TREATMENT UPDATE:

Colorectal Cancer

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Treatment Update: Colorectal Cancer

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In the United States, over 140,000 people are diagnosed with colorectal cancer every year.

Regular screening is one of the most powerful weapons for preventing colorectal cancer. The preferred test is a colonoscopy, in which a doctor uses a thin flexible tube equipped with a camera to look for polyps—small growths—on the wall of the colon. If undiscovered and untreated, polyps can become cancerous.

Personalizing Treatment: The Role of Genetic Mutations

Each tumor has its own biological makeup, based on the genes found in its cells. The genes in tumor cells are different from genes in healthy cells in the body. An important area of cancer research is understanding this biology. With this information, it's possible for doctors to know whether a particular tumor is likely to respond to a specific treatment, allowing for the best possible treatment approach. This is known as precision (or personalized) medicine.

To better understand the biological makeup of a person's tumor, doctors look for changes in genes within the tumor that may serve as "markers." Markers can predict whether a given treatment will be effective against a tumor and whether there is a high risk of the tumor recurring (the cancer returning).

There are tumor markers and genetic changes that can be identified in colorectal cancer:

RAS

A key group of tumor markers that have been found in colorectal cancer consists of changes in KRAS and NRAS—known collectively as the RAS genes. Forty percent of people with colorectal cancer have a mutation (change) in a RAS gene. Through clinical trials, researchers have learned that these people do not benefit from treatment with the EGFR inhibitors cetuximab and panitumumab (see "Targeted Therapy" section). However, the presence of these genetic alterations does not affect response to chemotherapy.

The other 60 percent of people with colorectal cancer have no RAS mutation; these people are said to have the RAS "wild-type" gene. These individuals have a higher likelihood of benefiting from treatment with EGFR inhibitors.

BRAF

As with RAS mutations, the majority of patients with mutations in the BRAF gene do not respond to EGFR inhibitors. Through clinical trials, doctors have learned there are certain drugs that may be able to block this BRAF gene, which may allow patients with this mutation to respond to treatment with EGFR inhibitors. This is an active area of research, and combination therapies that block the BRAF gene are now available.

MSI-H

About 4 percent of metastatic colorectal cancers (cancers that have spread to other parts of the body) have a genetic trait known as high microsatellite instability (MSI-H), which causes these tumors to have a large number of genetic mutations. Two drugs are approved by the U.S. Food and Drug Administration (FDA) for the treatment of this type of tumor (see "Immunotherapy" section) and additional treatment approaches are being studied in clinical trials.

NTRK Fusions

A genetic abnormality can cause the neurotrophic receptor tyrosine kinase (NRTK) gene in a cancer cell to become connected (fused) to another unrelated gene. When this occurs, it causes uncontrolled "signaling" of tropomyosin receptor kinase (TRK) proteins that can lead to tumor growth. A TRK inhibitor was recently approved by the FDA for the treatment of people with colorectal cancer that exhibits this genetic abnormality (see "Targeted Therapy" section).

Treatment Options

Treatment for colorectal cancer often involves a combination of surgery and medication.

Surgery

In approximately 80 percent of patients diagnosed with colorectal cancer, the cancer is localized (has not spread to other organs). Surgery is most often the first step in treating localized colorectal cancer. The surgeon will remove the section of the colon or rectum that contains the tumor and will also remove nearby lymph nodes, which are small organs located throughout the body that remove waste and fluids and help fight infection. Removing the colon or rectal tumor and nearby lymph nodes enables a pathologist (a physician who examines laboratory samples of body tissue for diagnostic purposes) to more accurately determine the stage of the cancer.

Chemotherapy

Chemotherapy is sometimes given before surgery to try to shrink the tumor (called "neoadjuvant" treatment), making the surgery an easier process and increasing its chances of success. Neoadjuvant chemotherapy is sometimes given in combination with radiation.

After surgery, cancer cells that are not detectable by tests may still exist, so doctors often suggest "adjuvant" treatment (chemotherapy given after surgery). The goal is to destroy any remaining tumor cells, decrease the chances of the cancer coming back and reduce the risk of tumor cells spreading to other parts of the body.

The chemotherapies most often given in adjuvant treatment are:

- **5-Fluorouracil (Adrucil),** also called 5-FU, is given intravenously (through a needle into a vein), often with the vitamin-like drug leucovorin (folinic acid) which helps it work more effectively.
- **Capecitabine (Xeloda and others),** taken in pill form, is changed by the body to 5-FU when it reaches the site of the tumor.
- **Oxaliplatin (Eloxatin)** is given intravenously in combination with 5-FU or capecitabine.

If the colorectal cancer has spread to other areas of the body, such as the liver or lungs, doctors often treat the tumor with chemotherapy alone. In addition to 5-FU and capecitabine, metastatic colorectal cancer can be treated with the intravenous drugs oxaliplatin (Eloxatin) and irinotecan (Camptosar).

In 2015, the FDA approved Lonsurf (a pill that combines two drugs, trifluridine and tipiracil) for people with advanced colorectal cancer which is no longer responding to other therapies.

Targeted Therapy

Targeted therapies focus on specific molecules and cell mechanisms thought to be important for cancer cell survival and growth, taking advantage of what researchers have learned in recent years about how cancer cells grow. Targeted therapies are meant to spare healthy tissues and provide treatment against cancer cells that is more focused than chemotherapy.

- **VEGF inhibitors.** These treatments "starve" the tumor by blocking the action of VEGF (vascular endothelial growth factor), a protein released by tumors that contributes to blood vessel growth (angiogenesis). VEGF inhibitors bevacizumab (Avastin), ramucirumab (Cyramza) and ziv-aflibercept (Zaltrap) are given intravenously, typically along with chemotherapy such as oxaliplatin, irinotecan, 5-FU and capecitabine. VEGF inhibitors can help make chemotherapy drugs more effective.
- **EGFR inhibitors.** EGFR (epidermal growth factor receptor) is a protein often found in high amounts on the surface of cancer cells. The targeted therapies cetuximab (Erbitux) and panitumumab (Vectibix), given intravenously, are designed to block the action of EGFR, preventing cancer cells from growing into tumors. For patients with RAS wild-type tumors, they are often given in combination with chemotherapy.
- **Kinase inhibitor.** Kinase proteins send important signals to the cell's control center, including signals that promote cell growth. The kinase inhibitor regorafenib (Stivarga), taken in pill form, is designed to help stop the growth of tumors by blocking several kinase proteins.

- **TRK inhibitor.** In November 2018, the FDA approved the TRK inhibitor larotrectinib (Vitrakvi) for the treatment of people with solid tumors (including colorectal cancer tumors) that have an NTRK gene fusion and have progressed following treatment or have no other satisfactory treatment alternative. Larotrectinib is "agnostic" in that it targets a genetic driver of cancer rather than a specific type of tumor.

Immunotherapy

Our immune system works constantly to keep us healthy. It recognizes and fights against danger, such as infections, viruses and growing cancer cells. In general terms, immunotherapy uses our own immune system as a treatment against cancer.

In 2017, the immunotherapy drugs pembrolizumab (Keytruda) and nivolumab (Opdivo), known as PD-1 inhibitors, were granted accelerated approval by the FDA for people with metastatic colorectal cancer that has progressed after chemotherapy and that has one of two specific genetic features (MSI-H or DNA mismatch repair deficiency), both of which can prevent DNA within cells from repairing itself.

In July 2018, the FDA approved nivolumab in combination with the immunotherapy ipilimumab (Yervoy) for the treatment of people with previously-treated metastatic colorectal cancer that is positive for either MSI-H or DNA mismatch repair deficiency.

Immunotherapy continues to be a key area of research in the treatment of metastatic colorectal cancer, including:

- **Vaccines.** Vaccines that boost the immune system have the potential to treat colorectal cancer or prevent it from recurring after treatment. A number of vaccines are being studied in clinical trials. One vaccine approach involves removing a person's own immune system cells from their blood, altering them with a substance that will instruct them to attack cancer cells and injecting them back into the person's body.
- **Immune checkpoint inhibitors.** Tumor cells often have "immune checkpoint" molecules that act as a shield, allowing the cancer to evade an attack by the immune system. This can be countered by immune checkpoint inhibitors, which are drugs designed to remove the shield and allow the immune system to attack the cancer cells.
- **Combining immunotherapy and targeted therapy.** PD-1 is a molecular "brake" that prevents the body's immune system from attacking tumors. Combining PD-1 inhibitors with targeted or other therapies that activate immune cells may stimulate the immune system to attack cancer cells.

The Importance of Clinical Trials

Clinical trials are the standard by which we measure the worth of new treatments and the quality of life of patients as they receive those treatments. For this reason, doctors and researchers urge people with cancer to take part in clinical trials.

Your doctor can guide you in making a decision about whether a clinical trial is right for you. Here are a few things that you should know:

- Often, people who take part in clinical trials gain access to and benefit from new treatments.
- Before you participate in a clinical trial, you will be fully informed as to the risks and benefits of the trial, including any possible side effects.
- Most clinical trials are designed to test a new treatment against a standard treatment to find out whether the new treatment has any added benefit.
- You can stop taking part in a clinical trial at any time for any reason.

Treatment Side Effects

All cancer treatments can cause side effects. It's important that you report any side effects that you experience to your health care team so they can help you manage them. Report them right away—don't wait for your next appointment. Doing so will improve your quality of life and allow you to maintain your treatment plan. It's important to remember that not all patients experience all side effects, and patients may experience side effects not listed here.

Side Effects of Chemotherapy

The side effects of chemotherapy depend on the type and dose of drugs given and the length of time they are used, and can include:

- Fatigue
- Nausea or vomiting
- Hair loss
- Increased risk of infection (from having too few white blood cells)
- Easy bruising or bleeding (from having a low platelet count)
- Changes in memory or thinking
- Peripheral neuropathy (numbness or tingling in hands and feet)

Chemotherapy can cause changes in the way food and liquids taste, including causing an unpleasant metallic taste in the mouth. Many people find that switching to plastic utensils helps. It may also help to avoid eating or drinking anything that comes in a can, and to use enamel-coated pots and pans for food preparation.

Side Effects of Targeted Therapy

Targeted therapy doesn't have the same effect on the body as do chemotherapy drugs, but they can still cause side effects. Side effects of targeted therapies can include diarrhea, liver problems (such as hepatitis and elevated liver enzymes), nerve damage, rash, high blood pressure and problems with blood clotting and wound healing.

Side Effects of Immunotherapy

Immunotherapy travels through the bloodstream, helping to prompt an immune response. Because it can trigger an attack on healthy cells as well as cancer cells, certain side effects may be experienced, including fatigue, decreased appetite, and digestive tract symptoms. The management of these potential side effects is discussed later in the next section of this booklet.

General Side Effects

Some side effects may occur across treatment approaches. This section provides tips and guidance on how to manage these side effects should they occur.

Managing Digestive Tract Symptoms

Nausea and vomiting

- Avoid food with strong odors, as well as overly sweet, greasy, fried or highly seasoned food.
- Eat meals cold or at room temperature, which often makes food more easily tolerated.

- Nibble on dry crackers or toast. These bland foods are easy on the stomach.
- Having something in your stomach when you take medication may help ease nausea.

Diarrhea

- Drink plenty of water. Ask your doctor about using drinks such as Gatorade which provide electrolytes as well as liquid. Electrolytes are body salts that must stay in balance for cells to work properly.
- Over-the-counter medicines such as loperamide (Imodium A-D and others) and prescription drugs are available for diarrhea but should be used only if necessary. If the diarrhea is bad enough that you need medicine, discuss it with your doctor or nurse.
- Choose fiber-dense foods such as whole grains, fruits and vegetables, all of which help form stools.
- Avoid food high in refined sugar and those sweetened with sugar alcohols such as sorbitol and mannitol.

Managing Loss of appetite

- Eating small meals throughout the day is an easy way to take in more protein and calories, which will help maintain your weight. Try to include protein in every meal.
- To keep from feeling full early, avoid liquids with meals or take only small sips (unless you need liquids to help swallow). Drink most of your liquids between meals.
- Keep high-calorie, high-protein snacks on hand such as hard-boiled eggs, peanut butter, cheese, ice cream, granola bars, liquid nutritional supplements, puddings, nuts, canned tuna or trail mix.
- If you are struggling to maintain your appetite, talk to your health care team about whether appetite-building medication could be right for you.

Managing Fatigue

Fatigue (extreme tiredness not helped by sleep) is one of the most common side effects of many cancer treatments. If you are taking a medication, your doctor may lower the dose of the drug, as long as it does not make the treatment less effective. If you are experiencing fatigue, talk to your doctor about whether taking a smaller dose is right for you.smaller dose is right for you.

There are a number of other tips for reducing fatigue:

- Take several short naps or breaks during the day.
- Take short walks or do some light exercise, if possible.
- Try easier or shorter versions of the activities you enjoy.
- Ask your family or friends to help you with tasks you find difficult or tiring.
- Save your energy for things you find most important.

Fatigue can be a symptom of other illnesses, such as anemia, diabetes, thyroid problems, heart disease, rheumatoid arthritis and depression. So be sure to ask your doctor if he or she thinks any of these conditions may be contributing to your fatigue.

Managing Pain

To help your doctor prescribe the best medication, it's useful to give an accurate report of your pain. Keep a journal that includes information on:

- Where the pain occurs
- When the pain occurs
- How long it lasts
- How strong it is on a scale of 1 to 10, with 1 being the least amount of pain and 10 the most intense
- What makes the pain feel better and what makes it feel more intense

There are a number of options for pain relief, including prescription and over-the-counter medications. It's important to talk to a member of your health care team before taking any over-the-counter medication to determine if they are safe and will not interfere with your treatments.

Physical therapy, acupuncture and massage may also be of help in managing your pain. Consult with a member of your health care team before beginning any of these activities.

Communicating With Your Health Care Team

As you manage your cancer, it's important to remember that you are a consumer of health care. The best way to make decisions about health care is to educate yourself about your diagnosis and get to know the members of your health care team, including doctors, nurses, dietitians, social workers and patient navigators.

Here are some tips for improving communication with your health care team:

Start a health care journal. Having a health care journal or notebook will allow you to keep all of your health information in one place. You may want to write down the names and contact information of the members of your health care team, as well as any questions for your doctor. Keep a diary of your daily experiences with cancer and treatment. You can separate your journal or notebook into different sections to help keep it organized.

Prepare a list of questions. Before your next medical appointment, write down your questions and concerns. Because your doctor may have limited time, ask your most important questions first and be as specific as possible.

Bring someone with you to your appointments. Even if you have a journal and a prepared list of questions or concerns, it's always helpful to have support when you go to your appointments. The person who accompanies you can serve as a second set of ears. He or she may also think of questions to ask your doctor or remember details about your symptoms or treatment that you may have forgotten.

Write down your doctor's answers. Taking notes will help you remember your doctor's responses, advice and instructions. You can also ask the person who accompanies you to take notes for you. If you have a mobile device, ask if you can use it to take notes. Keeping notes will help you review the information later.

Record your visit if your doctor allows it. Recording the conversation with your doctor gives you a chance to hear specific information again or share it with family members or friends.

Incorporate other health care professionals into your team. Your medical oncologist is an essential member of your health care team, but there are other health care professionals who can help you manage your diagnosis and treatment:

- Your primary care physician should be kept updated about your colorectal cancer treatment and any test results.
- Your local pharmacist is a great source of knowledge about the medications you are taking. Have all of your prescriptions filled at the same pharmacy to avoid the possibility of harmful drug interactions.
- Make sure your oncologist knows of any other medical conditions you have or any pain you are experiencing so that they can consult with your primary care physician or specialist as needed.

Remember, there is no such thing as over-communication.

Cancer*Care*'s Free Support Services and Programs

Receiving a diagnosis of cancer can be very difficult, and adjusting to the necessary changes in your life can be challenging.

Cancer*Care* can help. We are a national nonprofit organization providing free, professional services to anyone affected by cancer. Our licensed oncology social workers can provide support and education, help in navigating the complicated health care system, and provide information on support groups and other resources.

To learn more about how Cancer*Care* helps, call us at 800-813-HOPE (4673) or visit www.cancercare.org.

You will likely also build your own personal support network, comprised of family and friends. In doing so, it's best to take some time to think about the people in your life and how they are best suited to help. Match the task to their strengths—ask a family member who loves to shop to pick up something for you at the store; ask a friend who's a good listener to come over for a chat.

Frequently Asked Questions

Q: I have been diagnosed with colorectal cancer, and I'm concerned about my children's risk of getting the disease. What screenings or tests are recommended for them?

A: Typically, it is recommended that children undergo their first colonoscopy when they are ten years younger than their parent was at the time of their colorectal cancer diagnosis. It is also important to know whether you have an inherited condition, such as Lynch syndrome, which increases the risk of colorectal cancer. If your colorectal cancer is possibly inherited, your children should talk to their physician about genetic screening, in addition to undergoing colonoscopies at the recommended intervals.

Q: I was recently diagnosed with colon cancer and will soon have surgery. Will I definitely need to have a colostomy as part of the surgical process?

A: A colostomy is a procedure which diverts a portion of the colon to a small opening—called a stoma— in the wall of the abdomen. The stoma is attached to a pouch, which collects stools as they exit the body. Depending on the extent of your surgery, the need for a colostomy is possible, or even likely. However, there are options that may be available to you, which you should discuss with your surgeon or another member of your health care team.

If you do require a colostomy, there is support available to help you adjust to the change in your daily routine. It can be valuable to speak with an oncology social worker at Cancer*Care*; consulting with an enterostomal therapy nurse (who specializes in ostomy care and rehabilitation) and joining a local support group can also be very helpful.

Q: Are there any treatment options being studied for people with HER2-positive metastatic colorectal cancer?

A: The results of the phase II clinical trial HERACLES-A showed that the combination of two HER2-targeted therapies, trastuzumab (Herceptin) and lapatinib (Tykerb), had clinical benefit in people with HER2-positive metastatic colorectal cancer whose cancer had not responded to other treatments. This is an encouraging development, as people with this type of colorectal cancer often do not respond well to available targeted therapies.

Q: I heard about there being differences between left-side tumors and right-side tumors. What does that mean?

A: There are biological differences in tumors depending on their location within the colon. Metastatic colorectal cancer tumors originating from the left side of the colon (the descending colon, sigmoid colon and rectum) are associated with better outcomes than tumors originating from the right side of the colon (the cecum and ascending colon). These differences may help guide treatment approaches for people with metastatic colorectal cancer and will likely be the subject of increased focus in the coming years as researchers seek to more deeply understand the difference in treatment options and outcomes based on the location of the tumor.

Resources

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www.cancercare.org

American Cancer Society
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www.cancer.org

Cancer.Net
Patient information from the American Society of Clinical Oncology
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www.cancer.net

National Cancer Institute
800-422-6237
www.cancer.gov

Cancer Support Community
888-793-9355
www.cancersupportcommunity.org

National Coalition for Cancer Survivorship
877-622-7937
www.canceradvocacy.org

Colon Cancer Alliance
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www.ccalliance.org

Fight Colorectal Cancer
877-427-2111
www.fightcolorectalcancer.org

United Ostomy Associations of America
800-826-0826
www.ostomy.org

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