANCER

Some colorectal cancer cells have certain mutations in the oncogenes. Oncogenes are involved in cell growth and regulation. When the oncogenes are mutated, cells proliferate out of control because the cell growth cannot be regulated. Patients with these mutations can be treated with specific inhibitors against the biomarkers, which provide higher response rates and lower toxicity when compared with cytotoxic chemotherapy.¹⁷ The biomarker inhibitors are mostly used for metastatic disease and administered by mouth as a pill form.

Mutated oncogenes found in colorectal cancer are:

RAS mutation is seen in about 50% of colorectal cancer and large adenomatous polyps. Currently, clinical research is active for patients with the KRAS mutation with KRAS inhibitors.^{18,20}

BRAF mutation is found in 10–15% of patients; The BRAF inhibitors include encorafenib (Braftovi®), which is used with cetuximab (Erbix®).^{19,20}

HER2 overexpression, which is often seen in breast cancer, is detected in four–five % of colorectal cancer. The HER2 inhibitors currently available are trastuzumab (Herceptin®), pertuzumab (Perjeta®), lapatinib (Tykerb®), and fam-trastuzumab deruxtecan. (Enhertu®) The fam-trastuzumab deruxtecan (Enhertu®) is an antibody-chemotherapeutic drug conjugate.²⁰

NTRK fusion genes are rare (0.5–2%), but patients with this mutation respond well to anti-TRK inhibitor therapy. The TRK inhibitors include Larotrectinib (Vitrakvi®) and entrectinib (Rozlytrek®).²⁰

PIK3CA is a proto-oncogene encoding phosphatidylinositol-3-kinases (PIK3) involved in the EGFR (epidermal growth factor receptor) tyrosine kinase domain. Its mutation appears to activate AKT-mTOR signaling pathway and is found in about 30% of colorectal cancer. Idelalisib (Zydelig®) is an anti-PIK3CA inhibitor that is not yet approved by FDA for metastatic colorectal cancer.²⁰

ADJUVANT CHEMOTHERAPY AFTER COLON CANCER SURGERY

After surgical resection of all visible cancer, chemotherapy is given to patients with stage III or some high-risk stage II colon cancer patients to eradicate possible remaining cancer cells (adjuvant chemotherapy). Adjuvant chemotherapy reduces the recurrence and death rates by 30% in stage III patients. However, because the benefit of adjuvant chemotherapy for stage II colon cancer is minimal, it is given to high-risk patients such as those with bowel obstruction or perforation. The adjuvant chemotherapy has been given to patients for six months. However, clinical studies revealed that three month-chemotherapy has a similar five-year survival rate when compared with six month-therapy.²¹ However, very high-risk patients with stage IIIC (T4N2) may receive six months of adjuvant chemotherapy when the FOLFOX regimen is used. With CPOX (XELOX) regimen, there was no significant difference in five-year survival even in stage IIIC patients.²¹

FIGURE 3.

Capsule colonoscopy

AUTHOR DISCLOSURE:

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