

## Teacher Background

### Cancer Treatments and the Effects on Reproduction

**Note:** The Teacher Background Section is meant to provide information for the teacher about the topic and is tied very closely to the PowerPoint slide show. For greater understanding, the teacher may want to play the slide show as he/she reads the background section. For the students, the slide show can be used in its entirety or can be edited as necessary for a given class.

#### How Is Cancer Treated – An Overview?

Because of the metastatic nature of cancer cells, treatment for cancer involves trying to eliminate every cancerous cell in the body. This is attempted by surgical removal of the primary and metastatic secondary tumors, by use of chemotherapy to kill the fast growing cells including cancer, by use of targeted therapy to kill only cancer cells, and/or by use of radiation treatment targeted to kill cells in the path of the beam including cancer cells. (1, 2) Many of these treatments, particularly chemotherapy and radiation, can be damaging to normal cells leading to side effects. Many side effects like nausea are temporary but some of them like infertility are permanent. While the goal is to cure cancer (elimination of all of the cancerous cells in the body), this is easier said than done. If even one cancerous cell is left in the body after the treatment ends, it could grow into another tumor.

The particular treatment protocol for any individual cancer patient would depend on the type of cancer, the stage and grade of the tumor, the age of the patient and general health, and data from studies concerning results of treatment in other patients with the same cancer. Cancer is thought by many people to be one disease but actually each type of cancer is very different in its cell type, mode of growth and metastasis, and treatment.

Comparing prostate, breast, and colon cancers, it is clear how different these cancers are and that early detection of these types of cancer means less involved treatment and a higher probability of 5-year survival rate. Of the three types of cancer, prostate cancer is the slowest growing and with surgery and perhaps radiation, the patient would have the best 5-year survival rate of 100% for diagnosed stages I, II, and III and 31% for stage IV. Early detection of breast and colon cancers considerably increases the chance of survival since the cancer cells grow more quickly and metastasize and spread to other organs



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more readily. Detected at stage I, the 5-year survival rate for breast cancer is 100%, at stage II, 86%, stage III, 57%, and stage IV, 20% with increasingly more extensive surgery, radiation, and chemotherapy with each stage. Detected at stage I, the 5-year survival rate for colon cancer is 93%, at stage II, 80%, stage III, 58%, and stage IV, 7% with increasingly more extensive surgery, radiation, and chemotherapy with each stage. (3)

### How Is Cancer Detected?

As described in the previous unit on cancer, cancer can be detected by early screening such as through a Pap smear, mammogram, or colonoscopy, or by self-screening. Early signs of cancer that should be checked by a physician as soon as possible are a detection of a lump especially in breast or testicular tissue, unusual bleeding or discharge, a sore that doesn't heal, a change in the shape and/or color of a mole on the skin, unexplained coughing, and unexplained stomach, back, or abdominal pain. If something suspicious is found, a biopsy (or small sample) of tissue is taken and examined by a pathologist to check for cancerous cells. The tissue may be run through a proteomic profile or genomic microarray to determine if cancer-related proteins or genes are present in the tissue.

### After Cancer Is Detected, What Types of Scans Are Used to Determine Metastasis?

After cancer has been detected, different types of scans, such as 1) CT (computerized tomography), 2) PET (positron emission tomography), and 3) MRI (magnetic resonance imaging), are used to locate the tumor(s) in preparation for surgery. However, if the cancer patient is under 40 years old and is planning to have a family, a discussion with the oncologist and the fertility specialist regarding fertility preservation options would take place before any scans and treatment occur.

1. CT (computerized tomography) works by combining a series of x-ray views taken from different angles to give cross-sectional images of the bones and soft tissues. Soft tissues appear grey in a CT scan and bones appear bright white. Cancerous tumor(s) on the CT scan show up as a bright white spot(s) where they shouldn't be, such as in the liver, lungs, or bowel. X-rays are part of the electromagnetic spectrum as is visible light. Shorter wavelengths occur more frequently in a given amount of time and have higher energy. These include ultraviolet light, x-rays, and gamma rays. Longer wavelengths occur less frequently in a given amount of time and have lower energy. These include radio waves, microwaves, infrared light, and visible light. There is a potential risk of developing other cancers due to the use of CT because it gives much more x-ray exposure to the patient than a standard x-ray. For example, the absorbed dose of radiation is measured in grays (Gy). A conventional anterior-posterior abdominal x-ray results in a dose to the stomach of about 0.25 mGy, which is 50 times less than the corresponding stomach dose from an abdominal CT scan. (4) Dr. Ella Kazerooni, a professor of radiology at the University of Michigan Medical School said, "The radiation dose for a standard chest CT scan is equal to about 70 chest X-rays." (5) However, the benefits of using CT imaging to locate the cancer so treatment can be targeted far outweigh the potential risk.



2. With the PET (positron emission tomography) scans, bodily function can be measured, such as blood flow, oxygen consumption, glucose metabolism, or neurotransmitter activity, by using a radioactive substance (radiotracer) injected into the bloodstream, swallowed, or inhaled. The radiotracer collects in the organ or areas of the body being examined and gives off small amounts of gamma radiation. These rays can be detected by the PET scanner and, with help of a computer, a picture of both the structure and function of the organ can be constructed. Areas of higher metabolic activity show up on the scan as a bright spot (or sometimes as a darker spot) because more radiotracer has collected in those areas. Since the cancer cells are rapidly dividing, they metabolize glucose faster than normal cells surrounding them and can be detected using this method. Radiotracers used in PET scans include 18-fluorodeoxyglucose (FDG), nitrogen-13, carbon-11, and oxygen-15. The amount of radiation exposure is not a concern because these radiotracers have a very short half life and thus are not detectable for very long. Therefore, damage to the surrounding tissue is minimized. Nuclear medical diagnostic procedures have been used for over 50 years with no known long term side effects. Because PET scans only give a generalized location of the increased metabolic activity, they are often combined with CT scans to give a more precise location of the activity. (See the section called [What Is Radiation Therapy?](#) for more information on radioactivity.)
3. The MRI (magnetic resonance imaging) uses a large, powerful magnet and non-ionizing radiofrequency waves to produce a detailed, cross-sectional picture of the interior of the body. The MRI provides greater contrast between soft tissues of the body than a CT scan. They are especially useful for imaging brain, spine, connective tissue, and the inside of bones. The MRI scan is not harmful and there are no known long-term side effects. However, MRI scans cannot be used with patients who have an electronic implant like a pacemaker, metal implants including hip and/or knee replacement and pins and screws holding a bone together, or shrapnel wounds, because of the strength of the magnet. (6)

### What Comes Next After Detection and Scans?

Once the tumor(s) have been located, the surgery can be scheduled to remove the primary source of the cancer and as much of the secondary tumors as possible. If fertility preservation surgery is necessary to remove ovarian or testicular tissue, it could be completed at the same time as the cancer surgery. If, however, the scans show an enlarged stage III tumor and involvement of the lymph nodes, stage IV widely spread metastasized tumors, or the cancer is in a location where removal would lead to a critical loss of function, then surgery would not be the first step. In these cases, chemotherapy, targeted therapy, and/or radiation treatments would be prescribed to see if the tumors would shrink in size before planning the surgery. Fertility surgery would proceed prior to any chemotherapy or radiation therapy for those under 40 years old who wish to preserve their fertility.



For most other stages, the surgeon would plan the surgery based on information from the scan(s). If the tumor is in the body trunk, laparoscopic surgery is often used to minimize the number of incisions across muscle bands to hasten healing and to decrease the risk of infection. Laparoscopic surgery is one in which 3 to 5 short incisions are made, each usually around 5-12 mm in length, where a camera, light, probes, and clippers are inserted. The area is then inflated with carbon dioxide to increase the working space inside the body. All of the images of the surgery are projected onto a screen and the surgeon uses control knobs to move the instruments.

As cancerous tissues as well as associated lymph nodes are removed during the surgery, they are sent to the pathology department for confirmation of the type of cancer, the depth of penetration of the tumor into underlying tissue, and presence or absence of cancer cells in surrounding lymph nodes. When cancer begins to metastasize, it often spreads first into nearby lymph nodes. Sometimes the pathologist would work in the operating room with the surgeon to determine where the boundaries of the tumor are as the surgery proceeds to ensure the entire abnormal growth is removed and only normal tissue remains by the end of the surgery, as in case of skin cancer on the face and in the case of cancer in the esophagus or stomach.

If metastatic tumors are present, the surgeon will remove as many of those tumors as possible in a process called debulking. In some cases, if the metastatic tumors are too numerous, the laparoscopic procedure would end and a larger incision would be made, further opening the body cavity to expose more of the tissue for further debulking. For example, if the bowel needs to be rolled to one side to reach other tumors, the surgeon will be able to do that through the larger incision.

#### How Are the Stage and Grade of Cancer Determined and How Are They Used to Choose Treatment Options?

After the surgery has taken place, the patient would recover in the hospital for a short time and then return home to recuperate further. Within a few weeks and based on the pathologist's report from the surgery, the oncologist would meet with the patient to discuss stage and grade of the cancer and options for further treatment.

If the cancer was stage IA grade I and there was no indication of tumor in the underlying tissue and lymph nodes, there may be no further need for treatment. Stage 1A cancers have not invaded the underlying tissue and grade I cancers grow relatively slowly. If the cancer was stage 1A grade III and there was no indication of tumor in the underlying tissues and lymph nodes, then the patient would be started on chemotherapy within a few weeks after surgery since grade III cancers are more aggressive and could have possibly metastasized. Not all of the lymph nodes are tested so some cancer cells could have gone undetected.



If the cancer was more involved than that, such as stage IB and IC where the underlying tissue has been invaded, and stage II, III, and IV where the cancer has metastasized to surrounding tissues or beyond, then the patient would most likely be scheduled for chemotherapy, targeted therapy, and/or radiation would be prescribed regardless of grade and depending on the type of cancer.

### What Is Chemotherapy?

Chemotherapy (also known as chemo) is a therapy in which toxic drugs are given to the cancer patient to interfere with the growth of the cancer cells. The goal of chemotherapy is to cure cancer (eliminate all cancer cells), control cancer (slow the growth of cancer and prevent spreading), or to provide palliative care (to shrink the tumor to relieve pressure), depending on the stage and grade of the cancer.

There are many types of drugs used for chemotherapy. They can be characterized by:

- a) **How they kill cancer and other fast growing cells.** This type of chemotherapy drug are described as:

a1) **cell-cycle specific agents**, work by targeting the microtubules which form spindle fibers thus interfering with cell division and resulting in cell

a2) **cell-cycle nonspecific agents**, work by damaging the DNA and causing the DNA double-helix to break and/or interfering with the DNA repair mechanism.

Often the chemotherapy regimen will include one drug that works on the microtubules and another that targets the DNA of cancer cells. For example, in adjuvant treatment (curative treatment in which the goal is to eliminate any remaining microscopic cancer cells after surgery has been done to remove the primary tumor), a patient with Stage I Grade III ovarian cancer would be treated with paclitaxel (taxol) to target the spindle fibers of the cancer cells and carboplatin to target the DNA of the cancer cells in an effort to destroy all remaining cancer cells. (1)

- b) **Their derivation**, including alkylating agents, platinum, antitumor antibiotics, antimetabolites, and plant alkaloids, depending on their characteristics and nature of treatment.

b1) **Alkylating agents** are the most commonly used chemotherapy drugs and have been used for treating cancer since the 1940s. They are cell-cycle nonspecific agents so are effective during all phases of the cell cycle and work directly on the DNA by cross-linking subunits of DNA causing abnormal base pairing thus preventing synthesis and transcription. They are used to treat a wide variety of cancers and are most effective on solid tumors and leukemia. Alkylating agents can lead



to permanent infertility since they damage the eggs in females and sperm production in males. They can also lead to secondary cancers such as acute myeloid leukemia many years after the initial therapy. Examples of alkylating agents include chlorambucil for treating leukemia and lymphoma, cyclophosphamide for treating breast cancer and lymphoma, and carmustine for treating brain tumors.

b2) The **platinums** (informally called platins), used since the 1970s, kill cells in a similar way so are sometimes grouped with alkylating agents. Examples include cisplatin to treat testicular, bladder and esophagus cancer and which can cause severe kidney damage, oxaliplatin to treat colorectal, stomach, and pancreatic cancer and which can cause severe neuropathies (nerve damage in the periphery), and carboplatin to treat ovarian and lung cancer,

b3) **Antitumor antibiotics** were developed between the 1970s and the 1990s. They are cell cycle specific and include anthracyclines. They are isolated from natural resources such as the soil-dwelling fungus *Streptomyces peucetius* and act to interfere with the function of type II topoisomerase, an enzyme that makes transient double strand breaks in DNA to relax the supercoiled DNA so it can be repaired, transcribed, and replicated, especially during S phase of interphase in mitosis. By forming free radicals that break the DNA, the anthracycline doxorubicin works by enhancing the rate the type II topoisomerase breaks the double stranded DNA and/or reduces the rate these enzymes reseal the breaks, leading to cell death. Doxorubicin is useful in treating sarcoma, breast, and lymphoma cancers. Other examples include bleomycin which is used to treat lymphoma and testicular cancer and mitoxantrone which is used to treat prostate and lymphoma cancers. Heart and lung damage are serious side effects of antitumor antibiotics. (7)

b4) **Antimetabolites** have been used since 1948 and are cell-cycle specific. They hinder cell division by becoming incorporated into the DNA of cancer cells. The antimetabolites are similar in structure to vitamins, amino acids, and precursors to DNA and RNA found naturally in humans. An example includes widely used methotrexate, which works on the S phase of the cell cycle inhibiting an enzyme necessary for DNA synthesis and which is used for treating head and neck cancers and sarcomas. Other examples include 5-fluorouracil, which works by interfering with nucleotides to stop DNA synthesis and which is used for treating breast, esophageal, head and neck, and gastric cancers, and cytarabine, which is used for treating leukemia and lymphoma.

b5) **Plant alkaloids** have been used since ancient times but specifically for chemotherapy since the 1960s. They are derived from plants – vinca alkaloids from the periwinkle plant, the taxanes from the bark of Pacific Yew trees, podophyllotoxins from the roots of the May apple tree *Podophyllum peltatum*, and camptothecans from the bark of the Asian tree *Camptotheca acuminata*. Plant alkaloids are cell-cycle specific but the cycle affected varies from drug to drug. The vinca alkaloids and taxanes both interfere with the formation of spindle fiber microtubules



preventing mitosis. An example of a vinca alkaloid is vincristine used to treat mesothelioma, sarcoma, and lymphoma. An example of a taxane is paclitaxol used to treat breast, lung, and ovarian cancer and works by binding the tubulin protein thus inhibiting the formation of microtubules that are needed for cell division. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis. The podophyllotoxins and camptothecans both are topoisomerase inhibitors. The podophyllotoxins are a type II topoisomerase inhibitor which enhances the rate the topoisomerase breaks the DNA double strand and reduces the rate the enzyme reseals the break. They work in late G1 and S phases of the cell cycle. An example of a podophyllotoxin is etoposide used to treat lymphoma and lung cancer. The camptothecans are type IB topoisomerase inhibitors and work by stabilizing the covalent topoisomerase I- DNA complex. An example of a camptothecan is topotecan used for ovarian and lung cancer treatment. (1, 7, 8, 9, 10)

### How Is the Chemotherapy Administered?

The chemotherapy regimen of drug(s), dosage, and frequency of administration depend on the type of cancer, stage and grade, age, and health of the patient, and toleration to the chemo drugs. Often chemo drugs are given every 21 days (1 cycle) in order to kill rapidly dividing cancer cells while in the system for 1 week followed by a recovery period of 2 weeks. The chemo treatment is given for 4 – 12 cycles and sometimes longer depending on the type of cancer. While some chemotherapy treatments are taken orally by pill, by subcutaneous injection (a shot under the skin), intra-arterial (into an artery), or intraperitoneal (into the peritoneal cavity), most chemo treatments are given intravenously (into a vein) and require 5 – 6 hours to administer. For patients receiving many cycles of chemo, a port would be surgically implanted into the chest to use for easy access to the veins rather than accessing the veins on the back of the hands where the IV line would need to be reestablished for each cycle. (9, 11)

### What Is the Chemotherapy Process and What Are the Side Effects?

The process usually begins with the administering of fluids containing steroids which prevent an allergic reaction to the chemo drugs, an anti-emetic (anti-nausea) drug, and a saline solution to dilute the chemo drugs. Then the chemo drugs are administered one at a time. For many cancers, often two or more chemo drugs are used and each destroys the fast growing cancer cells by a different method. The side effects from the chemo don't begin usually until a day or two later after the steroids wear off.

For next five to six days (*the chemo phase*), side effects, including vomiting, diarrhea or constipation depending on the drugs used, difficulty swallowing, loss of appetite, general malaise, muscle aches especially in the legs and feet, and fatigue, may be experienced as the chemo drugs course through the



body. Most of the side-effects are managed by other drugs taken in pill form to control nausea, diarrhea or constipation, acid reflux, insomnia, and anxiety. The patient is advised to drink 80 – 120 ounces of fluid a day to flush the drugs out of the system (a process that requires 5-6 days) and to protect the kidney. Unfortunately, in addition to killing rapidly dividing cancer cells, the chemo drugs also kill other rapidly dividing cells, such as the bone marrow cells, skin cells, hair follicle cells, reproductive cells, axons of peripheral neurons, and cells lining the gastrointestinal tract, which explains many of the side effects.

After about a week, the patient usually begins to feel better and begins to build strength again (*the rebuilding phase*). Other side effects may include hair loss after day 14 of the first chemo cycle, mouth sores, dry mouth, acid reflux, peripheral neuropathy (numbness of the fingers and/or toes), and cessation of the menstrual cycle in women. Biotene toothpaste and mouthwash contain enzymes to fight mouth sores and dry mouth by stimulating salivary flow. To avoid peripheral neuropathy, a daily vitamin B complex is recommended and if the symptoms develop, acupuncture or drugs like Lyrica can decrease the severity of the symptoms. The chemo drugs are also thought to affect brain function in some patients causing temporary mild cognitive impairment, hence the term “chemo brain” or “chemo fog”. Some patients don’t experience any side effects but it doesn’t mean the chemo isn’t working. (12)

The biggest issue with chemotherapy is keeping the patient free of infection and well enough to continue an uninterrupted regular regimen of chemotherapy; therefore, timing the next dose so that the blood cells have time to hit the nadir (lowest point) in their production (about 10 days after treatment) and then recover but before the cancer cells can continue to multiply is very important. The goal is to time the cycles of chemo so the chemotherapy won’t be interrupted once started and won’t permanently damage the basal cells in the bone marrow that produce red blood cells, white blood cells, and platelets.

The blood contains red blood cells which carry oxygen to each cell, white blood cells which make up the immune system, and platelets which cause the blood to clot. Red cells circulate in the blood for about three months, are gradually taken out of the blood in the liver as they wear out, and are actively being replaced by production of new red blood cells in the bone marrow so the overall number of red blood cells in the blood (about 4-5 million/cubic cm) is kept relatively constant. White blood cells are actively being produced in the bone marrow and replaced in the blood every few days as they wear out. This helps keep the overall number of white blood cells in the blood (about 4000 – 11000/cubic cm) relatively constant. The number of white blood cells will increase in number if there are foreign antigens in the system, such as from a bacterial or viral infection. Platelets are actually fragments of megakaryocytes made in the bone marrow and are found circulating in the blood in fairly large numbers. The cancer patient’s complete blood count is done once a week for the first few cycles of chemotherapy to monitor the count of each cell type.





The cells of most concern during chemotherapy are the white blood cells because of their short lifespan in the blood and their role in fighting infection. If the white cell count goes too low, neutropenia can result in which the number of neutrophils (one of the main white blood cells) in the blood drops to dangerously low levels. Because neutrophils are the most numerous of the white blood cells and the one most involved in preventing infections, the neutropenic patient is very susceptible to infection, sometimes requiring hospitalization. To avoid a break in the cycles of chemotherapy due to infection, new drugs have been developed called Neulasta, Neupogen, and Leukine which are growth factors known as granulocyte-colony stimulating factors (G-CSFs). If given to the patient by subcutaneous injection a day or so after the chemo, the CSFs stimulate the bone marrow to produce more neutrophils. The production of neutrophils is so rapid after the injection of CSF that the patient may feel pressure or pain in the bones for a few days. A similar dramatic drop in the number of red blood cells is called anemia and the patient will begin to feel very tired due to lack of enough oxygen reaching the cells resulting in low amounts of ATP being produced. The patient can be given CSFs Aranesp, Protocrit, or Epogen by subcutaneous injection a day or so after the chemo session to boost production of red blood cells. The platelet count can decrease as well and the patient would experience increased time for the blood to clot. The patient would be advised to avoid situations that could lead to trauma, such as falling. (13)

Most side-effects diminish over the course of the year following the end of chemotherapy although some can take longer to diminish, such as neuropathy, heart damage, fatigue, and chemo brain while others may be permanent, such as severe neuropathy (nerve damage) and damage to the kidneys, heart, lungs, and to the reproductive organs. In women, the primordial and primary follicles in the ovaries can be permanently damaged causing infertility and early onset of menopause. The alkylating agents do the most harm, such as Cytoxan (cyclophosphamide) used to treat breast cancer, lymphoma, and some leukemias. Adriamycin (doxorubicin), anti-tumor antibiotic anthracycline used to treat breast cancer, is considered to be a moderate risk for women over 40 and minimal risk for women under 40. Methotrexate and 5-FU, antimetabolites used to treat many cancers tend to pose very little risk. Taxol (paclitaxel) and Taxotere, plant alkaloids, and oxaliplatin, a platinum, used to treat ovarian and colon cancer don't appear to damage fertility. Women should not be pregnant during chemotherapy or likely to become pregnant (use birth control) since chemotherapy drugs can harm the fetus especially in the first 3 months. In men, it can lower the sperm count and make the sperm less able to move or can cause other damage to the sperm. Men on chemotherapy should use birth control as well since the sperm damaged by the chemo drugs could cause birth defects. Another permanent side-effect is the possibility of the onset of another cancer, such as Hodgkin's disease, non-Hodgkin's lymphoma, and leukemia, probably due to cellular damage caused by the chemo and/or radiation therapy. (14, 15)



## What Are Targeted Therapies?

There are other drugs and biological treatments called targeted therapy, which are not considered to be chemotherapy, that are used to treat cancers; however, this targeted therapy is often used in conjunction with chemotherapy. There are fewer side effects with targeted therapy because instead of working on rapidly dividing cells, both cancerous and normal, they work only on the cancer cells.

The target therapies are either:

a) **small molecules** that are able to diffuse into the cell and act on targets found inside the cell. An example of a targeted therapy that is a small molecule is Gleevec used to treat chronic myelogenous leukemia (CML). See pages 1 -2 in Teacher Background on Cancer and slides 50 and 51 on DNA Mutations – Lecture and Animations and The Cause of Chronic Myeloid Leukemia (CML) in the PowerPoint on Cancer for more detail.

b) **monoclonal antibodies** that are a man-made version of a very specific immune system protein which cannot penetrate the cell membrane and work against targets that are found on the cell surface. Monoclonal antibodies were first approved by the Food and Drug Administration (FDA) in 1997. Some work by attaching to tumor-specific antigens on the cancer cells which make them recognized as 'not-self' by the body's immune system while others work by blocking the cell receptors to growth factors on the cancer cell surface thus preventing the cancer cell from growing. Monoclonal antibodies can also be combined with radioactive particles to directly deliver them to the cancer cell.

An example of a monoclonal antibody is Trastuzumab (Herceptin) used to bind to human epidermal growth factor receptor 2 (HER-2) in certain types of breast cancer. HER-2 occurs in larger amounts on the surface of cancer cells than on normal cells causing the cancer cells to grow and spread aggressively and when Herceptin is used, it blocks the growth of the cancer cells by binding to the HER-2 receptor. Herceptin can cause heart damage leading to congestive heart failure.

Both Gleevec and Herceptin block specific enzymes and growth factor receptors (called signal transduction inhibitors) involved in cancer proliferation. Other targeted therapies modify the function of proteins that regulate gene expression and other cell functions, induce cancer cells to undergo apoptosis, and block angiogenesis (growth of blood vessels to tumors). (10)

## What Is Radiation?

Many atoms that make up molecules and compounds are stable and are not radioactive. However, as atoms increase in size and mass, especially atoms as large as Bismuth (atomic number 83) or larger, they become more unstable and can undergo nuclear decay. In this unstable state, the atoms are called radioactive.



Some smaller atoms can have radioactive isotopes. An isotope is defined as two atoms with the same atomic number but different mass due to a different number of neutrons. For example, carbon has the atomic number of 6 and the atoms carbon-12, carbon-13, and carbon-14 are isotopes of carbon, with a mass of 12, 13, and 14, respectively. Carbon-12 has 6 protons and 6 neutrons for a total mass of 12, while carbon-13 has 6 protons and 7 neutrons for a total mass of 13, and carbon-14 has 6 protons and 8 neutrons for a total mass of 14. Only carbon-14 of the three isotopes is radioactive.

In the late 1800s and early 1900s, radioactivity was discovered and studied. Larger atoms, such as radium, polonium, radon, and others, were found to glow in the dark and after much scientific investigation by scientists, such as Marie and Pierre Curie, these atoms were found to go through radioactive decay. Radioactive decay is a spontaneous emission of a) alpha, b) beta, and/or c) gamma particles from the nucleus of the atom.

- a) Alpha emissions are the least dangerous and can be stopped by a piece of paper, clothing, etc. A new atom with a new nucleus is formed releasing an alpha particle containing 2 protons and 2 neutrons (a helium nucleus). The emission is a  ${}_2^4\text{He}$  alpha particle so the radioactive atom loses 4 units of mass since the mass of each proton and neutron has a mass of 1 unit and it loses 2 units of positive charge since each proton has a charge of +1 and the neutrons have 0 charges. For example, when the atom plutonium-236 emits an alpha particle, the atom changes to uranium-232 ( $236 - 4$  units of mass = 232). Plutonium has an atomic number of 94 and uranium has a mass number of 92 so two units of positive charge have been emitted ( $94 - (+2$  units of charge) = 92). Alpha radiation is not suitable for radiation treatment for cancer since it doesn't penetrate the skin. Alpha radiation, however, does damage tissue when ingested.
- b) Beta emissions can go through skin and clothing but are stopped by a thin sheet of aluminum or wood. A new atom with a new nucleus is formed by changing a neutron into a proton and an electron. The fast-moving and high energy electron  ${}_{-1}^0\text{e}$  is released as a beta particle. The new atom has no change in mass since the mass of a neutron is the same as the mass of a proton and it loses an electron which has a charge of  $-1$  and negligible (or zero) mass. For example, when the atom carbon-14 emits a beta particle, the atom changes to nitrogen-14 (atomic number of 7) ( $14 - 0$  units of mass = 14). Because of the loss of a  $-1$  charge, the atomic number increases by 1 unit ( $6 - (-1$  unit of charge) = 7).



- c) Gamma radiation is pure electromagnetic energy emitted from the atom so the atom does not change in mass or charge. Gamma radiation is a high frequency and short wavelength part of the electromagnetic spectrum. Gamma rays can penetrate skin, metal, concrete but is stopped by lead. X-rays are also high energy electromagnetic radiation and when used, a patient is protected by a lead shield on body parts not needing to be x-rayed or which are in danger of being damaged by the x-rays, such as the reproductive organs and the thyroid gland.

Radioactive elements may give off only one type of radiation or a combination. Example: polonium-90 is an alpha emitter, strontium-90 is a beta emitter, uranium is an alpha and gamma emitter, iodine-131 is a beta and gamma emitter, and plutonium emits alpha, beta, and gamma radiation.

Each radioactive substance has a unique half- life (the amount of time it takes for half of the original amount to be left after radioactive decay). Carbon-14 has a half-life of 5730 years. If one started with a 100.0 gram sample of carbon-14, 5730 years later there would be 50.0 grams of carbon-14 remaining and 50.0 grams of nitrogen-14 produced. The half-life of uranium-238 is  $4.468 \times 10^9$  years, plutonium-236 is 88 years, & uranium-226 is 0.35 seconds.

### What Is Radiation Therapy?

Radiation therapy uses high-energy electromagnetic radiation to shrink tumors and to kill cancer cells by directly damaging the DNA and/or by creating free radicals within the cell ultimately damaging the DNA. Some cancer patients have chemotherapy and/or targeted therapy only while others have radiation therapy only and still others have a combination of chemotherapy and/or targeted therapy and radiation therapy. About half of all cancer patients receive some type of radiation therapy.

In particular, radiation therapy for cancer treatment uses x-rays, gamma radiation, and charged particles, like beta particles. The radiation is delivered a) outside the body using external-beam radiation, b) inside the body using internal radiation (also called brachytherapy), or c) throughout the body using systemic radiation therapy. The precise location of the tumor may be determined by using a CT, PET, or MRI scan preceding the radiation treatment.

- a) The external -beam radiation therapy is most often delivered in the form of photon beams (either gamma rays or x-rays) using a machine called a linear accelerator (also called a LINAC) which uses electricity to create the photon beams. The most common type of external- beam radiation therapy is called 3-dimensional conformal radiation therapy (3D-CRT) which uses computer software to deliver radiation to a very precise target. To further enhance precision, use of intensity modulated radiation therapy (IMRT) helps define the contours of organs to be treated. The goal is to kill the cancer cells and spare the surrounding normal tissue.



In order for the beam to be aimed at the exact location each time, maximizing the destruction of the cancer cells and minimizing the destruction of normal cells, the skin of the patient is tattooed. In addition, restraints may be used to hold the body in a certain position and shields may be placed to block radiation from reaching unaffected parts of the body. The dose and duration of each treatment and total number of treatments would depend on the type of cancer, stage and grade of the cancer, and the age and health of the patient. Often the patient would receive this type of treatment in daily sessions over several weeks.

- b) For internal radiation or brachytherapy, the radiation is delivered from radiation sources placed inside or on the body and the patient may receive a low-dose-radiation rate or high-dose radiation rate. *Brachy-* means short in Greek so the brachytherapy is radiation that only travels short distances.

In low-dose rate treatment, cancer cells receive continuous low-dose radiation over several days to months from the implanted source. Low-dose rate brachytherapy uses implanted seeds containing iodine-125 (half-life = 56.9 days, gamma emitter) or palladium-103 (half-life = 17 days, gamma emitter). The implanted seeds might remain in the body for several days or in some cases, the sources are sealed within body and left there. The remaining radioactive material does not cause any discomfort or harm to the patient and will eventually lessen in radioactivity over a period of months due to the short half-life and small amount of source used.

In high-dose rate brachytherapy treatment, a robotic machine attached to delivery tubes placed inside the body would insert one or more radioactive sources into or near the tumor and then remove the source at the end of the session. The robotic machine allows the doctors and staff to deliver the therapy from another room. This type of treatment can be given in one or more treatment sessions using rods of iridium-192 (half-life = 73.8 days, beta emitter). Most of the time, the patient will temporarily be radioactive while the source is in place but once it is removed, the patient is no longer radioactive. Brachytherapy may be delivered at higher dose rates of radiation than external-beam therapy while causing less damage to normal tissue.

- c) With systemic radiation therapy, the patient receives an injection of a radioactive substance or swallows the substance. Examples include using a radioactive iodine -131 (half life = 8.02 days, beta emitter) to treat thyroid cancer or a radioactive substance bound to a monoclonal antibody for B-cell non-Hodgkin lymphoma. Some of these patients may temporarily have radioactive body fluids and should avoid children under 18 and pregnant women.

The radiation therapy side effects are largely caused by external-beam radiation treatment. The therapy kills cancer cells very effectively but it also kills or damages normal cells in the path of the beam as well. This can lead to both early (called acute) and late (called chronic) side effects.



Regardless of the body part treated with radiation therapy, fatigue is a common acute side effect. The acute side effects are seen in fast growing tissue, such as in skin irritation, damage to salivary glands, and hair loss when treating the head or neck area or urinary and bladder problems when treating the abdominal area. Most of the acute side effects are short term but there can be permanent hair loss and salivary gland damage.

The chronic side effects are permanent and may include infertility, memory loss, and damage to bowels causing diarrhea and bleeding, damage to the bladder leading to leakage of urine, and fibrosis where tissue is replaced with scar tissue, limiting movement. Sometimes, a second cancer can occur years later caused by the radiation exposure during cancer treatment, such as in the bones. The lifetime risk of a second cancer is highest in cancer patients treated as children or young adults.

Since internal radiation or brachytherapy is very localized, side effects might include minor scarring of the targeted tissue and perhaps irritation in the adjacent tissues. With systemic radiation treatment, the half-life of the radioactive source is so short that side effects are minimal. (16)

### What Are Clinical Trials?

Cancer patients may be offered the opportunity to become part of a clinical trial which incorporates chemotherapy, other targeted drugs, and/or radiation therapy. They are used for research to determine the most effective treatment for certain cancers. Sometimes new drugs are introduced and sometimes new combinations of therapies are being investigated. There are risks since the new therapy may not be better or even as good as the standard treatments but, on the other hand, it might possibly be much better than the standard treatment. Clinical trials are especially useful if treatment has not worked in the past or if the cancer is beyond the stage where usual treatments have worked. (17) The studies run about 2 years from the administration of the treatment through follow-up care. Insurance companies may or may not pay for clinical trials, depending on the insurance company.

An example of a clinical trial for treating a rare and very aggressive form of uterine cancer entailed two arms to the study. One arm of the study included full pelvic external-beam radiation which was considered the current standard treatment and the other arm of the study included 4 cycles of chemotherapy and 2 treatments of brachytherapy. It had been previously found that the standard treatment had many permanent side effects, such as fistulas (or holes) in the bowel and bladder, and also there had been recurrences of the cancer outside the pelvic region, especially in the lungs and brain, even after the pelvic radiation. Independently, instead of treating patients with this type of cancer with full pelvic radiation, some hospitals and institutions already had moved to treating these patients with 4 – 6 cycles of chemotherapy and 4 sessions brachytherapy and there were fewer reported



recurrences. The clinical trial was being conducted to see if the standard treatment should be ruled out altogether. The risk to the patient for this particular clinical trial was that those chosen randomly for the pelvic radiation were susceptible to permanent radiation damage and to possible recurrence of the cancer in the lung or brain. Whether to be part of a clinical trial or not is left to the patient to decide but once enrolled in the clinical trial, the patient would not be able to change his/ her mind if he/she were randomly chosen for an arm of the study in which he/she didn't want to participate.

### What Happens After Cancer Treatment Ends?

During and following treatment, cancer patients are encouraged to eat a healthy diet containing lots of fruits and vegetables, whole grains, and lean meats and to avoid processed foods high in sugar and fat. If overweight, they are encouraged to lose weight in order to lower their body mass index into the normal weight range. Smokers are encouraged to stop smoking. In addition, they are encouraged to exercise daily, lower their stress levels, and get plenty of sleep.

Once cancer treatment has ended, the patient would be seen by the oncologist every 3 months for the first few years, depending on the type of cancer. At each appointment, blood tests and further biopsies are done to see if the cancer has returned. If the cancer does appear to have recurred, additional chemotherapy, targeted therapy, and/or radiation would begin.

If no evidence of cancer is found, the patient would eventually be seen every six months. Usually after the 5 year cancer-free mark has been reached, the patient is seen only once a year for another 5 years. There are some cases of recurrence of cancer after the 5 year mark but the likelihood of recurrence decreases sharply with time. Because of this, the 5 year cancer-free mark is usually considered a time for celebration!

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